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ASSESSMENT AND REPORTING OF ADVERSE DRUG REACTIONS TO IOPROMIDE

A STUDY OF RISK PERCEPTION AND PHARMACOVIGILANCE

TESIS DOCTORAL

João José de Morais Joaquim

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ASSESSMENT AND REPORTING OF ADVERSE DRUG REACTIONS TO IOPROMIDE

A STUDY OF RISK PERCEPTION AND PHARMACOVIGILANCE

Trabajo presentado para optar al grado de Doctor en Farmacia por la Universidad de Salamanca por:

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Bajo la dirección científica de

Profesora D. Ramona Mateos-Campos

Se presenta esta tesis en compendio de artículos, a la Universidad de Salamanca, para la obtención del grado de doctor, con los manuscritos a seguir presentados y desarrollados durante este trabajo.

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Dña. RAMONA MATEOS CAMPOS, Profesora Titular de Medicina Preventiva y Salud Pública de la Universidad de Salamanca,

CERTIFICA:

Que D. **João José Joaquim** ha realizado bajo su dirección el trabajo titulado ***"Assessment and Reporting of Adverse Drug Reactions to Iopromide. A Study of Risk perception and Pharmacovigilance",*** y que autoriza su presentación en el formato de **Compendio de artículos,** para optar al Grado de Doctor por la Universidad de Salamanca, al considerar que se han alcanzado los objetivos inicialmente previstos.

Y para que conste, firma el presente certificado en Salamanca, a 16 de Junio de dos mil veintitrés.

Firmado por MATEOS CAMPOS, RAMONA (FIRMA) el día 16/06/2023 con un certificado emitido por AC DNIE 004

Fdo.: R. Mateos Campos

Dedicación

A mi familia y a todos aquellos que con su amistad, enseñanzas y sabiduría me permitieron alcanzar este sueño.

"*La verdadera ciencia enseña, por encima de todo, a dudar y a ser ignorante*."

Miguel de Unamuno

"I have no special talent. I am only passionately curious."

Albert Einstein

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Tables and figures

List of acronyms

ADR - Adverse Drug Reactions
BAT - Basophil Activation Test
CM - Contrast Media
DPT - Drug Provocation Test
DRP – Drug Related Problems
ESI – Electrical Source Imaging
GBCM - Gadolinium-based Contrast Media
HCP - Healthcare Professionals
ICM - Iodinated Contrast Media
IHR – Immediate Hypersensitivity Reaction
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde
IRCM – Iodinated Radiocontrast Media
LTT - Lymphocyte Transformation Test
MC - Medios de Contraste
MCY - Materiales de Contraste Yodados
MRI - Magnetic Resonance Image
MRS – Magnetic Resonance Spectroscopy
MSI – Magnetic Source Imaging
NIHR - Non-immediate hypersensitivity reaction
NSAID - Non-steroidal anti-inflammatory drugs
OMS-UMC – Organización Mundial de la Salud-Uppsala Monitoring Centre
OMS – Organización Mundial de la Salud
PET - Positron Emission Tomography
PV - Pharmacovigilance
RAM - Reacciones Adversas a Medicamentos
SNE – Sistema de Notificación Espontanea
SRE - Spontaneous Reporting System
TC - Tomografía Computarizada
WHO - World Health Organization

RESUMEN GENERAL

I. INTRODUCCIÓN

Los Sistemas de Farmacovigilancia, que comenzaron a desarrollarse a principios de los años 60 con la catástrofe de la talidomida, nacen con la conciencia, por parte de organizaciones y profesionales de la salud internacionales, de la importancia de las reacciones adversas a medicamentos (RAM). Varios medicamentos, además de la talidomida, causaron graves problemas de seguridad en humanos. Practolol [síndrome oculo-mucocutáneo], benoxaprofeno [reacciones de fotosensibilidad], los anticonceptivos orales [tromboembolismo venoso] son algunos de los casos descritos en la literatura [1] y un estudio reciente [2] presenta el número de medicamentos retirados del mercado debido a reacciones adversas graves. El curso clínico de las reacciones adversas a medicamentos puede, en casos extremos, causar la muerte de los pacientes, y pueden ocurrir otras situaciones peligrosas, como hospitalización, prolongación de la estancia hospitalaria, y la baja notificación es una realidad y una característica reconocida de los informes espontáneos [3-5]. El seguimiento de las RAM atañe especialmente a la legislación portuguesa (Diário da República, 2006). Sin embargo, la infra notificación de reacciones adversas a medicamentos es difícil en el Sistema de Notificación Espontánea (SNE) reflejado en los estudios de seguridad de medicamentos [4, 6]. Otro problema con la notificación espontánea es que se notifican menos del 10 % de todas las RAM graves y del 2 al 4 % de las RAM no graves [7]. Considerando el subregistro, una de las principales limitaciones del sistema de notificación RAM en cualquier programa de monitoreo es que no puede caracterizar adecuadamente la seguridad de los medicamentos comercializados. Sin embargo, la notificación espontánea sigue siendo un método esencial para identificar reacciones adversas. En comparación con los consumidores

potenciales, el número relativamente pequeño de pacientes incluidos en las fases II y III de los ensayos clínicos hace que sea problemático determinar la aparición y la frecuencia de RAM extremadamente raras. Los estudios de vigilancia posterior a la comercialización y los estudios observacionales, por lo tanto, brindan la oportunidad de obtener una mejor comprensión de la seguridad y la tolerabilidad de un agente de contraste en el contexto del "mundo real" [8].

Para realizar pruebas de diagnóstico por la imagen, muchas veces es necesario utilizar medios de contraste para una mejor visualización de las estructuras anatómicas. Desde la década de 1920, los medios de contraste yodados (MCY) se han utilizado para la angiografía y se estima que 75 millones de procedimientos necesitan medios de contraste [9]. Esto conducirá necesariamente a la promoción de estudios que presenten la realidad asociada a los efectos adversos [9, 10], la prevención [11, 12] y el tratamiento [13, 14]. Seguridad [10, 14-16] y notificación de reacciones a los sistemas de farmacovigilancia por profesionales de la salud [14, 17] y por pacientes [18].

La seguridad en el uso de los medicamentos ha tenido especial atención por parte de las Autoridades Nacionales y Europeas, profesionales sanitarios, pacientes, medios de comunicación y los Sistemas de Farmacovigilancia han mostrado algunas dificultades para recoger la información antes. Uno de los problemas crónicos por el bajo índice de informes está relacionado con el compromiso de los profesionales de la salud, de organización, entre otros [14, 16, 19, 20]. Se sabe que mejora la seguridad de los medios de contraste. Con el crecimiento de la oferta en la medicina privada, se produce un paulatino aumento de los exámenes que utilizan la imagen y, por supuesto, un aumento generalizado del uso de medios de contraste en diferentes técnicas, como la resonancia magnética y la tomografía computarizada (TC). Aun así, estos pueden inducir situaciones graves e incluso fatales, lo que justifica una atención especial a las prácticas y datos para identificar la frecuencia de las reacciones adversas.

Sin embargo, desde la seguridad asociada a los medios humanos y tecnológicos para intervenir en caso de riesgo para la vida, los centros privados necesitan una mayor y mejor atención a estos procedimientos que generan información a partir de sus prácticas, y que pueden inducir mejores prácticas antes de la riesgo y capacidad de intervención sobre ocurrencias, especialmente de reacciones severas. La reacción adversa más grave es el desarrollo de anafilaxia que pone en riesgo la vida del paciente y justifica una evaluación específica e individualizada de las condiciones de administración (p. ej., personal especializado) y de la intervención (p. ej., medicamentos y soporte vital necesario).

II. OBJETIVOS

i) Evaluar el conocimiento de los pacientes sobre los riesgos de RAM y el Sistema de Farmacovigilancia Portugués;

ii) Revisar las RAM y la evaluación de seguridad asociada a los medios de contraste de iopromida;

iii) Proporcionar un análisis retrospectivo de reacciones adversas a iopromida en una unidad privada de radiología portuguesa;

iv) Arrojar luz sobre enfoques innovadores, incluidas estrategias centradas en el paciente, destinadas a eludir la infra notificación de RAM.

III. METODOLOGÍA

Para lograr los objetivos de la tesis, organizada em compendio de artículos, se realizaron dos artículos originales, uno para evaluar el conocimiento de los pacientes sobre los riesgos de RAM y el Sistema de Farmacovigilancia de Portugal y otro para proporcionar un análisis retrospectivo de RAM a iopromida en una unidad privada de radiología portuguesa.

Además, para reforzar los antecedentes de la tesis, se agregaron dos artículos de revisión, uno que utiliza una revisión narrativa de la evaluación de la seguridad de la iopromida que se centra en los eventos adversos y una revisión de alcance de enfoques integrales para aumentar la notificación de reacciones adversas a medicamentos.

IV. JUSTIFICACIÓN Y ESQUEMA DE LA TESIS

La seguridad en el uso de medicamentos ha tenido especial atención de las Autoridades Nacionales y Europeas, profesionales de la salud, pacientes y medios de comunicación. Sin embargo, los Sistemas de Farmacovigilancia han mostrado algunas dificultades para recolectar la información antes. El compromiso de los profesionales y organizaciones de la salud, entre otros, es un problema recurrente por el bajo índice de informes [14, 16, 19]. Con el crecimiento de la oferta en la medicina privada, hay un aumento paulatino de exámenes que utilizan imágenes biomédicas y, por supuesto, un crecimiento generalizado en el uso de Medios de Contraste Yodados (MCY) en diferentes técnicas de imagen. Anualmente, se estima el uso de millones de procedimientos con ICM que son generalmente reconocidos como seguros [3]. Aun así, pueden ocurrir RAM a MCY, siendo la anafilaxia la reacción adversa más grave que pone en riesgo la vida del paciente, lo que justifica una evaluación específica e individualizada de las condiciones de administración (por ejemplo, personal especializado) así como de las intervenciones putativas (por ejemplo, medicamentos y apoyo básico) de vida. En este sentido, los proveedores de salud, incluidos los centros privados, deben conocer cada vez más los procedimientos que generan información a partir de sus prácticas para identificar la frecuencia de ocurrencia de las reacciones adversas y disponer de los medios humanos y tecnológicos para intervenir en caso de riesgo. La iopromida, un medio de contraste monomérico no iónico de baja osmolaridad que contiene yodo se usa en todo el mundo desde 1985. Al igual que cualquier otro agente de contraste monomérico no iónico, la incidencia de reacciones adversas a la iopromida se atribuye principalmente a su contenido de iones, el pH de los medios de contraste, hidrofilia y viscosidad [21]. Cabe destacar que se percibió una mayor tasa de reacciones adversas a la iopromida, caracterizada por una mayor incidencia de manifestaciones

cutáneas, gastrointestinales y faciales [22]. Más recientemente, la iopromida parecía facilitar también la aparición de encefalopatía inducida por contraste [23]. Aunque se ha informado que las reacciones adversas a los MCY no iónicos ocurren con una frecuencia modesta de alrededor del 0,5 % al 3 % de los pacientes [24], todavía existe el riesgo de una notificación insuficiente continua, concretamente en la medicina privada, donde el aumento general del uso de MCY está bien establecido. Dado que se siguen produciendo reacciones de hipersensibilidad potencialmente mortales, el diagnóstico, la notificación y el tratamiento de las reacciones adversas a los MCY, en particular a la iopromida, merecen más atención. En consecuencia, este trabajo tuvo como objetivo proporcionar una caracterización más amplia de las RAM a la iopromida y evaluar la percepción del riesgo de los pacientes y la notificación de RAM en Portugal con el fin de empoderar a los ciudadanos y proveedores de atención médica con competencias para una gestión adecuada de las RAM del sistema de imágenes biomédicas privado de atención médica nacional.

V. RESULTADOS

Para una mayor claridad, la recopilación y el análisis de datos se presentan como se describe a continuación:

- Capitulo 1 - "*Assessment of risk perception by patients concerning adverse drug reactions*"

adjunta información original sobre el conocimiento de los pacientes sobre los riesgos de RAM y del Sistema de Farmacovigilancia Portugués;
Este trabajo destaca la mala percepción de riesgo de los pacientes con una tasa de respuestas negativas del 85,7%. Aunque algunos de los que respondieron conocían la posibilidad de informar una RAM, solo algunos participantes estaban familiarizados con el Sistema de Farmacovigilancia Portugués. Además, solo cinco pacientes, de la gran mayoría de los que se habían encontrado previamente con una RAM, informaron el evento a INFARMED.

- Capitulo 2 - "*Safety assessment of iopromide contrast media: a narrative review focusing on adverse events*"

proporciona una revisión narrativa de RAM y evaluación de seguridad de los medios de contraste de iopromida;
Esta revisión narrativa presenta un informe completo de los datos disponibles sobre las reacciones adversas a iopromida. También analiza su ocurrencia y frecuencia con diversos factores de riesgo potenciales (por ejemplo, edad, sexo, condiciones preexistentes).

- Capitulo 3 - "*Iopromide safety assessment in a radiology department: a seven-year retrospective characterization of adverse events*"

presenta un análisis retrospectivo de los eventos adversos de la iopromida en una unidad privada de radiología portuguesa;
Los eventos de hipersensibilidad fueron inmediatos, desarrollándose en la mayoría de los casos eventos con compromiso cutáneo y grado leve, donde los más recurrentes fueron pápulas (n=60), prurito (n=42), eritema (n=27) y urticaria (n= 14). Los eventos graves están representados principalmente por vómitos (n=11), estridor (n=8), dificultad para respirar (n=7) y síncope (n=3). El examen que mostró más efectos adversos fue la tomografía computarizada abdomino-pélvica.

- Capitulo 4 - "*All-round approaches to increase adverse drug reaction reports: a scoping review*"

busca arrojar luz sobre enfoques innovadores, incluidas las estrategias centradas en el paciente, destinadas a eludir el subregistro de RAM.
Seis estrategias mejoraron la recopilación de informes de RAM, a saber, incentivos económicos, intervenciones educativas para profesionales de la salud y pacientes, atención de los medios, uso de redes sociales en la búsqueda proactiva de RAM y aplicaciones para teléfonos inteligentes y campañas. Estas estrategias permitieron la evolución en PV, permitiendo la detección temprana de RAM graves por parte de la industria y los reguladores. La creación de estrategias que permitan la implicación de los pacientes destacó su papel en la Farmacovigilancia.

VI. DISCUSIÓN

Una reacción adversa a medicamentos se refiere a cualquier resultado indeseable e imprevisto experimentado por una persona como resultado de tomar un medicamento. Estas reacciones pueden incluir efectos esperados e inesperados, que van desde consecuencias terapéuticas hasta no terapéuticas. Si bien todas las personas que toman medicamentos corren el riesgo potencial de sufrir RAM, la forma en que cada paciente percibe este riesgo puede diferir significativamente. Cuando las personas consumen medicamentos, lo hacen para mejorar su salud o controlar una afección en particular. Sin embargo, los medicamentos a veces pueden provocar efectos secundarios no deseados que varían en gravedad e impacto. Estas reacciones adversas pueden manifestarse como síntomas físicos, efectos psicológicos o cambios en el bienestar general del individuo. La aparición de RAM puede depender de varios factores, como el medicamento específico que se toma, la dosis, la duración del uso y las variaciones individuales en la fisiología y el metabolismo. Además, ciertas poblaciones, como los ancianos o aquellos con funciones orgánicas comprometidas, pueden ser más susceptibles a experimentar RAM. La percepción del paciente del riesgo asociado con las RAM puede influir en gran medida en su proceso de toma de decisiones y en la adherencia general a la medicación. Algunas personas pueden ser conscientes de los posibles efectos secundarios y estar preparadas para ellos, mientras que otras pueden tener conocimientos limitados o conceptos erróneos sobre las reacciones adversas a los medicamentos. Además, las experiencias previas con medicamentos, ya sea personal o de boca en boca, pueden dar forma a la percepción de las reacciones adversas de un individuo. Factores como la ansiedad, el miedo y las experiencias negativas pasadas con medicamentos pueden contribuir aún más a una mayor percepción de los riesgos involucrados [25-27]. El estudio actual destaca una

percepción preocupante del riesgo entre los individuos y los profesionales de la salud. Muchas personas tienen la firme creencia de que los medicamentos son intrínsecamente seguros y efectivos, asumiendo que los extensos procesos de investigación y desarrollo garantizan su confiabilidad sin tener en cuenta los riesgos potenciales. Además, existe la idea errónea de que los medicamentos recetados por los médicos son inherentemente más confiables. Otro hallazgo preocupante es la creencia de que los medicamentos recetados genéricos son menos efectivos en comparación con sus contrapartes de marca.

Curiosamente, el estudio indica que las personas con mayores niveles de educación tienden a reconocer que no existe una diferencia sustancial entre los medicamentos recetados y los de venta libre. Sin embargo, todavía tienen la creencia de que los medicamentos recetados genéricos son inferiores a otras opciones disponibles en términos de efectividad. Estas percepciones de riesgo pueden tener implicaciones significativas para la adherencia a la medicación y los resultados de salud del paciente. Cuando las personas confían en los medicamentos sin considerar los riesgos potenciales, pueden pasar por alto o minimizar las reacciones adversas a los medicamentos y no informarlas a los proveedores de atención médica. Esto puede llevar a que no se notifiquen las RAM y dificultar la identificación de posibles problemas de seguridad. Para abordar estos conceptos erróneos, es crucial mejorar la educación pública y crear conciencia sobre los riesgos potenciales asociados con los medicamentos, independientemente de su estado de prescripción o marca. Los profesionales de la salud juegan un papel clave en el fomento de una comunicación abierta y transparente con los pacientes, discutiendo los beneficios y riesgos de las diferentes opciones de tratamiento y abordando cualquier inquietud o concepto erróneo que puedan tener. Además, promover información precisa sobre medicamentos genéricos y disipar la creencia de que son inherentemente menos efectivos puede ayudar a las personas a tomar

decisiones más informadas sobre sus opciones de tratamiento. Proporcionar recursos basados en evidencia y capacitar a los pacientes para que participen activamente en sus decisiones de atención médica puede contribuir a una percepción más equilibrada de los riesgos de la medicación. La comprensión del participante del Sistema de Farmacovigilancia portugués también se consideró adecuada. Sin embargo, cuando se les pregunta sobre el proceso de notificación utilizado por las organizaciones, los niveles de alfabetización siguen siendo los mismos, lo que impide que los pacientes notifiquen activamente las RAM. La perspectiva de utilizar un sistema de notificación integrado para la identificación y gestión de RAM es algo que el 46,2 % de los encuestados, a pesar de su conocimiento parcial del sistema de notificación, conoce. Los grupos de edad más jóvenes y mayores representan el grupo de edad con poca información sobre el Sistema de Farmacovigilancia portugués. Las personas más cualificadas son, sin duda, más conocedoras de las reacciones adversas a los medicamentos y de la necesidad crítica de denunciarlas.

Los proveedores de atención médica desempeñan un papel crucial al abordar las percepciones y preocupaciones de los pacientes sobre las reacciones adversas a los medicamentos. La comunicación efectiva entre los pacientes y los profesionales de la salud puede ayudar a aliviar la ansiedad y brindar información precisa sobre la probabilidad y la gravedad de los posibles efectos adversos. Al fomentar un diálogo abierto y de confianza, los proveedores de atención médica pueden empoderar a los pacientes para que tomen decisiones informadas sobre sus planes de tratamiento, lo que incluye sopesar los beneficios potenciales frente a los riesgos de las RAM. La percepción de riesgo puede afectar significativamente el comportamiento del paciente [28], ya que los pacientes que perciben un alto riesgo de RAM pueden optar por no tomar sus medicamentos o dudar en comenzar con nuevos medicamentos. Esto puede tener un impacto negativo en su salud y puede resultar en el uso de terapias alternativas que no están basadas

en evidencia. Buscando los factores que pueden influir en la percepción de riesgo de los pacientes, es posible destacar la edad, las experiencias previas, la cultura y creencias y el miedo y la ansiedad [28]. La experiencia del consumidor es esencial porque otorga significado y valor a los informes de RAM y permite identificar posibles reacciones nuevas. Como resultado, los profesionales de la salud deben ganar gradualmente más autoridad para reconocer las RAM probables, informarlas e informar completamente a los pacientes sobre los efectos secundarios de los medicamentos y el Sistema de Farmacovigilancia portugués [15, 29]. La influencia del comportamiento de los profesionales de la salud en los pacientes puede ser grande. Por lo tanto, la comunicación centrada en el paciente es un tema clave para que el paciente ejerza un papel activo en el proceso de toma de decisiones de los sistemas de atención médica [18, 19, 30]. Entre varios temas candentes por cumplir, los temas que comprenden el reconocimiento de los requisitos reglamentarios y se alienta ampliamente la educación sobre los estándares aplicables y las responsabilidades con respecto a la seguridad del producto [30, 31]. Se deben mejorar los canales de comunicación para traducir las preocupaciones de los pacientes sobre las RAM en una conciencia efectiva mediante informes de rutina dentro de los sistemas de farmacovigilancia [32]. En el contexto de la desprescripción de medicamentos, los profesionales de la salud deben tener una comprensión integral de la percepción del riesgo. Esta comprensión puede ayudar a identificar a las personas que pueden beneficiarse de la reducción de la dosis o la suspensión de ciertos medicamentos. Al utilizar técnicas de desprescripción para evaluar críticamente los medicamentos, los médicos pueden mejorar la seguridad del paciente y mejorar los resultados generales de salud al reducir la probabilidad de reacciones adversas a los medicamentos. Al considerar la percepción del riesgo, los profesionales de la salud pueden evaluar cómo los pacientes perciben los riesgos y beneficios potenciales

asociados con su régimen de medicación actual. Esta evaluación implica comprender las preocupaciones, creencias y actitudes de los pacientes hacia sus medicamentos, incluidas las aprensiones que puedan tener sobre los efectos adversos o el uso a largo plazo.

Con base en este entendimiento, los proveedores de atención médica pueden identificar a los pacientes que podrían tener un mayor riesgo de experimentar reacciones adversas a los medicamentos o que podrían beneficiarse potencialmente al reducir o suspender medicamentos específicos. Al participar en la toma de decisiones compartida con los pacientes, los médicos pueden analizar los posibles beneficios y riesgos de la desprescripción, teniendo en cuenta las preferencias y prioridades individuales de los pacientes. La desprescripción implica una revisión cuidadosa de los medicamentos para determinar si aún son necesarios o si las opciones de tratamiento alternativas pueden ser más adecuadas. Este proceso tiene como objetivo simplificar los regímenes de medicamentos, reducir la polifarmacia (el uso de múltiples medicamentos) y minimizar el potencial de interacciones farmacológicas y efectos adversos. Al implementar estrategias de desprescripción, los profesionales de la salud pueden mejorar la seguridad del paciente al mitigar los riesgos asociados con el uso de medicamentos. Este enfoque requiere un seguimiento continuo, una reevaluación periódica de los planes de tratamiento y una comunicación eficaz con los pacientes para garantizar su comprensión y cooperación [33]. Los estudios subrayan la conciencia inadecuada entre los pacientes sobre las RAM y los sistemas nacionales de notificación. Es crucial priorizar iniciativas futuras que apunten a mejorar la divulgación pública para la seguridad del paciente e involucren a los sistemas de farmacovigilancia. Existe una gran necesidad de educar a los pacientes sobre las RAM, asegurando que tengan acceso a información precisa y completa. Es posible que muchas personas no sean plenamente conscientes de los riesgos potenciales asociados con los medicamentos que toman o de la

importancia de informar cualquier efecto adverso que experimenten. Mejorar los esfuerzos de divulgación pública puede ayudar a cerrar esta brecha de conocimiento y capacitar a los pacientes para que tomen decisiones informadas sobre su atención médica. Además, la participación de los sistemas de farmacovigilancia es esencial para recopilar datos completos sobre RAM y monitorear la seguridad de los medicamentos a nivel nacional. Estos sistemas juegan un papel fundamental en la detección y evaluación de los riesgos potenciales asociados con los medicamentos. Al involucrar activamente a los pacientes y a los profesionales de la salud en la notificación de RAM, los sistemas de farmacovigilancia pueden capturar una gama más amplia de datos, lo que conduce a una mayor seguridad del paciente.

Aunque los medicamentos relacionados con las imágenes (agentes de contraste), comúnmente utilizados para mejorar la visualización de imágenes biomédicas, generalmente se consideran seguros, ocasionalmente provocan eventos adversos en los pacientes. Si bien el agente de imagen ideal proporciona un contraste mejorado con poca interacción biológica, se ha percibido una tasa significativa de reacciones adversas a la iopromida, un medio de contraste monomérico no iónico de baja osmolaridad que contiene yodo [23]. Sin embargo, el riesgo de subregistro, particularmente en el sistema de imágenes biomédicas privadas de salud nacional, dificulta continuamente la detección temprana, evaluación y prevención de RAM o cualquier otro problema relacionado con medicamentos. Como se indica en el segundo artículo, los enormes tamaños de muestra de la investigación incluida mejoraron la validez de los resultados y permitieron descubrir incluso RAM raras. El artículo también destacó algunas variables de riesgo vinculadas a las reacciones adversas a la iopromida, ofreciendo orientación a los MCY. La existencia de ciertos resultados contradictorios, que pueden estar relacionados con variaciones en los diseños, la demografía o la metodología del estudio, fue una de las deficiencias del estudio. La mayoría de los ensayos del

estudio se centraron en las reacciones adversas agudas o a corto plazo, que podrían no reflejar con precisión el perfil de seguridad a largo plazo de la iopromida. Finalmente, aunque la evaluación reconoció los vínculos entre los factores de riesgo específicos y las reacciones adversas, los factores de confusión adicionales que no se consideraron o ajustaron en estos estudios podrían afectar los resultados. La aparición de efectos secundarios de MCY es actualmente difícil de identificar, lo que puede causar que se subestime la realidad. Esto se debe a que los MCY se desarrollan lentamente, son difíciles de identificar y no es necesario registrarlos, lo que expone estas reacciones y conduce a un diagnóstico y notificación insuficientes [34]. Los principales factores de riesgo relativos para el desarrollo de reacciones de hipersensibilidad están asociados con antecedentes de reacciones a medios de contraste, asma bronquial, alergia a medicamentos, alergia alimentaria y el género femenino [35].

Estudios previos mostraron que las reacciones inmediatas son predominantemente síntomas cutáneos, autolimitados y de severidad leve [36], lo cual sigue los resultados obtenidos, siendo las pápulas (57,1%) y el prurito (40,0%) los síntomas más comunes entre los pacientes. Finalmente, las reacciones de grado I (70,5%) fueron las más prevalentes y de curso específico y limitado. Las reacciones graves afectan principalmente a los sistemas respiratorio y cardiovascular. En cuanto a la medicación, es fundamental evaluar las reacciones adversas para elegir un tratamiento adecuado. Dado que no existe una sugerencia de estándar de oro debido a la falta de investigación aleatoria controlada, las preocupaciones éticas y el desarrollo continuo de los MCY utilizados en la práctica clínica, se pueden adoptar varias terapias según las características clínicas distintivas de cada caso. En este estudio, las reacciones leves se resolvieron con la administración de un antihistamínico (clemastina) y un corticoide (hidrocortisona) para reducir el riesgo de desarrollar síntomas cutáneos y respiratorios. En algunos casos fue necesario reforzarlo con metilprednisolona por la

persistencia de los síntomas [37]. Hay un creciente cuerpo de investigación que destaca el descubrimiento de reacciones adversas a medicamentos asociadas con los medios de contraste, que se usan comúnmente en procedimientos de imágenes médicas y que no se habían reconocido anteriormente. Un ejemplo de ello es la aparición de fibrosis sistémica nefrogénica como efecto secundario novedoso en los últimos años. Esto subraya la importancia de monitorear y estudiar de cerca los efectos adversos de los medios de contraste. La identificación de nuevas reacciones adversas a medicamentos asociadas con los medios de contraste exige una mayor atención y vigilancia en el seguimiento de sus riesgos potenciales. La fibrosis sistémica nefrogénica, en particular, se ha reconocido como un efecto secundario significativo que justifica una cuidadosa consideración e investigación. Para garantizar la seguridad del paciente, es fundamental realizar una vigilancia y un seguimiento exhaustivos de los efectos adversos relacionados con los medios de contraste. Los proveedores de atención médica, las agencias reguladoras y los investigadores deben colaborar para establecer sistemas de farmacovigilancia efectivos que rastreen y analicen los eventos adversos asociados con estos agentes. Al monitorear de cerca los efectos adversos de los medios de contraste, los profesionales de la salud pueden obtener una comprensión más profunda de sus riesgos potenciales y tomar las precauciones necesarias. Este conocimiento puede informar la toma de decisiones clínicas, el asesoramiento del paciente y el desarrollo de pautas para minimizar la aparición y la gravedad de las reacciones adversas.

Además, los proveedores de atención médica deben mantenerse actualizados con los últimos hallazgos de investigación y participar en programas de educación y capacitación continuos. Esto les permitirá reconocer y manejar con eficacia las reacciones adversas relacionadas con los medios de contraste, mejorando así los resultados de los pacientes y reduciendo los daños potenciales [38]. A pesar del aumento reciente en el número de informes de pacientes, estudios

recientes enfatizan la necesidad de crear conciencia entre los pacientes y los profesionales de la salud sobre la necesidad continua de promover el informe de RAM [18]. Además, las autoridades competentes deben implementar métodos innovadores para fortalecer la notificación de RAM para superar barreras tales como la falta de promoción activa debido a la escasez de recursos para apoyar campañas publicitarias y la incapacidad de hacer frente a una sobrecarga de informes [39]. El estudio de alcance para el tercer artículo incluyó una selección de búsqueda innovadora que reunió varias estrategias para promover el informe de RAM. Sin embargo, hubo ciertos inconvenientes a señalar, como la ausencia de artículos sobre incentivos económicos bajo los requisitos de inclusión. Esto se debe a que algunas naciones necesitan más medios financieros para implementar esta medida y debido a que las redes sociales y las aplicaciones para teléfonos inteligentes se han utilizado recientemente en PV, hay menos información sobre su uso en las bases de datos verificadas. Aquí, identificamos seis métodos para mejorar la recopilación de informes de RAM en PV, incluidos incentivos financieros, iniciativas de educación para pacientes y profesionales de la salud, atención de los medios, el uso de las redes sociales para la búsqueda proactiva de RAM y aplicaciones y campañas para teléfonos inteligentes. La implementación por parte de varios países de un sistema de notificación de RAM para pacientes les permitió informar espontáneamente una RAM, lo que proporcionó un gran avance en PV, aumentando el número de recopilaciones de RAM y la detección temprana de signos [39] Es más probable que los pacientes notifiquen reacciones graves [18], brinden más información sobre el impacto en la calidad de vida y las notifiquen con mayor frecuencia que los profesionales de la salud [40]. El uso de aplicaciones para teléfonos inteligentes, formularios de notificación en línea, como los del portal de notificación de RAM, el uso generalizado de las redes sociales, campañas de difusión e iniciativas educativas, junto con mejoras en los procedimientos de notificación y una promoción más proactiva de

PV, hacen que los notificadores sean más conscientes de los problemas asociados con el uso del medicamento y van acompañados de un aumento en el número de reacciones adversas notificadas cada año [41]. A través de estos medios, se divulgan las diversas herramientas que posibilitan el reporte, facilitando la participación del paciente de forma activa; donde muchos desconocen la existencia de un sistema fotovoltaico en el país, solo los jóvenes y las personas con educación superior tienen algún conocimiento sobre las posibilidades del informe [18].

Cada país ha diseñado su propio conjunto de políticas para fomentar la notificación espontánea de RAM en función de factores como las características de la población, los recursos disponibles y el nivel de avance de sus sistemas fotovoltaicos. En algunas naciones, la cobertura de los medios de comunicación de las RAM ha desempeñado un papel crucial en generar interés público y conciencia sobre la PV, facilitando así la recopilación de informes de RAM. Reconociendo las necesidades y circunstancias únicas de sus poblaciones, los países han implementado estrategias personalizadas para promover la notificación de RAM. Estas estrategias consideran factores como la infraestructura de atención médica, las capacidades tecnológicas y el nivel de accesibilidad de la atención médica.

Al alinear sus políticas con estas consideraciones específicas, los países pueden optimizar la eficacia de sus sistemas fotovoltaicos y alentar a los profesionales de la salud y a los pacientes a informar las RAM. La cobertura mediática de las RAM ha demostrado ser influyente para aumentar el interés y el conocimiento del público sobre la energía fotovoltaica. Cuando las RAM reciben una gran atención de los medios, se genera conciencia entre la población en general sobre la importancia de denunciar tales incidentes. Esta mayor concienciación contribuye a que se envíe un mayor número de informes RAM, lo que proporciona información valiosa para las actividades de PV. La distribución de información a través de los canales de los medios ha demostrado ser

beneficiosa para la recopilación de informes de RAM. Cataliza la participación pública, alentando a las personas a compartir sus experiencias e informar cualquier sospecha de reacción adversa que hayan encontrado. La cobertura de los medios también puede educar al público sobre los riesgos potenciales asociados con los medicamentos, capacitando a los pacientes para que tomen decisiones informadas y participen activamente en el control de la seguridad de los medicamentos. Es importante reconocer que el enfoque de cada país para promover la notificación de RAM debe adaptarse a su contexto y requisitos específicos. Mediante la comprensión de las características de la población, la asignación de los recursos apropiados y el avance continuo de sus sistemas fotovoltaicos, las naciones pueden mejorar efectivamente la notificación espontánea de RAM [39, 40, 42].

En 2014, el lanzamiento del proyecto WEB-RADR trabajó en el desarrollo de un Aplicación para teléfonos inteligentes que permite el informe de sospechas de RAM a los reguladores de la Unión Europea, lo que permite informes directos e instantáneos para pacientes y profesionales de la salud y un medio para que los reguladores comuniquen a las partes interesadas la información más reciente sobre PV [39, 43, 44] . Esta aplicación ya se usa en varios países europeos, como el Reino Unido, los Países Bajos y Croacia [56], con más de 10 mil descargas[44]. Según el proyecto WEB-RADR, es posible detectar, extraer, estandarizar y analizar información relacionada con las redes sociales, que puede ser utilizada como fuente de información sobre RAM en el futuro[44]. Con los avances tecnológicos, las redes sociales y las aplicaciones para teléfonos inteligentes se utilizan cada vez más, lo que sugiere que serán los métodos más exitosos para informar las reacciones adversas [44].

El uso de redes sociales es un método con alta sensibilidad [45] y calidad [46], mayor detección de RAM y alta concordancia en comparación con los métodos tradicionales, lo que permite una

información más detallada [47] y, sobre todo, es un método de bajo costo [48]. Las aplicaciones para teléfonos inteligentes tienen un formulario de notificación simplificado, lo que permite suscribirse a noticias sobre los medicamentos del paciente, presentar la información más reciente sobre la seguridad de los medicamentos y utilizarla en varios países [44, 49].

El programa internacional de monitoreo de drogas de la OMS permite el intercambio de información entre países sobre campañas, material educativo y videos sobre PV, que luego pueden ser adaptados a la realidad de cada país [50].

Suecia, donde se encuentra la OMS-UMC, es un ejemplo de proactividad en campañas de promoción de PV [51, 52], intervenciones educativas [53], publicación de carteles científicos [54-56] y revistas internacionales sobre PV [49, 51, 52, 57], y también en el desarrollo de la aplicación para teléfonos inteligentes [43, 49]. Además de Suecia, el Reino Unido, Croacia y los Países Bajos, a nivel europeo, también están involucrados en varios PV actividades, tales como campañas [58], programas emitidos en medios de comunicación [40, 42], y también cuentan con aplicaciones para smartphone para reporte de RAM [43, 44, 49, 56, 59]. La recopilación de informes RAM y el uso efectivo de esos datos continúan siendo cuestionados. Los pacientes deben recibir intervenciones frecuentes, idealmente en combinación con otras intervenciones, en la población potencialmente informante para reconocer, determinar la causa e informar correctamente una RAM. Además, se debe hacer accesible el soporte de programación suficiente para garantizar la aplicación de soluciones de eficacia comprobada.

VII. CONCLUSIONES

En conclusión, las reacciones adversas a medicamentos son efectos secundarios no deseados y desagradables que pueden ocurrir como resultado de tomar medicamentos.

Si bien todos los usuarios de medicamentos son susceptibles a las RAM, la forma en que las personas perciben este riesgo puede variar mucho.

1. Comprender y abordar las percepciones de los pacientes sobre las RAM es esencial para promover la adherencia a la medicación y garantizar el bienestar del paciente.

2. A través de una comunicación y educación efectivas, los proveedores de atención médica/salud pueden ayudar a los pacientes a tomar decisiones informadas sobre su tratamiento mientras mitigan las preocupaciones relacionadas con las RAM.

3. Los profesionales de la salud deben estar completamente capacitados, emplear el estilo de comunicación adecuado y considerar el género, la edad y los antecedentes culturales del paciente para explicar los peligros a los pacientes con éxito.

4. Se deben utilizar estrategias innovadoras para informar a las personas sobre los procesos de presentación de informes y su importancia.

Sin embargo, dicha discusión debe manejarse con cautela, en un grupo pequeño, idealmente uno a uno en lugar de frente a otros.

5. Alternativamente, puede resultar en desorden y confusión entre los pacientes, interrumpiendo las terapias debido a la falta de comunicación de varias personas de diversos orígenes socioeconómicos y raciales.

6. Debido a sus características, es más probable que las poblaciones de mayor edad tengan dificultades para adherirse a la técnica de notificación de RAM.

7. El sistema nacional de farmacovigilancia, en particular el proceso de notificación de reacciones sospechosas debe ser más conocido.

8. Las RAM vinculadas a la iopromida muestran cómo varía su frecuencia según diversas variables, como la edad, el sexo y los problemas médicos subyacentes.

9. La iopromida tiene una mayor incidencia de reacciones adversas que otros agentes de contraste como el iopamidol y el iodixanol, según algunas investigaciones.

10. Para llenar los vacíos de investigación y aumentar nuestra comprensión del perfil de seguridad de la iopromida, necesitábamos más estudios sobre el tema.

11. Estos estudios deben incluir estudios prospectivos bien diseñados, ensayos controlados aleatorios e investigaciones sobre la seguridad a largo plazo.

A pesar de todos los datos disponibles, el uso de iopromida conlleva algunos riesgos y su perfil de seguridad aún no está completamente establecido.

12. Puede ser un desafío interpretar adecuadamente estas reacciones, dado que las personas mayores y las que toman varios medicamentos tienen una mayor frecuencia de reacciones desfavorables de MCY.

13. Realizar una historia clínica completa, identificar las reacciones adversas y clasificarlas correctamente puede ayudar a reducir los eventos adversos.

El uso de iopromide CM se considera seguro a pesar de la posibilidad de reacciones adversas menores y la frecuencia extremadamente baja de eventos adversos significativos.

14. Para producir un perfil más representativo, es crucial recopilar datos de hospitales y clínicas adicionales. En general, este estudio insta a realizar investigaciones adicionales para documentar los efectos negativos del tratamiento de la CM.

15. Para fomentar la notificación de las RAM, es importante sensibilizar tanto a los pacientes como a los profesionales sanitarios.

Este estudio examina varias estrategias empleadas por diferentes países para mejorar la notificación de RAM y las sintetiza. Para aumentar efectivamente la recopilación de informes de RAM dentro de los sistemas de farmacovigilancia, se deben implementar técnicas innovadoras como incentivos financieros, intervenciones educativas, participación de los medios y el uso de redes sociales y aplicaciones para teléfonos inteligentes. En particular, los pacientes ahora tienen la oportunidad de informar RAM en un número cada vez mayor de países, lo que significa su papel crucial y una mayor participación en el proceso de seguridad de los medicamentos. Las organizaciones internacionales como la OMS están activamente interesadas en promover la energía fotovoltaica a través del intercambio de conocimientos y campañas. Varias naciones han establecido varias técnicas para impulsar la notificación espontánea de RAM. Mejorar la recopilación de RAM en PV requiere estrategias de vanguardia, incluidos incentivos financieros, intervenciones educativas, atención de los medios y el uso de redes sociales y aplicaciones para teléfonos inteligentes. Las plataformas de redes sociales y las aplicaciones para teléfonos inteligentes se usan con más frecuencia como herramientas efectivas para informar RAM.

La dirección futura y la garantía de la seguridad de los medicamentos se basan únicamente en prácticas de farmacovigilancia proactivas que involucran la participación de todas las partes interesadas. Queda mucho trabajo por hacer para potenciar los beneficios derivados de la notificación de los pacientes, tanto una contribución como una expresión de la "alfabetización en salud" que tiene una influencia considerable en las decisiones regulatorias basadas en evidencia para preservar y proteger la salud de los pacientes. estados de salud La

farmacovigilancia sirve como un componente crítico para garantizar la seguridad y la eficacia de los medicamentos a lo largo de su ciclo de vida. Implica la recopilación, el análisis y la evaluación sistemáticos de datos relacionados con las RAM y otros problemas relacionados con los medicamentos. Al identificar y comprender los riesgos potenciales asociados con los medicamentos, PV tiene como objetivo prevenir daños y mejorar los resultados de los pacientes.

ABSTRACT

Introduction

The Pharmacovigilance Systems, which began to develop in the early '60s with the thalidomide catastrophe, was born with the awareness, on the part of international health organizations and professionals, of the importance of adverse drug reactions (ADR).

To perform diagnostic imaging tests, it is often necessary to use contrast media for better visualization of the anatomical structures. Since the 1920s, iodinated contrast media (CM) has been used for angiography, and it is estimated that 75 million procedures need contrast media. This will necessarily lead to the promotion of studies that present the reality associated with adverse effects, prevention, and treatment. Safety and reporting of reactions to pharmacovigilance systems by health professionals and by patients play a crucial role in understanding and managing the adverse effects associated with the use of iodinated contrast media for diagnostic imaging tests.

Objectives

i) To evaluate patients' awareness of ADR risks and the Portuguese Pharmacovigilance System;

ii) To review the ADR and associated safety assessment to iopromide contrast media;

iii) To provide a retrospective analysis of ADR to iopromide in a Portuguese private unit of radiology;

iv) to shed light on innovative approaches, including patient-centered strategies, aimed to circumvent ADR under-reporting.

Methodology

To achieve the thesis goals, two original articles were performed, the first to evaluate patients' awareness of ADR risks and the Portuguese Pharmacovigilance System and the second to provide a retrospective analysis of ADR to iopromide in a Portuguese private unit of radiology. In addition, to reinforce the background of the thesis, two review articles were incorporated: a narrative review of the safety assessment of iopromide focusing on adverse events and a scoping review of all-round approaches to increase adverse drug reaction reporting.

Discussion

To ensure patient safety, it is crucial to conduct comprehensive surveillance and monitoring of adverse effects related to contrast media. Healthcare professionals, regulatory agencies, and researchers should collaborate to establish effective pharmacovigilance systems that track and analyse adverse events associated with these agents.

By closely monitoring the adverse effects of contrast media, healthcare professionals can gain a deeper understanding of their potential risks and take necessary and timely precautions. This knowledge can inform clinical decision-making, patient counselling, and the development of guidelines to minimize the occurrence and severity of adverse reactions.

Patient perception of the risk associated with ADRs can greatly influence their decision-making process and overall medication adherence. Some individuals may be aware of potential side effects and be prepared for them, while others may have limited knowledge or misconceptions about ADRs. Moreover, previous experiences with medications, either personal or through word-of-mouth, can shape an individual's perception of ADRs.

Furthermore, healthcare professionals should stay updated with the latest research findings and participate in continuous education and training programs. This will enable them to effectively recognize and manage adverse reactions related to contrast media, thereby improving patient outcomes, and reducing potential harm.

Conclusions

Understanding and addressing patient perceptions of ADRs is essential to foster medication adherence and ensure patient well-being. Through effective communication and education, healthcare professionals can help patients make informed decisions about their treatment while mitigating concerns related to ADRs. Healthcare practitioners must be thoroughly trained, employ the proper communication style, and consider the patient's gender, age, and cultural background to explain hazards to patients successfully. Innovative strategies must be used to inform people about reporting processes and their significance.

However, such discussion should be handled cautiously, in a small group, ideally one-on-one rather than in front of others. Alternatively, it may result in disorder and confusion among the patients, interrupting therapies due to the miscommunication of several people from various socioeconomic and racial backgrounds. Due to age-related features, older populations are more likely to struggle to adhere to the ADR reporting technique. The national pharmacovigilance system, particularly the reporting process of suspicious reactions, should therefore be made more widely knowing iopromide CM is considered safe despite the possibility of minor adverse reactions along with the extremely low frequency of significant adverse events. To produce a more representative profile, gathering data from additional hospitals and clinics is crucial. Overall, this study urges additional research to document the negative effects of CM treatment to establish timely and well-suited safety procedures.

CHAPTER 1

INTRODUCTION

I. INTRODUCTION

1. Pharmacovigilance Systems

World Health Organization (WHO) defines Pharmacovigilance "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problems" [60].

Pharmacovigilance's primary goals are to prevent harm from adverse drug reactions in humans that may result from the use of authorised medicinal products, either within or outside the parameters of marketing authorization, or from occupational exposure; and to promote the safe and effective use of medicinal products by promptly informing patients, healthcare professionals (HCPs), and the public about the safety of medicinal products [60].

Adverse drug reactions are now widely acknowledged to be a public health issue with a considerable clinical impact on morbidity and mortality, leading to an increase in the usage of healthcare services in industrialised nations [61, 62].

About 2-3% of patients who were admitted with an ADR died as a result. ADRs are thought to be the cause of about 6% of hospital admissions, and many of them were deemed preventable [62-64]. Additionally, ADRs may occur in 6-20% of patients admitted to hospitals, lengthening the length of hospitalisation and raising associated healthcare costs [65] as well as having indirect effects on patients and their families in terms of the economy, society, and mental health [66].

Pharmacovigilance is required to learn more about the potential negative effects of a drug because medicines are evaluated on a small, homogeneous population and not all ADRs of a product are known once it is given marketing authorisation. WHO states that [60] pharma-

covigilance is essential in ensuring that HCPs, including doctors, chemists, and nurses, as well as patients, have enough knowledge to make an informed choice when selecting a medicine for treatment [67]. Although the safety profile and efficacy of a medical drug have been previously investigated, the information acquired during the pre-marketing period is invariably constrained and insufficient regarding potential adverse drug responses [68-70]. Since the drug is used in a real-world setting and in a broad and varied population, relevant and unrecognised ADRs may arise after marketing authorisation. As a result, pharmacovigilance is crucial because the majority of new ADRs are effectively discovered during this period [68].

A "regional or national system for the reporting of suspected adverse drug reactions" is how the WHO defines spontaneous ADR reporting [71]. Although there is room for optimisation and improvement, the usage of spontaneous reporting systems has shown to be effective in discovering patient safety issues [66]. As a result, it is a key technique in pharmacovigilance and effective for detecting signs of uncommon, severe, and unanticipated adverse effects [68, 72]. When understanding of a drug's safety profile is based on very limited exposure data from premarketing clinical studies, this is especially crucial for rare or serious reactions to established pharmaceuticals or reactions to recently released medicines. Spontaneous reporting has helped to identify several significant ADR indications [73-75].

Patient safety depends on the monitoring of ADRs by pharmacovigilance [20]. One of the most flexible pharmacovigilance systems is voluntary ADR reporting because, among other benefits, it covers the entire population and drugs throughout their commercial life. Additionally, voluntary ADR reporting is a method that provides the highest volume of data with relatively low maintenance costs when compared to other pharmacovigilance methods [72].

In fact, spontaneous reporting of ADRs is still one of the best ways to identify new, uncommon, and significant drug responses. It is also the

strategy that is utilised the most frequently in pharmacovigilance [20, 74, 75]. The majority of post-marketing safety evidence has come from spontaneous reporting, which helps with the early detection and assessment of drug safety issues and supports a variety of regulatory actions, including product withdrawal, ongoing monitoring, labelling changes, and new medication-related communications, among others [76].

Any spontaneous reporting system depends on the active engagement of reporters to succeed or fail [60]. HCPs have traditionally been the primary sources of case reports of suspected ADRs [77, 78]; however, systems for direct reporting of suspected adverse reactions by patients have been introduced in some European nations at the start of the 2000s, including the Netherlands (2003), Denmark (2003), and the UK (2005) [66]. The United States of America and Canada, which established consumer reporting schemes in the 1960s and gather a significant amount of reports each year, can be recognised as the pilot countries worldwide [66].

The higher quality and quicker signal detection should, however, be reflected in the greater quantity of reports received. The calibre of patient reports seems to be comparable to that of those from HCPs [79].

Since it makes it easier to understand consumer opinions, direct patient reporting has had a good effect in these nations [80-82]. "Users of drugs (or their parents or carers) reporting suspected ADRs directly to a spontaneous reporting system" is how patient reporting is characterised [83, 84].

2. History of Iodinated Contrast Media (ICM)

Contrast media (CM) are substances used to improve the differentiation between different tissues in medical images by altering the response of some tissues to electromagnetic or ultrasound radiation [85]. The contrast media available are radiographic, magnetic resonance image (MRI), and ultrasound contrast media. Radiographic CM can be divided into positive or negative, and the latter attenuates X-rays to a lesser extent than adjacent tissues (such as water). In contrast, positive CM attenuates X-rays more than surrounding tissues. Positive radiographic CM include ICM and barium [85]. It comprises a class of agents that once introduced into the body provides opacification of blood vessels, tissues or organs, improving their visualization [86]. In the context of this thesis, only the positive contrast agents associated with iodine will be discussed as negative media (e.g. carbon dioxide) are of little interest nowadays [87].

Between 1900 and 1927, the visualization of the urinary tract prompted the development of many approaches for X-ray-based imaging [88]. Moses Swick, a young American urologist, directed the first clinically successful intravenous urogram in humans utilizing a nonionic pyridone with a single attached iodine, denominated as uroselectan, whose radiopacity was early noticed. Over the next 3 years, a series of additional compounds were synthesized and Swick and Wallingford revolutionized the field with the utilization of a substituted benzene ring that stands as the basis of iodinated contrast agents [89]. Later on, a fully substituted tri-ionated benzene ring was shown to exhibit decreased toxicity [87].

ICM is mainly used for studies such as Computed Tomography (CT), angiography, fluoroscopy, or conventional radiography to opacify structures that are generally not radiodense [90].

The iodine molecule allows an excellent visualization of the anatomical structure since it absorbs X-rays in that segment of the spectrum where clinical systems work [91]. Accordingly, they have been used to improve the visibility of internal organs and structures and/or to perform cardiac catheterizations and percutaneous coronary interventions [28]. Soft tissues such as muscles, fatty tissue and neoplastic tissue are particularly insensitive due to X-ray attenuation performance [29]. Table 1 aims to present the current diagnosis use of available ICM.

Table 1: Current diagnostic use of the available x-ray contrast media. (Taken from: Bourin *et al*., 1997 [86])

Contrast medium	**Diagnostic use**
Diatrizoate	Angiography/urography
Iodixanol	Angiography/urography
Iohexol	Angiography/myelography
Iopamidol	Angiography/urography
Iopentol	Angiography
Iopodate	Biliary contrast
Iosimide	Angiography/urography
Iothalamate	Angiography/urography
Iotroxate	Biliary contrast
Ioversol	Angiography
Ioxaglate	Angiography/urography
Metrizamide	Myelography
Metrizoate	Angiography/urography

Three general modes of ICM use are present in clinical practice: i) direct injection into a vascular structure for vascular lumen opacification; ii) to monitor ICM distribution in body fluid compartments and iii) to visualize ICM route of excretion of the body [30]. For example, ICM diffuse preferentially into brain tumors since they lack blood-brain barrier and quantification of the distribution volume is obtained from CT and blood hematocrit ratio and calculated as 100 times the ratio of tissue concentration/plasma concentration [31].

3. Classification and Physicochemical Properties of ICM

All iodinated contrast materials in current use are chemical modifications of a basic chemical structure comprising a benzene ring with, at least, 3 iodine atoms in the 1, 3 and 5 positions (tri-iodobenzene) [32, 33]. ICM can display a monomeric or dimeric structure when they have a benzene ring or a benzoic nucleus covalently bound, respectively [92]. The attachment of structural elements to the benzene ring determines their pharmacological and physicochemical characteristics [32, 33]. For instance, radiopacity increases with the number of iodine atoms in each molecule. By the other hand, ICM also diverge on the basis of their ionization capacity (reflecting their ability to generate ions or charged particles in aqueous solution), and osmolality (the number of particles generated in solution) and are classified as high-osmolality ICM (≥1400 mOsm/kg H2O), low-osmolality (500-900 mOsm/kg H2O) and isosmolar ICM (290 mOsm/kg H2O) [87, 93]. Osmolality determines the osmotic pressure as it represents the ratio of contrast medium to water molecules in the solution. Even though solutions of high molarity do not always display high viscosity, some of these ICM show high viscosity as well [86]. Osmolality is also linked with tonicity: radiopharmaceuticals (as well as ICM) are mostly isotonic solutions equaling that of blood (290 mOsm/Kg of water), without negative concerns on surrounding cells [87].

ICM are significantly more viscous than radiopharmaceuticals, a feature that can be reduced by injecting the agent at body temperature (37ºC) rather than room temperature, particularly for nonionic agents [94]. Low-viscosity ICM allows them to be administered in a rapid bolus standing as an advantage.

Based on the number of triiodobenzene rings and the capacity for ionization, four classes of ICM are commercially available [95]:

Ionic monomers: salts comprising 1 negatively charged triiodinated benzene ring; display the highest osmolality (>1400 mOsm/kg H2O);

Ionic dimers: consist of 2 triiodobenzene rings; have low osmolality (600 mOsm/kg H2O);

Nonionic monomers: second-generation triiodinated compounds; have low osmolality (500-850 mOsm/kg H20);

Nonionic dimers: contain 2 nonionic triiodinated benzene rings; display the lowest osmolality of all ICM (290 mOsm/kg H20).

Figure 1 aims to represent ionic monomer, ionic dimer, nonionic monomer, and nonionic dimer chemical structures based on 2,4,6-triiodinated benzene ring.

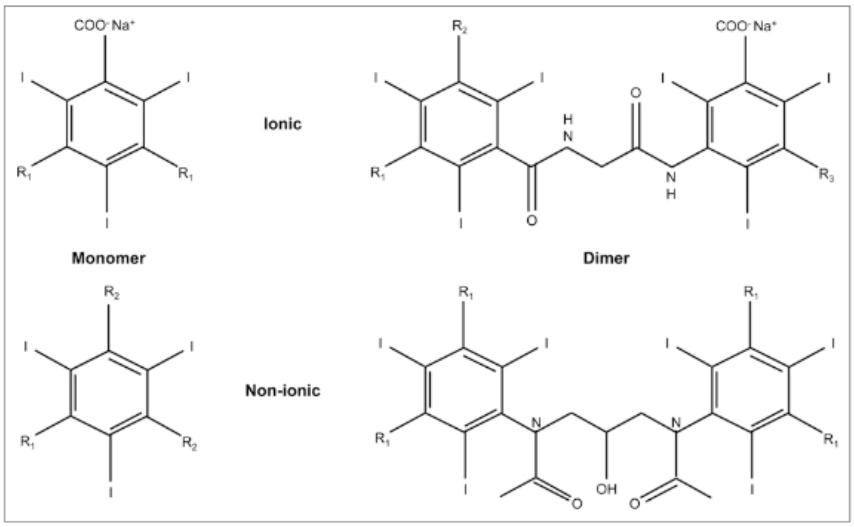

Figure 1. Chemical structure of iodinated CT contras tis based on 2,4,6-triiodinated benzene rimg and provides 4 major cassifications of iodinated CT contrast agents: ionic monomer, ionic dimer, nonionic monomer, and nonionic dimer. For ionic contrast media, carboxyl group (COOH) ionizes (COO^-) with sodium or meglumine to form anion and cation pairs. Side chains (R) vary but tend to be longer for nonionic contrast media (Taken from: Currie; 2019 [87]).

Stability, solubility, hydrophilicity, osmolality, and viscosity are among the most important physicochemical parameters for ICM development. Notably, all criteria that improve osmolality, hydrophilicity and solubility are inversely correlated with viscosity [86].

Among key-properties that impact ICM behavior, the iodine (mg) *per* unit volume (mL) - iodine concentration – strongly impacts the degree of radiopacification and tolerability.

The current generation of ICM are non-ionic and the common iodinated contrast agents display iodine concentrations in the order of 300mg/mL, the range varying between 200 and 400mg/mL [87]. Table 2 features some key properties of iodinated contrast agents relevant for their behavior.

Table 2: Examples of modern contrast media. (Taken from: Hogstrom and Ikei, 2015 [96])

Name	Iodine content (mgI/mL)	Ionicity	Structure	Osmolality (mOsmol/kg)	Viscosity 20°/37°C (CP)
Iopamidol (Isovue 370)*	370	Non-ionic	Monomeric	796	20.9/9.4
Iohexol (Omnipaque 350)*	350	Non-ionic	Monomeric	844	20.4/10.4
Ioxilan (Oxilan350)*	350	Non-ionic	Monomeric	721	16.3/8.1
Iopromide (Ultravist 370)*	370	Non-ionic	Monomeric	774	22/10
Ioxaglate (Hexabrix)*	320	Ionic	Dimeric	600	15.7/7.5
Iodixanol (Visipaque 320)*	320	Non-ionic	Dimeric	290	26.6/11.8
Iosimenol†,‡	340	Non-ionic	Dimeric	290	23.2/9.3

*US Prescription Information 2015; †Sovak M et al. Invest Radiol. 2004;39:171; ‡Not commercially.

4. Pharmacokinetics of ICM

ICM pharmacokinetics determine the imaging efficiency. Contrast media are often administered via the intravenous, intra-arterially, intrathecal routes or directly into cavities (*e.g.* gastrointestinal, genitourinary tract) and diagnostic procedures are based on differential distribution to organs and between normal and abnormal tissue [97]. ICM are generally used in g/Kg dose ranges and in concentrations 10 times higher than the concentration of body fluids [31].

Contrast enhancement, determined by X-ray absorption, is closely related to plasma/tissue concentrations of iodinated contrast molecules and with the vascularization of each tissue [98]. Within a few seconds post-administration, ICM distribute within the intravascular phase and can be used in angiography [99]. Yet, they undergo rapid distribution to the interstitial phase and once the equilibrium between interstitial and plasma concentrations is obtained, they spread throughout the extracellular space [100]. The pharmacokinetics of ICM are based on a 2-compartment model with a biphasic iodine concentration profile: the first phase is due to the rapid diffusion from the plasma compartment into the interstitial and extracellular space and the second corresponds to slow urinary excretion [86, 98, 101].

The half-life of iodinated contrast agents is less than 60 minutes, all compounds present limited plasma protein binding (1-3%), minimal hepatic excretion and are excreted mostly by glomerular filtration [32]. ICM molecules do not enter cells and within the first 24 hours most of the injected dose is recovered unmetabolized in urine [86, 102]. Table 3 displays pharmacokinetic parameters for various ICM in humans [45].

Table 3: Mean (± SD) pharmacokinetic parameters for various contrast agents in human. (Taken from: Hartwig *et al*., 1989 [45])

	Iohexol	**Iopamidol**	**Iopromide**	**Iosimide**	**Meglumine**
Distribution					
Phase (min)	11.4 + 5.2	8.8+1.5	13.0+6.2	12.9 + 4.5	6.8 + 3.3
Volume (Ukg)	0.19+0.02	0.17+0.02	0.19 + 0.06	0.20+0.04	0.19+0.05
Half-life					
Blood (min)	174.5 + 81.6	191.7+ 101.9	274.1 + 190.8	171.7 + 57.3	155.6 + 59.5
Urine (min)	199.6 + 73.8	235.3 + 126.9	432.3 + 507.4	203.12+69.4	184.6 + 41.6
Percentage of dose in urine					
to 2 hours	36.6 + 12.3	32.2 + 10.2	31.7+16.0	33.4 + 9.7	35.2+7.8
to 24 hours	89.7+6.0	86.3+ 10.6	84.7+ 12.6	87.0+5.1	91.1 + 6.8

5. ICM interactions

ICM are not highly pharmacologically agents but still, interactions between contrast agents and therapeutic medications are quite possible [103].

According to Morcos and colleagues (2005), they are generally divided as follows [104]:

– Drugs which will be retained in the body because of reduction in renal function induced by contrast media;
– Drugs which enhance the renal effects of contrast media;
– Drugs which enhance allergic-like reactions to contrast media;
– Drugs interfering with the hematological effects of contrast media;
– Contrast media and interference with neuroleptic drugs;
– Drugs which enhance the effects of contrast media on the heart;
– The effects of contrast media on isotope studies;
– Mixing contrast media with other drugs;
– The effects of contrast media on biochemical assays.

Besides, ICM can impact the pharmacokinetics of other drugs, namely those presenting renal excretion. An example relies on the potential reduction in renal function induced by contrast media that may elicit metformin retention and the potentiation of lactic acidosis [105, 106]. Non-steroidal anti-inflammatory drugs (NSAIDs), gentamicin, cyclosporine and cisplatin also have the potential to increase the renal effects of contrast media [107]. Of note, an increased tendency to develop allergy-like reactions following the administration of contrast media is observed upon β-receptor blockers, interleukins or interferons administration [104]. Accordingly, patients taking β-receptor blockers was shown to display a 3-fold increased risk to iodinated contrast

agents [87]. Lastly, calcium channel blockers and digoxin were found to display synergistic effects with ICM [87].

Overall, medications with a narrow therapeutic index or that mostly relies on renal elimination may display increased susceptibility to toxicity [103].

6. Adverse reactions to ICM

ICM elicit both local and systemic effects. Alterations in hemodynamics, vascular resistance and electrolyte balance are observed upon ICM direct injection [106]. ICM viscosity increases the resistance of vascular bed while high osmolality causes dehydration of red cells and endothelial cells along with the loss in water in tissue extravascular space [108]. These processes justify the vasodilation observed shortly following injection [109, 110]. Systemically, intravenous, and intra-arterial injections may induce hypotension and bradycardia [111-113].

Adverse Drug Reactions (ADR) integrate a large group of drug-related problems (DRP), which also includes unnecessary pharmacological treatments, inappropriate choice of medications and untreated situations [114] and in addition to the clinical costs, several authors have studied the economic costs that affect health systems[115-118]. Adverse drug reactions are incorporated and accepted in the benefit-risk assessment of a commercialized drug due to the limitations imposed on the studies carried out during the research phases in the clinical trials [119].

The high incidence of ICM adverse reactions due to high-osmolality agents (approximately 15% with a high-osmolality agent Vs only 3% with low-osmolality) justifies their decreased use [120]. Chemotoxicity, osmotoxicity and ionic toxicity underly ICM toxicologic effects. Among osmotic effects are pain, hypotension, vasodilation and

red blood cells rigidification [93]. These events decreased markedly when ICM display an osmolality below 700 mOsm/Kg [28].

Substituted tri-iodinated benzene rings, the presence and an even distribution of hydroxyl groups around the molecule and the absence of carboxyl groups are known to limit the *in vivo* toxicity of ICM [96].

Adverse reactions to ICM media are classified as mild, moderate, severe, or organ-specific [16]. On the other hand, they can also be classified as acute or late [12].

Acute adverse reactions can be further classified as mild, moderate, or severe [12, 15].

Mild acute adverse reactions

They are self-limited signs and symptoms without evidence of progression. They include nausea, vomiting, cough, feeling hot, headache, dizziness, taste disturbance, itching, paleness, redness, chills, sweating, rash, hives, nasal congestion, conjunctival inflammation, swelling of the face and anxiety. These reactions require observation to confirm their resolution or non-progression. They usually do not require treatment. Reassessment of the patient is helpful.

Moderate acute adverse reactions

The signs and symptoms are more pronounced. There are clinically evident signs or symptoms of moderate degree, focal or systemic. These include tachycardia/bradycardia, hypertension, generalised or

diffuse erythema, dyspnea, bronchospasm, laryngeal oedema, mild hypotension. They often require prompt treatment and close and careful observation for possible progression to a potentially fatal event. [9]

Severe acute adverse reactions

These signs and symptoms frequently threaten the patient's life, including progressive laryngeal oedema, lack of response, cardiorespiratory arrest, seizures, marked hypotension, or clinically manifest arrhythmias. They require rapid recognition and aggressive treatment. Treatment often requires hospitalization [9].

In opposition, late adverse reactions are defined as those that appear between 1 hour and 1 week after the administration of the contrast medium. Most of the late reactions are cutaneous [16].The most common manifestation is a maculopapular rash seen in more than 50% of affected individuals. Other cutaneous manifestations are angioedema, urticaria and erythema. Table 4 displays the most-common acute adverse reactions.

Table 4: Symptoms and Signs of Mild, Moderate, and Severe Adverse Acute Reactions (Adapted from: Zhang *et al.* 2016 [22])

Mild	Moderate	Severe
Cutaneous manifestations	Cutaneous manifestations	Cardiovascular manifestations
Rash	Severe urticaria	Severe hypotension
Mild urticaria	Gastrointestinal manifestations	Cardiac arrest
Flushing	Severe vomiting	Nervous system manifestations
Itching	Nervous system manifestations	Conscious disturbance
Gastrointestinal	Mental confusion	Convulsion
Manifestations	Respiratory manifestations	Respiratory manifestations
Nausea	Dyspnea	Respiratory arrest
Mild/moderate vomiting	Cardiovascular manifestations	Other manifestations
Abdominal pain	Hypertension	Foaming at the mouth
Nervous system manifestations	Tachycardia/bradycardia	Urine incontinence
Anxiety	Mild hypotension	Death
Dizziness/headache	Other manifestations	
Cardiovascular	Hoarseness	
manifestations	Systemic shaking (or chills/trembling)	
Transient chest pain and stuffiness	Laryngeal edema (not severe or rapidly progressing)	
Respiratory manifestations		
Coughing and sneezing		
Nasal stuffiness		
Facial manifestations		
Mild eyelid swelling and localized facial swelling		
Transient blurred vision		
Conjuntival congestion and tears		
Oral and lip numbness		
Pallor		
Other manifestations		
Acratia		
Numb limbs		
Mild trembling or shivering or shaking		
Thirst		
Sweats		
Systemic fever		

6.1. Incidence and risk factors

Adverse reactions have decreased over time with the exchange of contrast media from ionic, high-osmolality to nonionic, low-osmolality formulations by a factor of 5 for mild reactions and of 10 for severe reactions [9, 121, 122]. In other words, mild reactions are encountered in 15% and 3% of patients receiving ionic and non-ionic contrast media, respectively [123]. Moderate reactions are seen in 1–2% of patients with ionic and 0.2–0.4% of patients with non-ionic contrast media [121]. Severe reactions can occur in 0.04% of patients receiving ionic contrast media and 0.004% of patients receiving non-ionic contrast media [121]. Overall mortality from acute reactions to ICM is 1:13,000 to 1:169,000 [97]. Signs and symptoms of acute and delayed reactions are presented in Table 5.

Table 5: Signs and symptoms of Adverse Reactions to Iodinated Contrast Agents (Taken from: Pasternak and Williamson, 2012 [97])

Acute Reactions	Delayed Reactions
Nausea, vomiting	Rash and pruritus
Pain on injection	Severe skin reactions (eg, Stevens Johnson reactions can occur but are very rare)
Hemodynamic changes	Nausea
Vagal reaction (bradycardia and hypotension)	Vomiting
Arrhythmia	Diarrhea
Anaphylaxis or anaphylactoid reaction	Hypotension (rare)
Rash (pruritic urticaria)	
Angioedema	
Flushing/rash	
Bronchospasm	
Cardiovascular collapse	

Regarding delayed reactions, they may occur after the administration of both ionic and non-ionic contrast media. The overall incidence after the administration of an ICM can be as high as 14% [124]. In this sense, iso-osmolar agents (i.e., nonionic dimers) are associated with the highest risk of causing a delayed reaction by a factor of 3 when compared with the use of a nonionic monomer or an ionic dimer [125]. Aforesaid reactions can manifest with similar signs and symptoms to acute reactions, cutaneous manifestations being the most common, typically featured as a pruritic maculopapular rash or urticaria [124].

Several risk-predisposing factors increase the incidence of contrast adverse reactions (Table 6). The most significant risk factor is a previous adverse reaction to ICM, displaying a prevalence between 17-35% that increases the risk of adverse reactions by five times with either high- or low-osmolality ICM [16, 123]. History of allergy increases the risk of severe reactions to CM three times and asthma increases the incidence of severe adverse reactions by ten times with high-osmolality ICM and by six times with low-osmolality ICM [123]. Patients on β-adrenergic blockers are also more susceptible to adverse contrast reactions [126, 127].

Thus, knowing the presence of predisposing risk factors as well the appropriate record of adverse reactions are important issues in clinical practice.

Table 6: Predisposing risk factors for general adverse reactions to contrast media.

Previous adverse reaction
History of asthma
History of allergy
Heart disease
Dehydration
Hematological conditions like sickle cell anemia, polycythemia, and myeloma
Pre-existing renal disease
Infants and elderly
Anxiety
Beta-blockers, non-steroidal anti-inflammatory drugs, interleukin-2

6.2. Pathophysiology

The pathophysiology of ICM adverse reactions diverge when non-renal and renal side effects are studied. They may be physiologic and anaphylactoid. Immediate non-renal side effects are mostly related to histamine release from basophils and mast cells or by direct activation of the complement system. Fewer reports show the production of IgE antibodies (a hallmark of true anaphylaxis) as an alternative mechanism for immediate hypersensitivity. In contrast, late adverse reactions appear to be T-cell mediated [128, 129].

Since some allergy-like reactions seem to be irresponsive to anti-histaminic drugs, the suggestion that other mediators may be involved emerged. Leukotrienes and its metabolites (cysteinyl-leukotrienes, cys-LT) are derived from polyunsaturated fatty acids and are known to be *de novo* synthesized upon an adequate stimulus. Both iopromide or iotrolan allergy-like reactions of late onset were suggested to depend on cys-LT and in such cases, both glucocorticoids and leukotriene receptor antagonists may play a key-role in allergy-like reactions management [130]. Therefore, the pathophysiological explanations include the activation of mast cells and basophils (Figure 1), in addition to the release of histamine, tryptase, and other mediators [131]. The activation and release of mediators can occur through the IgE-mediated immune pathway and non-specific pathways, such as activation of the complement systems, activation of the XII clotting system (leading to the production of bradykinin and conversion of L-arginine into nitric oxide) [132], and formation of "pseudoantigens" [133].

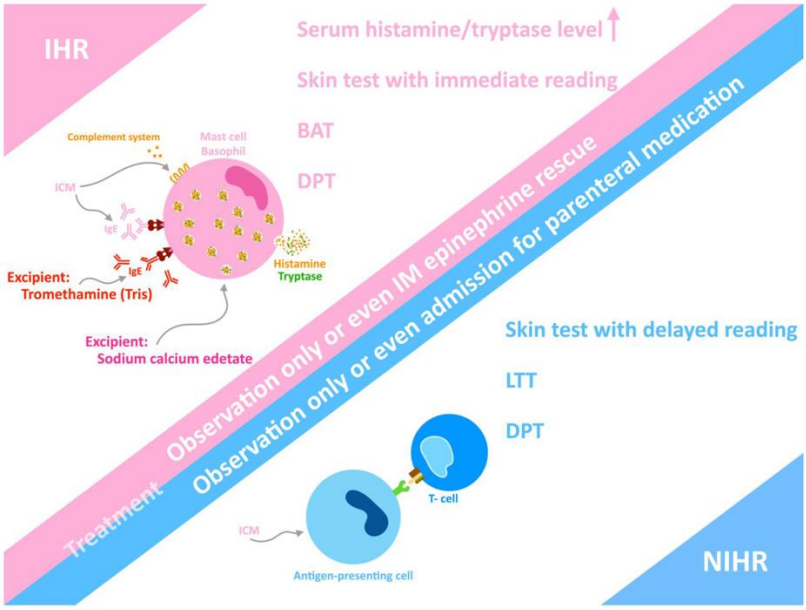

Figure 2. Summary of iodinated contrast media (ICM)-induced hypersensitivity. ICM or excipients may activate basophils or mast cells to release histamine and other mediators linked to immediate hypersensitivity reaction (IHR) via IgE-mediated or non-IgE pathways, such as the complement system pathway. Non-immediate hypersensitivity reaction (NIHR) induced by ICM can be evoked by a T-cell mediated pathway. Skin test, basophil activation test (BAT), drug provocation test (DPT), and lymphocyte transformation test (LTT) can achieve the diagnosis of ICM hypersensitivity. In patients with anaphylaxis or severe, prolonged symptoms of NIHR, a prompt and appropriate intervention is needed. Taken from: Chiu *et al.*, 2022 [134].

Kidney microcirculation and oxygenation are negatively impacted by ICM who display direct cytotoxicity in *in vitro* models of renal tubular epithelial and endothelial cells [97]. ICM-induced changes in red blood cell structure aggravates kidney medullar hypoperfusion. Furthermore, ICM accumulate in tubules and distal nephron due to their negligible tubular reabsorption that exponentiate nephrotoxicity [135].

The increased risk of contrast-induced nephropathy upon hyperosmolar solutions administration led to their replacement by low-osmolality ICM and the significant reduction of the incidence of

generalized contrast reactions. Since modern contrast agents display much less toxicity, re-evaluation of policy constrains of ICM administration is necessary since the restraints inflicted on imaging diagnosis may hinder optimal clinical practice [136].

6.3. Diagnosis

The evaluation of a patient with adverse reactions to ICM can be initiated during the earliest phase. In immediate reactions, the elevation of serum histamine and plasmatic tryptase levels, in comparison with baseline, can help to identify the type of reaction [10, 131, 137]. Due to their elimination half-live (15 to 20 min for histamine and 90 min to 2h for tryptase), these two blood tests should be performed as soon as possible for histamine and 1 to 2 hours after the onset of symptoms for tryptase [131, 137]. Additionally, serum tryptase levels are recognized as a valuable biomarker to support the diagnosis of anaphylaxis due to their recognized positive correlation with the severity of immediate hypersensitivity reaction [134].

For both immediate and nonimmediate reactions, skin tests are invaluable for the investigation of possible alternative ICM, with negative predictive values of 94.2% (95% CI, 89.6% to 97.2%) and 86.1% (95% CI, 72.1–94.7%) [138]. However, the number of positive skin test results is attenuated if not performed 2-6 after the reaction [139]. Therefore, the standardization of skin tests for ICM is a major task to be solved for accurate diagnosis and prevention [140]. Currently, the recommended method of ICM-related skin testing is the skin prick test (SPT) using undiluted ICM [140]. In cases of negative SPT it is recommended an intradermal test with a 1:10 diluted solution of ICMs [141]. For cross-reactivity verification, it is recommended to

perform SPT and intradermal tests with all ICMs available and relevant for the radiological departments [24, 142].

In vitro tests, for identifying the culprit ICM, basophil activation test and lymphocyte transformation test are indicated for patients with high-risk or severe hypersensitivity phenotype, as well as in cases when a skin test is not available [143]. The basophil activation test (BAT) is used to detect basophil activation markers (CD45, CD18 and CD63) and has been considered a useful approach in the identification of culprit drugs ICM with good correlation with skin and drug provocation tests [144]. This test is especially useful for severe forms of IHR such as anaphylactic shock, for which skin tests and drug provocation tests are contraindicated [134]. The sensitivity and specificity of BAT are 46–63% and 89–100%, respectively, depending on the threshold chosen [145, 146]. However, this technique is not widely available and needs to be validated in more populations [95].

The lymphocyte transformation test (LTT) is based on the ability of T-cells to proliferate and measures the proliferation of circulating lymphocytes specific to the antigen of the culprit drug or ICM upon stimulation by the antigen [134]. The sensitivity and specificity of LTT differ for different antigens, ranging from 13 to 75%, and is not currently used in routine diagnosis [147]. More physiologically relevant tests such as the coculture of dendritic cells and lymphocytes may be useful in the future, although further research is required [148].

Drug provocation tests (DPTs) are considered the last step of the diagnosis algorithm and the gold standard for the diagnosis of drug hypersensitivity reactions [149]. They may play an important role in identifying safe alternative ICMs in patients who have experienced severe immediate HSRs, such as anaphylaxis [140]. DPTs are performed throughout the administration of increasing doses of the ICM (5, 15, 30, and 50 cc) at 30-45–minute intervals for immediate

reactions and at 1-hour intervals for nonimmediate reactions [144, 150]. Currently, there is no consensus on when to implement ICM-related DPT and an established standard protocol, emerging the need for additional discussion and validating studies [134, 140].

6.4. Treatment

ICM reactions are usually mild and do not require active treatment. However, in some situations, they range to life-threatening situations. Considering their unpredictability, a vigilant performance is fundamental. All staff involved in the administration of ICM should be adequately trained in cardiopulmonary resuscitation and the equipment (e.g., crash trolly, defibrillator and necessary drugs) should be checked regularly and must be readily available. Adrenaline injection and rapid administration of intravenous fluids are usually required for the effective management of acute anaphylaxis-like reactions [94]. The first-line treatment is 0.01 mg per kilogram of body weight to a maximum of 0.5 mg of adrenaline at a concentration of 1:1000, which should be injected intramuscularly in the lateral aspect of the thigh [95].

In cases of mild adverse reactions to low-osmolality ICM they only require observation or oral H1-antihistamine [79]. The H-1 antihistamines are sufficient for mild hypersensitivity symptoms such as itching [96]. Adequate oxygen supply can be critical in cases of airway manifestations, breathing, and circulation symptoms [79]. Anti-emetics are also an option in patients who developed severe or persistent vomiting [97].

NIHR has mild to moderate severity and is usually self-limiting, with most cases requiring little or no therapy [98]. The most common type

of NIHR is maculopapular exanthema, but severe NIHR may also include acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, toxic epidermal necrolysis [79]. In these cases, systemic corticosteroids are frequently used [99]. However, they usually need to be referred to a specialist for treatment first.

7. Iopromide at a Glance

Iopromide, in the market as Ultravist®, is a low osmolar nonionic contrast medium containing iodine. It was first approved in February 1985 and as of June 30, 2021, more than 306 million have been administered to patients worldwide [151, 152].

It was originally developed for angiography, urography and computed tomography (CT) and has the nonproprietary name 5-methoxyacetylamino-2,4,6-triiodoisophthalamic acid- [(2,3,-dihydroxy-N-methylpropyl)-(R,S-2,3-dihydroxypropyl)]-diamide. It has a renal elimination half-life of 16 minutes and only 6% is excreted via the bile [153]. Figure 3 presents iopromide chemical structure.

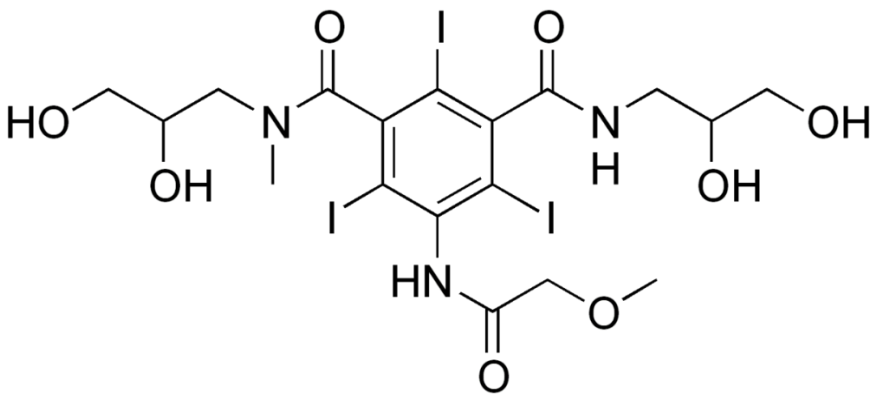

Figure 3. Iopromide chemical structure

Iopromide is approved in a variety of indications, namely contrast CT of the head and body for lesion evaluation, including neoplasia's. It provides good or excellent image quality in CT when administered using concentrations of 300 mg iodine (I)/mL and 370 mg I/mL [154]. Yet, and just like any other non-ionic monomeric contrast agent, the incidence of iopromide adverse reactions is mainly attributed to their ion content, the pH of contrast media, hydrophilicity and viscosity [21]. Iopromide adverse reactions may occur within 1 hour after the contrast medium injection. Notably, when compared to iopamidol, iopromide presented a higher incidence of cutaneous (rash, flushing, itching), gastrointestinal (vomiting, abdominal pain), nervous system (dizziness, headache), respiratory (nasal stuffiness) and facial (mild eyelid swelling, localized facial swelling, conjunctival congestion) manifestations. Besides aforesaid mild complications, iopromide was also associated with the increased incidence of hypertension (moderate adverse reaction) as well as of severe hypotension (severe adverse reaction) [22]. Likewise, iopromide appeared more likely to facilitate the appearance of contrast-induced encephalopathy when compared to ioversol [23]. Importantly, a higher rate of adverse reactions was observed in women, possibly related to the high estrogen load and the corresponding proposed role in the development of allergic responses [22].

Some measures may increase the safety and tolerability of iopromide use, the extrinsic warming the most well-studied. While media at room temperature are irritants and elevates heart rate, blood pressure and mastocyte degranulation due to the high dynamic viscosity, their warming to human body temperature (37ºC) reduces their viscosity by 50% and the incidence of adverse reactions [154]. The risk of hypersensitivity reactions to iopromide is also lower after intra-arterial *versus* intravenous administration [152]. Moreover, hypersensitivity reactions to iopromide seem to be less frequent in children or elderly

when compared with adults, even though both groups might be unable to communicate their adverse effects [151].

CHAPTER 2

JUSTIFICATION AND THESIS OUTLINE

II. JUSTIFICATION AND THESIS OUTLINE

The safety in the use of medicines has had particular attention of the National and European Authorities, health professionals, patients and communication media. Yet, the Systems of Pharmacovigilance have shown some difficulties in collecting the information earlier. The commitment of health professionals and organizations, among others, is a recurrent problem for the low index of reports [4-6, 19].

With the growth of the offer in private medicine, there is a gradual increase in examinations that use biomedical imaging and, of course, a generalized growth in the use of Iodinated Contrast Media (ICM) in different imaging techniques. Annually, it is estimated the use of millions of procedures with ICM that are generally recognized as safe [9]. Still, ADR to ICM can occur, anaphylaxis the most severe adverse reaction that puts the patient's life at risk justifying a specific and individualized evaluation of the conditions of the administration (e.g. specialized personnel) as well as of putative interventions (e.g. medications and basic support of life). Accordingly, healthcare professionals, including private centers, need to be increasingly aware of procedures that generate information based on their practices to identify the frequency of occurrence of adverse reactions and hold the human and technological means to intervene in case of risk.

Iopromide, a low osmolar non-ionic monomeric contrast medium containing iodine, is used worldwide since 1985. Just like any other non-ionic monomeric contrast agent, the incidence of iopromide adverse reactions is mainly attributed to their ion content, the pH of contrast media, hydrophilicity and viscosity [21]. Notably, a higher rate of adverse reactions to iopromide, featured by a higher incidence of cutaneous, gastrointestinal and facial manifestations was perceived [22]. More recently, iopromide appeared more likely to facilitate the appearance of contrast-induced encephalopathy as well [23]. Even

though ADR to nonionic ICM have been reported to occur in a modest frequency of about 0,5%-3% of patients [24], there is still a risk of continuously under-reporting, namely in private medicine where the generally increase in the use of ICM is well-established. Since potentially fatal hypersensitivity reactions continue to occur, the diagnosis, reporting and management of ADR to ICM, particularly to iopromide, deserves further attention. Accordingly, this work aimed to provide a broader characterization of ADR to iopromide and to assess patients risk perception and ADR reporting in Portugal in order to empower citizens and healthcare professionals with competencies for a well-suited ADR management of the national healthcare private biomedical imaging system.

For a better clarity, data collection and analysis are presented as outlined below:

- **Chapter 1**

  "*Assessment of risk perception by patients concerning adverse drug reactions*"

  encloses original information on patients' awareness of ADR risks and of the Portuguese Pharmacovigilance System;

- **Chapter 2**

  "*Safety assessment of iopromide contrast media: a narrative review focusing on adverse events*"

  provides a narrative review of ADR and safety assessment of iopromide contrast media;

- **Chapter 3**

  "*Iopromide safety assessment of iopromide in a radiology departmente: a seven-year retrospective characterization of adverse events*"

  presents a retrospective analysis of adverse events to iopromide in a Portuguese private unit of radiology;

- **Chapter 4**

  "*All-round approaches to increase adverse drug reaction reports: a scoping review*"

  seeks to shed light to innovative approaches, including patient-centered strategies, aimed to circumvent ADR under-reporting.

CHAPTER 3

RESULTS

III. RESULTS

1. Assessment of risk perception by patients concerning adverse drug reactions

Article published
Curr. Issues Pharm. Med. Sci.
DOI: 10.2478/cipms-2023-0018

2. Safety assessment of iopromide contrast media: a narrative review focusing on adverse events

Article accepted
Curr. Issues Pharm. Med. Sci.

3. Iopromide safety assessment in a radiology department: a seven-year retrospective characterization of adverse advents

Article possible accepted under revisions
Int. J. Risk Saf. Med.

4. All-round approaches to increase adverse drug reaction reports: a scoping review

Article published
Drugs Ther Perspect (2023)
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1. Assessment of risk perception by patients concerning adverse drug reactions

Assessment of risk perception of patients concerning adverse drug reactions

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RESUMEN

Introducción

El uso de medicamentos implica compensaciones entre sus beneficios terapéuticos y los riesgos inherentes. Varios estudios muestran que numerosas reacciones adversas a medicamentos (RAM) podrían evitarse aumentando la conciencia de los pacientes sobre los riesgos de los medicamentos. Aunque las etiquetas de los medicamentos contienen información relevante sobre riesgos y beneficios, esta información a menudo requiere la educación de los pacientes para mejorar la adherencia a la medicación y la educación general sobre la salud, evitando así la frecuencia de RAM.

Objetivo

Describir la conciencia de los pacientes sobre los riesgos de RAM y el Sistema de Farmacovigilancia Portugués.

Métodos

Se realizó un cuestionario de 27 preguntas en un centro de salud de Coimbra, Portugal. Este estudio incluyó a noventa y un pacientes. La percepción del riesgo se calificó como positiva (≥ 2,5 puntos) o negativa (< 2,5 puntos). Los resultados fueron analizados por SPSS v 27.0.

Resultados

Este trabajo destaca la mala percepción de riesgo de los pacientes con una tasa de respuestas negativas del 85,7%. Aunque algunos de los que respondieron conocían la posibilidad de informar una RAM, solo algunos participantes estaban familiarizados con el Sistema de Farmacovigilancia portugués. Además, solo cinco pacientes, de la gran mayoría de los que se habían encontrado previamente con una RAM, informaron el evento a INFARMED.

Conclusión

Es necesario mejorar con urgencia la escasa alfabetización de los pacientes sobre las RAM y los sistemas nacionales de notificación. Las estrategias de comunicación centradas en el paciente para reconocer los requisitos reglamentarios y los estándares de seguridad de los productos son medidas importantes para lograr una concienciación efectiva a través de informes de rutina dentro de los sistemas de farmacovigilancia.

Palabras clave

Reacciones adversas a medicamentos; Percepción del riesgo; sistema de farmacovigilancia; notificación de RAM

Abstract

Introduction The use of medicines involves trade-offs between their therapeutic benefits and inherent risks. Several studies show that numerous adverse drug reactions (ADRs) could be avoided by increasing patients' awareness of medicine's risks. Even though drug labels enclose relevant information about risks and benefits, this information often requires patient education and overall to improve medication adherence, thereby preventing ADRs frequency.

Aim To describe patient awareness of ADR risks and the Portuguese Pharmacovigilance System.

Methods A questionnaire comprising 27 questions was conducted at a health centre in Coimbra, Portugal. This study included ninety-one patients. Risk perception was scored as positive (≥ 2.5 points) or negative (< 2.5 points). Results were analysed by SPSS v 27.0.

Results This work highlights poor patient perceptions of risk with a rate of negative responses of 85,7%. Although some responders were aware of the possibility of reporting ADRs, only some participants were familiar with the Portuguese Pharmacovigilance System. Additionally, only five patients—out of the vast majority of those who had previously encountered an ADRs—reported the event to INFARMED.

Conclusion Patient low literacy regarding ADRs and the national reporting systems need to be urgently improved. Patient-centered communication strategies for recognising regulatory requirements and standards of product safety are important measures to achieve effective awareness through routine reporting within the Pharmacovigilance systems.

Keywords Adverse Drug Reactions; Risk perception; Pharmacovigilance system; ADR reporting

Introduction

According to Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010, an adverse drug reaction (ADR) is defined as a "noxious and unintended effect to a medical product" [155]. Such a directive was an outcome of the thalidomide tragedy in 1961, which accelerated the development of an international system aimed at improving drug safety while identifying ADRs previously unknown [60].

In July 2012, Directive 2010/84 was adopted in several European countries who that committed to implementing an automatic reporting system where healthcare professionals and patients could share integrated reporting channels towards active participation [156]. The Portuguese Pharmacovigilance System was earlier and was put in place in 1992 under the regulatory frame of INFARMED. It was intended to accomplish three challenging goals: i) improve risk/benefit analysis, ii) provide early notice of ADRs and iii) enable data analysis and accurate information divulgation [157]. Accordingly, every spontaneous report was to be is analysed to identify and properly integrate public health concerns. Under the directive, healthcare professionals and patients are both encouraged to report to the Pharmacovigilance System [18, 158, 159].Hospital reports are crucial because they often disclose risks in administration of new and innovative drugs, hence, allowing earlier detection of risk, and more accurate data analysis [17, 160]. Still, ADRs elicited by over-the-counter drugs are equally relevant given their frequent misuse due to poor literacy.

Age, education, health status, information, media, culture and beliefs are among the factors that influence patient perception of risk. Individual vulnerability strongly impacts ADR risk and further contributes to data heterogeneity. Noticeably, an expressive number of mistaken beliefs subsist. For example, the false statement that the

occurrence of an ADR in a given individual parallels its frequency in a population still prevails [25]. Moreover, perception exists that generic prescription drugs display far more risks the corresponding brand-name products or that the more security-related information there is, the riskier a product remains. [25]. The major factors that foster misleading perceptions have yet to be fully discussed. Yet, it is well-accepted that healthcare professionals need to become more familiar with the ADR report system [158, 161]. Patients need to be properly informed about the possible side effects that can be experienced, and communication strategies conveyed by simple verbal and written information favor the bi-directional risk communication process [25, 161-163]. However, evidence discloses patients' poor literacy regarding medicine's benefit/risk assessment and adequate adherence. Therefore, the application of proper communication strategies are strongly recommended [162, 164-168]. Collectively, there is consensus on the pertinence of complementary policies raise awareness within the pharmacovigilance systems towards improved ADRs prevention and management [79, 169, 170].

Nowadays, ADRs are a substantial cause for concern worldwide being responsible for extended admission times in healthcare units, permanent disability and/or increased morbidity and mortality [79, 160, 171, 172]. There are still many obstacles to positive communication strategies between patients and healthcare professionals that jeopardize risk perception [18]. Healthcare professional risk perception and communication are core to improve reporting and to empowering citizen health literacy [173]. This work aimed to characterize patient risk perception of medicines, and to reveal the awareness of their knowledge of ADRs and the national reporting system.

Material and Methods

Ninety-one participants were enrolled in this observational cross-sectional study conducted at a health centre in Coimbra, Portugal. For it, a questionnaire was adopted from two previous studies to assess and describe risk perception by patients [170, 174] The result was the Electronic Supplementary Material Portuguese Version of Questionnaire. Accordingly, twenty-seven questions comprising i) socio-cultural factors, ii) participants' attitudes towards medicines and iii) the knowledge and awareness of the ADR reporting system were applied. Each participant was informed about the study's main objective and confidentiality prior to signing the informed consent. Patients under 18-years old were excluded from this study, as well as those displaying impediments that could affect their ability to participate and/or that could add bias study results, such as cognitive or physical disabilities, mental health conditions, chronic medical conditions, substance abuse or dependence, language barriers and prior participation in a similar study. In this study, data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 27.0.

This allowed efficient computation of descriptive statistics to provide an accurate summary and understanding of the collected information. Age and qualifications were stratified in four and three groups, respectively.

To assess risk perception and the knowledge on the ADRs reporting system, five questions were scored (0; 0,5; 1 value) and classified as a positive (≥ 2.5) or negative (< 2.5) perception.

Results

Ninety-one respondents were included in this study, ranging from 18- to 85-years-old (Table 1). Most respondents were women (67%; n=61), whereas 33% (n=30) were men.

Table 1 – Age and qualification distribution.

Group Age	Percentage	Frequency
18-30	10%	9
31-50	44,4%	40
51-65	23,3%	21
66-85	22,3%	20
Qualifications		
None - Middle School	24,2%	22
Senior School	24,2%	22
Higher Education	51,6%	47

When asked whether they were currently taking any medicines, 74,7% (n=68) responded affirmatively, 54,4% (n=37) of which claim to be acknowledged of their side effects. Moreover, 60,4% (n=55) preferred to use a medication they are familiar with, when needed due to common health-related issues (e.g. headache, flu or cough) instead of requesting the corresponding advice from a healthcare professional. In contrast, it was clear that most respondents accept healthcare recommendations, as evidenced in their answers to several questions were intended to evaluate participants' perceptions and knowledge of the ADR reporting system (Figure 1 and Figure 3). Overall, it is possible to conclude that individual's perception is negative with only 13 positive responses (Figure 2).

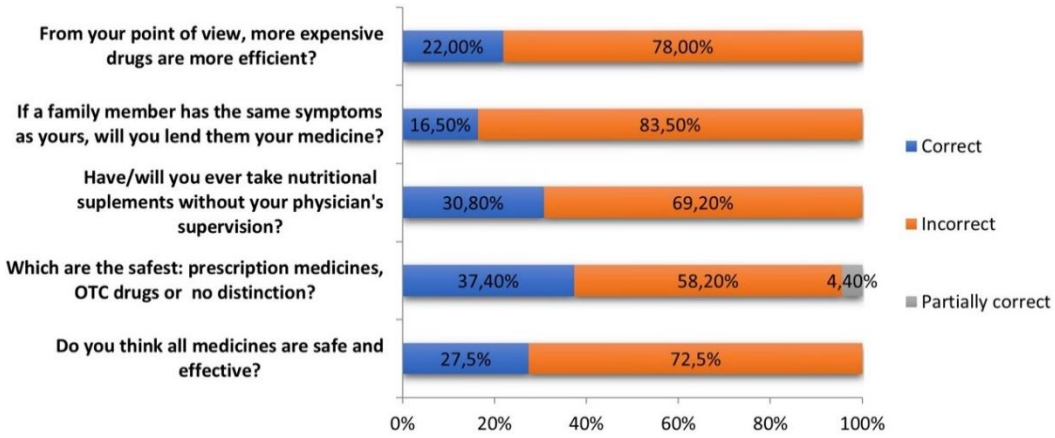

Figure 1 - Questions applied to evaluate participants' perception about medicines.

When knowledge about medicines was assessed, it was possible to identify a low perception level that is strongly related with safety issues. Results all scored below 50% of correct answers which represents a challenge to medicinal communication. Among the results, what stands out are difficulties to properly correlate the efficiency of medicines to their costs (78%; n=71), also the fact that the medicines that are at home are correctly used by family members with similar symptoms (83,5%; n=76) and, lastly, the wrong perception that all medicines are effective and safe (72,5%; n=66). – Figure 1. Figure 2 a show a positive symmetric distribution and unveil a low literacy about medicines.

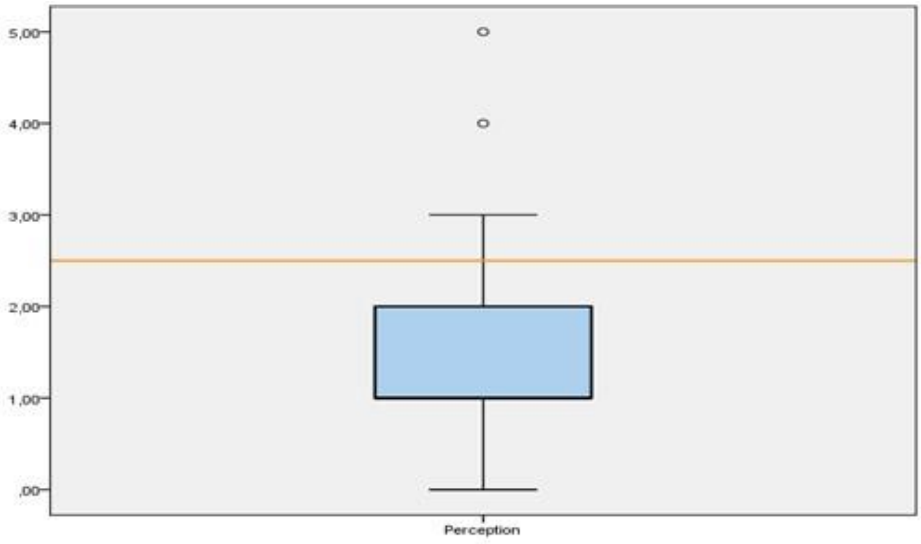

Figure 2 - Individuals' risk perception.

A second endpoint was related to the assessment of held knowledge on the current reporting system in Portugal. Figure 4 clearly shows a global lack of information among respondents (Figure 4). Only 17,6% (n=16) recognized the Portuguese Pharmacovigilance System, despite the evident aim to learn more about the reporting procedure (93,4%; n=85). Additionally, 39,6% (n=36) of the respondents stated that they had experienced a side effect, yet only 13,9% (n=5) reported this to INFARMED. Alternatively, they preferred to report the event to their physician (61,1%; n=22), pharmacist/ pharmacy technician (5,6%; n=2), or not to inform at all (33,3%; n=12).

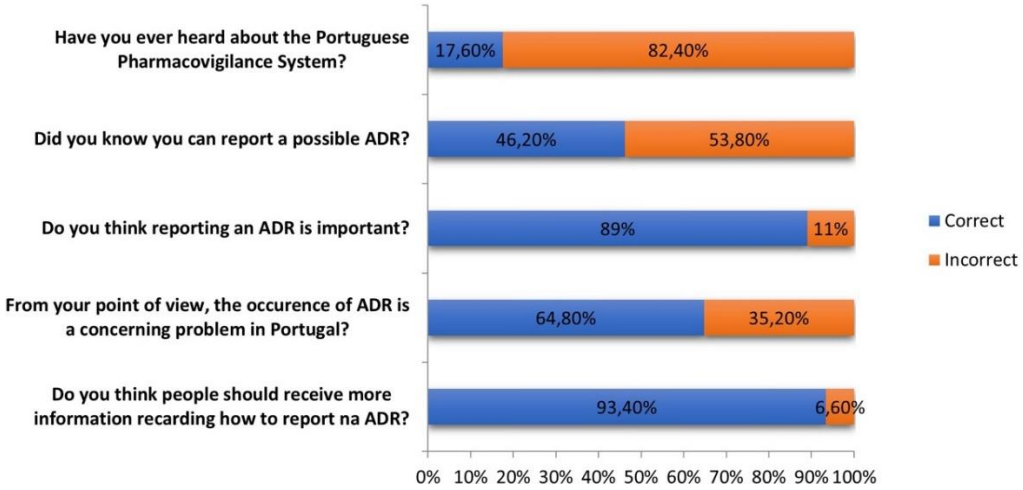

Figure 3 – Questions applied to assess the level of held knowledge regarding the Portuguese Pharmacovigilance System.

Considering the relevance of a robust system of pharmacovigilance, it is important to understand the level of held knowledge of patients as they are important players on reporting suspected ADRs. When asked about the system, 82,4% (n=75) respondents were unaware of the national System of Pharmacovigilance. Nevertheless, an impressive 89% (n=81) held high perceptions of the importance of reporting problems related with medicines. Another issue that should be highlighted and maybe considered by the National Authority, is the fact that 93,4% (n=85) of all respondents considered it important to have

more information on how to report (Figure 3). In Figure 4 it is possible to find symmetric distribution and information that points to a slightly satisfactory level of knowledge.

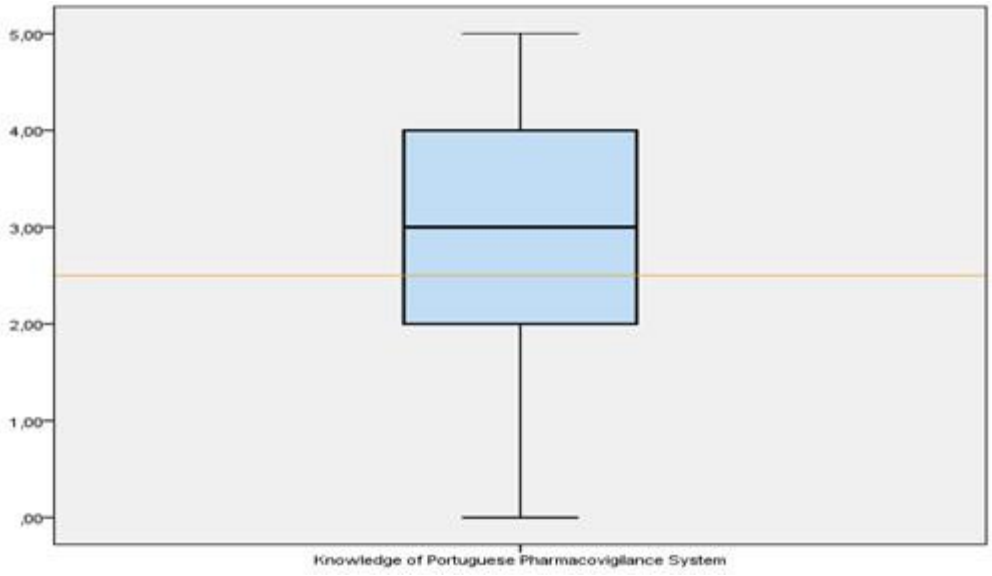

Figure 4 – Level of knowledge regarding the Portuguese Pharmacovigilance System

Lastly, a third set of questions aimed to examine participant use of their medicine, as well as their communication flows with their physicians (Figure 5). It was interesting being able to verify that patients thought that they received enough information from their physicians.

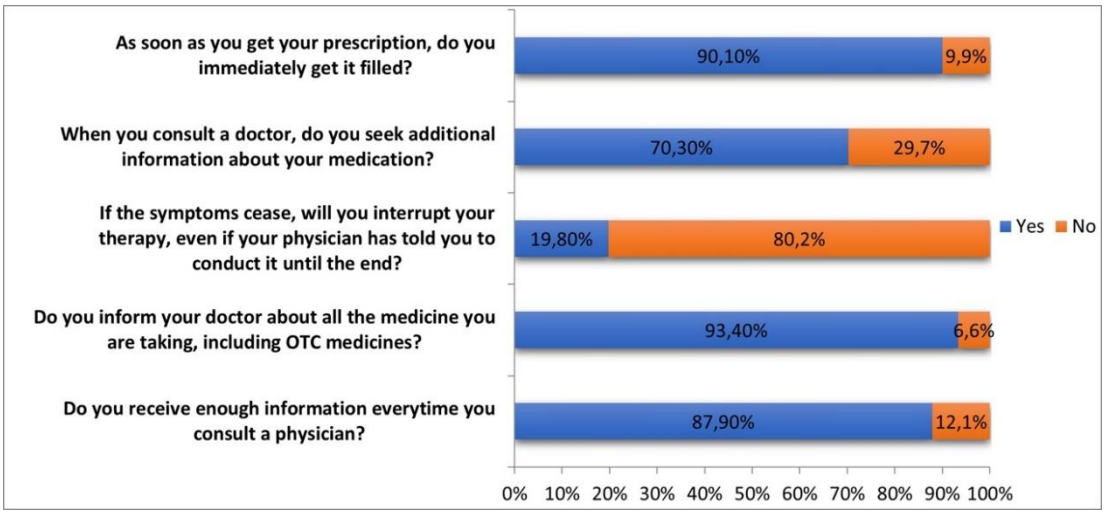

Figure 5 – Questions applied to assess participant use of medicines and the communication between them and their doctors.

It is important to highlight that the results of this study show a fairly good quality of understanding of the medication used, as well as of the information received by patients through their doctors. Yet, it is important to point out that 19.8% (n=18) of all respondents ceased their pharmacological treatments once their symptoms disappeared, which indicates a low perception of the importance of medicines adherence (Figure 5).

Discussion

ADRs are a major concern for patients and healthcare systems. Any unpleasant and unintended reaction to a medication, including therapeutic and non-therapeutic effects, is referred to as an ADR. All medicated patients can experience an ADRs, but patient own perception about the risk can vary significantly [25-27].

The present study reveals that risk perception is openly negative among patients and healthcare professionals. Most people still believe that medicines, given their long and rigorous process of research and development, are necessarily safe and efficient, and their hazards in intake are not even questioned. In addition, they falsely consider prescription drugs to be less harmful when physician instruction is given. What is also concerning is the misconception that generic prescription drugs are less efficacious than the corresponding brand-name ones. Indeed, while those with higher qualifications tend to find no distinction between prescription and OTC drugs, they are likewise convinced that generic prescription drugs are not as efficient as the brand medicaments available in the market.

Moreover, although the participant' knowledge of the Portuguese Pharmacovigilance System was found satisfactory, yet, when asked about the methodology applied to report, the literacy levels fall,

preventing patients from actively reporting ADRs. Albeit they are not entirely aware of the reporting system, 46,2% did prior knowledge of the possibility of using an integrated reporting system for ADR identification and management. Younger and older ages represent the age group with less levels of information regarding the Portuguese Pharmacovigilance System. Moreover, those with higher qualifications are irrefutably more acquainted with the occurrence of ADR and the significant need to report them.

The perception of risk can have a significant impact on patient behavior [28], as patients who perceive a high risk of ADRs may choose not to take their medications or may hesitate to start new medications. This can have a negative impact on their health and may result in the use of alternative therapies that are not evidence-based. Looking for the factors that can influence the risk perception of patients it is possible to highlight the age, previous experiences, culture and beliefs and fear and anxiety [28].

Consumer experience is absolutely crucial as it adds significance and value to ADR reports while enabling the identification of possible new reactions. Therefore, healthcare professionals need to be gradually more empowered to identify new potential ADRs and report them as well as to thoroughly educate patients about drug side effects and the Portuguese Pharmacovigilance System [5,29]. The behavioral influence of the health professionals on patients can be significant. Thus, a patient-centered communication is a key-issue for enabling patients to play active roles in the decision-making process of healthcare systems.[18,19,30] Among several hot-topics to fulfill, issues comprising the recognition of the regulatory requirements and the education on applicable standards and responsibilities regarding product safety are widely encouraged.[30,31] Communication channels need to be improved in order to translate patient concerns

about ADRs into effective awareness by routine reporting within pharmacovigilance systems.[32]

Furthermore, an accurate understanding of risk perception is crucial for healthcare professionals when considering the de-prescribing of medicines, as it helps identify patients who might benefit from a reduction or discontinuation of certain medications. By employing de-prescribing tools, clinicians can systematically evaluate medications and minimize the potential for ADRs, thus improving patient safety and overall health outcomes. [33]

Collectively, this work emphasizes patient low literacy regarding ADRs and national reporting systems. Future initiatives to improve public communication for the safety of patients through engaging the pharmacovigilance systems, are strongly advised.

Strengths and limitations

This preliminary study was conducted in Portugal and brings new data to properly characterize patient perception on ADRs risks, which can highlight future research on the topic. However, the lack knowledge of the topic limits a proper expression of perception. Moreover, more patients should be included to reflect the characteristics of the Portuguese population and build a more assertive and effective communication.

Further studies

It is important to conduct more research in this area to improve our understanding of risk communication and patient reporting procedures,

increase public awareness of medication-related risks, and inspire and encourage the reporting of suspected ADRs. In order to emphasize their characteristics, it is also important to study the special patient populations, such as the elderly and polimedicated populations.

Conclusions

To effectively communicate risks to patients, healthcare professionals must be fully trained, use the appropriate communication styles, and take into consideration the patient's gender, age, and cultural background. It is also necessary to apply new tactics to educate people about reporting processes and their importance. However, such conversation must be carried out with caution, on a limited scale, and ideally one-on-one rather than globally, otherwise it may result in disorder and disarray among patients, as well as the interruption of therapies due to the misunderstanding among numerous ethnically and socially diverse individuals. Of note, older populations are more apt to have more difficulties adhering to the reporting method of ADRs due to their unique characteristics. Over all, it would be beneficial to increase awareness of the national pharmacovigilance system, in particular the method for reporting suspected reactions.

Declarations

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Conflicts of interest: The authors declare no conflict of interest.

Ethics approval: The study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Participants consented to submission of the manuscript to the journal.

Availability of data and material: The datasets presented in this study are available on request from the corresponding author upon reasonable request.

Code availability: Not applicable.

2. Safety assessment of iopromide contrast media: a narrative review focusing on adverse events

Safety assessment of iopromide contrast media: a narrative review focusing on adverse events

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RESUMEN

Muchos contextos clínicos requieren exámenes radiológicos basados en la aplicación de diferentes medios de contraste (CM). El CM yodado (ICM) representa uno de los tipos de agentes de contraste más utilizados y estudiados en los exámenes radiológicos. Los diferentes ICM varían mucho en cuanto a sus propiedades, usos y la aparición de reacciones adversas (RA). Por lo tanto, una comprensión básica de la aparición de RA, los factores de riesgo, las características clínicas y el manejo de estas sustancias es cada vez más importante en la práctica clínica. La iopromida es un MCI no iónico ampliamente utilizado en la práctica clínica debido a su favorable perfil de seguridad y numerosas aplicaciones. Esta revisión narrativa presenta un informe completo de los datos disponibles sobre los RA de iopromida. También analiza su ocurrencia y frecuencia con diversos factores de riesgo potenciales (por ejemplo, edad, sexo, condiciones preexistentes).

Palabras clave medios de contraste yodados; iopromida; Reacciones adversas; seguridad de los medicamentos; factores de riesgo

Abstract

Introduction: Many clinical contexts require radiological exams based on applying different contrast media (CM). Iodinated CM (ICM) represents one of the most used and studied types of contrast agents in radiological examinations. Different ICMs vary greatly in their properties, uses, and the occurrence of adverse reactions (ARs). Therefore, a basic understanding of ARs occurrence, risk factors, clinical features, and management of these substances is increasingly important in clinical practice. Iopromide is a nonionic ICM widely used in clinical practice due to its favourable safety profile and numerous applications. This narrative review presents a comprehensive report of the available data concerning iopromide ARs. It also analyses their occurrence and frequency with diverse potential risk factors (e.g., age, sex, pre-existing conditions).

Keywords: iodinated contrast media, iopromide, adverse reactions, safety, risk factors

Introduction

Medical imaging became an important branch of medicine playing important roles in earlier detection, accurate diagnosis, and drug development [128]. These techniques and processes allowed observations through internal structures for various clinical purposes such as medical procedures, diagnosis, or medical science, including the study of normal anatomy and function [175]. This type of biological imaging incorporates radiology, which uses a panoply of imaging technologies like X-ray radiography, X-ray computed tomography (CT), endoscopy, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), thermography, medical photography, electrical source imaging (ESI), digital mammography, tactile imaging, magnetic source imaging (MSI), medical optical imaging, single-photon emission computed tomography (EIT) [176]. The sophistication process of these techniques contributes to the recognition of patient's situation.

Contrast agents consist of chemical compounds integrated into many imaging examinations (e.g. radiology), which are increasingly used to enhance the effectiveness of visualization and detection rate of internal structures [177]. Currently, iodinated contrast media (ICM) and gadolinium-based contrast media (GBCM) are the two most used contrast media for enhanced CT and MRI scanning, as CT and MRI, respectively, and the mainly used imaging modalities in daily practice [178, 179] as revealed by the estimation that more than 120 million doses of both ICM and GBCM administered worldwide per year [102, 180].

Iopromide ($C_{18}H_{24}I_3N_3O_8$), also known as Ultravist, is a nonionic contrast-enhancement agent used in clinical applications and considered one of the most favorable [29]. It is monomeric with low osmolality and is mainly applied by the intravascular route [152]. It is

mostly used in cerebral, and peripheral coronary arteriography applications, and neoplastic visualization implications for the brain [181]. Despite their appropriate safety record, the risk of adverse reactions (ARs) is present in any kind of contrast agents, which in rare cases can even be fatal [141].

There are few studies that analyze the occurrence of ARs in contrast media. Consequently, investigations about adverse events after the administration of these compounds are extremely relevant to clinical practice. Thus, this review focused on the ARs of iopromide by reviewing the current literature and providing an overview of all collected studies.

Methods

Search strategy and selection criteria

To conduct this narrative review, a comprehensive literature search was performed using the electronic databases PubMed, Scopus, and Web of Science. The search was carried out from inception up to September 2021. The keywords and phrases used in the search strategy included "iopromide," "adverse reactions," "contrast media," "contrast agents," "safety," and "hypersensitivity." Both Medical Subject Headings (MeSH) terms and free-text terms were combined using Boolean operators "AND" and "OR." Additionally, the reference lists of relevant articles were manually searched for further eligible studies.

Inclusion and exclusion criteria

The inclusion criteria for selecting studies were as follows: (1) original research articles, including observational, experimental, and

randomized controlled trials; (2) studies focusing on the adverse reactions and safety profile of iopromide; (3) studies published in peer-reviewed journals; and (4) articles written in English. Exclusion criteria included: (1) review articles, editorials, letters to the editor, and conference abstracts; (2) studies with insufficient or unclear data on adverse reactions; and (3) articles that did not specifically investigate iopromide or did not provide separate data for iopromide.

Study selection and data extraction

Two independent reviewers screened the titles and abstracts of the identified articles for relevance. Full-text articles were obtained and assessed for eligibility according to the predefined inclusion and exclusion criteria. Any disagreements between the reviewers were resolved by discussion and consensus or, if necessary, by consulting a third reviewer.

The following data were extracted from the included studies: study design, study population, sample size, main outcomes, and relevant findings. Due to the heterogeneity of the study designs and outcomes, a narrative synthesis approach was used to summarize and discuss the results.

ICM classification, chemical properties, and overall safety profile

ICM agents are acknowledged as an indispensable diagnostic aid that has revolutionized clinical practice since the late 1950s[85]. Since their introduction, intravascular ICM are amongst the most widely used pharmacological agents, with about 75 million annual applications worldwide [102]. Therefore, their development helped to make

substantial advances in the design of safe and more effective compounds [92, 182].

These compounds are arranged in different categories according to their different properties, namely ionization in solution (ionic vs nonionic agents), osmolality (high vs low), and their structure (monomeric vs dimeric) (Figure 1) [183]. The chemical structure consists of a 2, 4, 6 tri-iodinated benzene ring (responsible for producing radiopacity), which linkage of structural elements to the ring determines their pharmacological and physicochemical characteristics [95]. Thus, the major properties that justify the safety and effectivity of iodine for contrast media (CM) use include the high-contrast density, firm binding to the benzene molecule, and low toxicity [184]. ICM structures are ionic when converted into ions in an aqueous solution or nonionic if remain an electrically neutral particle in solution. The ionization capacity of a given medium is directly related to the frequency and severity of the AR [95].

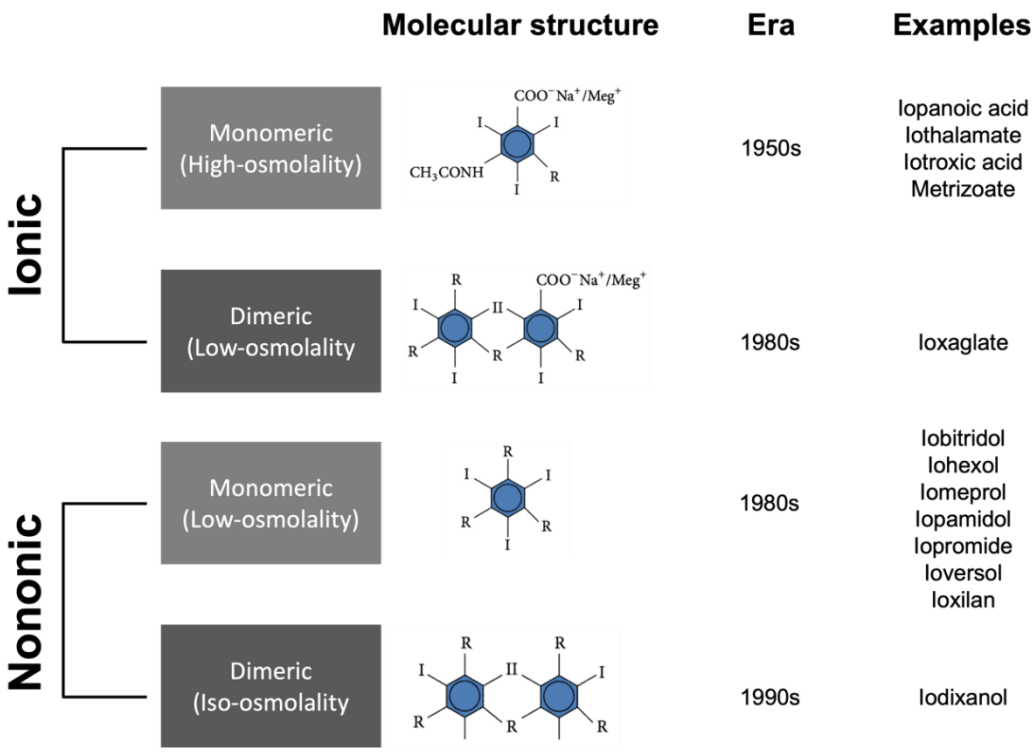

Figure 1. Classification of iodinated contrast media according structural and chemical properties.

The pharmacokinetic properties of ICM are such that they are distributed in the extracellular fluid only, are minimally protein bound, are not metabolized, and with a rapid excretion through glomerular filtration (50% in 2h) in patients with normal kidney function [185, 186]. Although their recognized high safety profile their use is not completely without risks [187]. ARs to CM are a relevant problem, which can be ranging from mild to life-threatening reactions [188]. According to some reports, ARs to ICM can range from 1 to 12%, where the most severe comprises 0.01 to 0.2% [9].

Since the ICM properties change according to their structure, the incidence of ARs might also depend on the ICM used [183]. The knowledge of the occurrence rate and the severity of ADRs related to each individual ICM is essential to ensure patient safety [189].

Iopromide adverse events assessment

The safety profile of iopromide has been characterized through extensive studies reporting the ARs, possibly by applying it to the databases records. Although vast clinical experience with CM, including iopromide, a lot of questions on the safety is not been fully elucidated yet [25]. Despite being described as safe with rare serious ARs, ICM can be potentially severe or even lethal [26-28].

The summary of safety results from the studies is shown in table 1. In all studies, the population was considered homogenous concerning gender which bespeaks the important role of these compounds in medical practice for all patients.

Two recent studies performed by Endrikat et al highlighted the risk of iopromide HSR, higher in adults when compared with children and elderly [25] and via IV route (compared with IA) [10, 26].

Controversially, other two studies reported a higher risk of adverse acute reaction (AAR) in elderly patients (50-69 years) [28] and no relation between the occurrence of ARs with age [27].

Table 1. Summary of developed studies for iopromide adverse reactions.

Study type	Population	Main outcomes	Ref.
Pooled analysis	132,850 patients F - 57,864 (43.6%) M- 74,986 (56.4%)	• HSR were significantly less frequent in children (0.47%; p<0.042) and elderly (0.38%; p<0.001) compared with adults (0.74%). • The reporting rate for HSRs in children (0.0114%) and elderly (0.0071%) was significantly lower as compared with adults (0.0143%) (all p<0.0001).	
Pooled analysis	133,331 patients F - 58,074 (43.6%) M- 75,257 (56.4%)	• 822 patients with HSR: 766 patients (0.7%) and 56 patients (0.2%) after IV or IA administration, respectively (p<0.0001). • Major risk factors for hypersensitivity reactions were method of injection (IV vs IA), age (18 to <50 years vs ≥65 years), history of allergy or previous contrast media reaction (all p<0.001), and asthma (p=0.005).	[152]
Randomized clinical trial	137,473 patients F - 53,614 (39.0%) M- 83,859 (61.0%)	• AARs (in iopromide and iopamidol) were observed in 428 patients (0.31%): 330 mild (77,1%), 82 moderate (19,2%), and 16 severe (3,7%), including 1 death. • More incidence of AAR in iopromide than iopamidol (0.38% vs 0.24%, P<0.001), but only for mild AARs (0.32% vs 0.16%, p<0.001). • Higher risk of AAR in female patients (n=221, 0.43%, p<0.001), emergency patients (n=11, 0.51%, p<0.001), elderly patients aged 50 to 60 years (n=135, 0.43%, p<0.001), and patients who underwent CTA (n=55, 0.51%, p<0.001).	[22]
Prospective cohort	132,012 patients F – 59,517 (45.1%) M – 70,911 (53.7%) NS – 1584 (1.2%)	• 3823 patients (2.49%) reported an AR (2632; 1.99% mild). • More AR frequency in female patients (n = 1680; 2.8%) than men patients (n = 1586; 2.2%). • Most common ARs: injection site heat, nausea/vomiting, and dysgeusia. • Increased AR in patients with established risk factors: previous CM reaction	[154]
Prospective cohort	120 patients (block randomizatio n method)	• Associated pain and heating sensation were more frequent in iopromide in comparison with iodixanol (p=0.03). • ↑ frequency of immediate reactions (e.g., nausea and vomiting) in iopromide (p=0.01). • ↓ frequency in delayed skin reactions in iopromide (p<0.01).	[190]
Retrospectiv e cohort	74,717 patients F – 16,852 (47.1%) M – 39,192 (52.9%)	• 1069 (1.5%) patients with at least one AR, 14 (0.02%) of them serious. • ↑ incidence of AR in women aged between 18 and 30 years. • ↑ AR rate reported following intravenous administration compared with Intraarterial use (2.1% versus 1.1%, respectively; p<0.0001). • Increased risk for developing AR in patients with established risk factors: previous CM reaction (7,4%; 6.2-fold increase) or allergic diathesis (7.4%; 3.4-fold increase). • No alterations in AR incidence with the use of premedication.	[8]
Pooled analysis	29,508 patients F – 16,852 (56%) M - 12,656 (43%)	• ARs were observed in 211 patients (0.7%): 188 mild (89%), 19 moderate (9%), and 4 severe (2%), including 1 death. • ARs required treatment in 89 patients (42%). • History of allergies in 92 patients (44%), and 29 (14%) had a previous AR to a contrast medium. • No relationship between the occurrence of AR and patient age or dose. • ↑ incidence of AR in female (p<0.001) and outpatients (p<0.001).	[191]

AAR, Adverse acute reaction; CTA, computed tomography angiography; F, Female; HSR, Hypersensitivity reactions; M, men; NS, non-specified.

On the other side, patients with established risk factors as of allergy previous CM reaction were positively associated with increased ARs [10, 26, 29]. Other risk factors like asthma, emergency and underwent CTA patients were positively connected with the frequency and the severity of the ARs [10, 28]. Furthermore, in the analyzed data, a significant number of studies reported an increased risk and frequency of ARs in female patients [26-29]. Notably, when compared with other (nonionic) ICM, namely iopamidol and iodixanol, iopromide had a higher frequency of ARs [28, 30].

Discussion

Although CM agents are routinely used in clinical practice and considered safe, the total knowledge regarding the susceptibility, prevention, and overall impact of ARs is still abroad to be reached. Since its introduction in the 1950s, ICM has been among the most commonly prescribed drugs in the history of modern medicine [97]. This fact highlights the need to better understand their safety profile and patients' susceptibilities.

Despite some literature regarding the occurrence of ARs in ICM [16, 97, 183], these studies compared a couple of substances that difficult to better understand the patterns of adversity by a single agent. Considering the changing profile of ARs according to the compound's chemical structure [183], it is fundamental to perform a focused analysis in each agent individually. Additionally, the pharmacological and physicochemical properties are also directly implicated in the frequency and severity of ARs [183]. Thus, we performed an overview of ARs including some perspectives about patients' characteristics of iopromide reported in the literature. To the best of our knowledge, this is the first review focused on the safety profile of iopromide, providing

useful analysis and extremely relevant not only for the professionals in clinical practice but also to encourage researchers to higher scrutiny the profile of ARs in CM compounds.

Some findings indicate that iopromide-associated HSRs were higher in adults compared to children and the elderly [151] as well suggest the IV route with more incidence of ARs [8, 152]. However, other studies reported conflicting findings, with higher risks of adverse acute reaction observed in elderly patients [22] or no clear relationship between age and the occurrence of ARs[191]. This discrepancy highlights the need for further research to better understand the risk factors for iopromide-associated ARs across different age groups. Furthermore, several studies found a higher frequency and severity of ARs in female patients [8, 22, 154, 191], suggesting a potential gender-related predisposition that warrants further investigation.

Strengths and limitations

This review presented several strengths as the large sample sizes in included studies, which enhances the reliability of the findings and helped to identify even rare ARs. The review also highlighted several risk factors associated with ARs to iopromide, providing useful information for CM decision.

The limitations identified in this study were the occurrence of some inconsistent findings, which may be attributed to differences in study designs, populations, or methodologies. In addition, most of the included studies focused on short-term or immediate ARs, which may not fully capture the long-term safety profile of iopromide. Lastly, while the review acknowledged associations between certain risk factors and ARs, there might be other confounding factors not considered or controlled for in these studies, which could influence the findings.

Conclusions

This review examined the ARs associated with iopromide, revealing their variating frequency according to diverse factors such as age, gender, and pre-existing conditions. Some studies reported a higher incidence of ARs with iopromide compared to other contrast agents, such as iopamidol and iodixanol. Further research was needed on this topic, including well-designed prospective studies, randomized controlled trials, and investigations into long-term safety to expand the knowledge of iopromide's safety profile and address the research gaps, ultimately to clinicians optimize their use and improve patient outcomes while minimizing AR.

Declarations

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3. Iopromide safety assessment in a radiology department: a seven-year retrospective characterization of adverse events

Iopromide safety assessment in a radiology department: a seven-year retrospective characterization of adverse events

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RESUMEN

Introducción Desde mediados del siglo XX, los agentes de contraste han sido ampliamente utilizados en radiología debido a su capacidad para proporcionar imágenes radiográficas de alta definición y una mayor precisión en los exámenes de diagnóstico. En el diagnóstico por imágenes se utilizan diferentes tipos de agentes de contraste, a saber, medios radiológicos (por ejemplo, productos yodados, incluida la iopromida). A pesar de ser considerado seguro, aún existen dudas sobre su perfil de seguridad, interacciones e incidencia de reacciones adversas a medicamentos.

Objetivos Caracterizar el patrón de eventos adversos, durante 7 años, en una unidad de radiología.

Métodos Realizamos un estudio observacional y descriptivo retrospectivo en un Centro de Imagen en Portugal entre agosto de 2012 y octubre de 2019. Se registraron un total de 77.449 tomografías computarizadas, de esos 15.640 casos se utilizó iopromida como agente de contraste. Los autores han accedido, bajo autorización, a los datos de eventos adversos y procedimientos posteriores al evento.

Resultados La mayoría de los eventos de hipersensibilidad fueron inmediatos o de corto tiempo de aparición, desarrollando la mayoría de los casos eventos con compromiso cutáneo y grado leve, donde los eventos más comunes fueron pápulas (n=60), prurito (n=42), eritema (n=27) y urticaria (n=14). Los eventos graves, incluida la hipersensibilidad, estuvieron representados principalmente por vómitos (n=11), estridor (n=8), dificultad para respirar (n=7) y síncope (n=3). El examen de tomografía computarizada (TC) abdomino-pélvica presentó una mayor frecuencia de eventos adversos.

Conclusiones A pesar de toda la información actual sobre el uso de iopromida, la utilización de este agente no está exenta de riesgos y su perfil de seguridad no está completamente establecido. Los síntomas más frecuentes fueron locales, como eventos adversos cutáneos, incluyendo pápulas, prurito y eritema. Los medicamentos comunes utilizados para tratar o controlar los eventos adversos fueron con frecuencia hidrocortisona, clemastina y metilprednisolona.

Abstract

Background Since the mid-20th century, contrast agents have been widely used in radiology due to their ability to provide high-definition radiographic images and greater precision in diagnostic exams. Different types of contrast agents are used in image diagnosis, namely radiological media (*e.g.,* iodinated products, including iopromide). Despite being considered safe, there are still uncertainties about their safety profile, interactions, and incidence of adverse drug reactions.

Objectives To characterise the pattern of adverse events, during 7 years, in a radiology unit.

Methods We performed a retrospective observational and descriptive study at an Image Center in Portugal between August 2012 and October 2019. A total of 77.449 computed tomography were registered, from those 15.640 cases of iopromide was used as a contrast agent. The authors have accessed, under the authorization, the data of adverse events and procedures after the event.

Results Most of the hypersensitivity events were immediate or with a short time of onset, with the majority of cases developing events with skin involvement and mild degree, where the most common events were papules (n=60), pruritus (n=42), erythema (n=27) and urticaria (n=14). Severe events, including hypersensitivity, were mainly represented by vomiting (n=11), stridor (n=8), breathing difficulties (n=7) and syncope (n=3). Abdominal-pelvic computed tomography (CT) exam presented a higher frequency of adverse events.

Conclusions Despite all the current information about iopromide usage, the utilization of this agent is not abstent of risks and its safety profile not fully established. Most frequent symptoms were local, as skin adverse events, including papules, pruritus and erythema. Common medications used to treat or control adverse events were frequently hydrocortisone, clemastine and methylprednisolone.

Introduction

Administration of contrast media used in radiodiagnosis allowed the quality improvement of radiographic images, providing high-definition images and a greater precision in diagnostic exams [192, 193]. Since the mid-20th century, distinct contrast agents have been widely used in radiology for image diagnosis [152, 194], namely radiological media (*e.g.* iodinated products, including iopromide), and non-radiological media, used in examinations without radiation (*e.g.* gadolinium) [195]. The iodinated contrast media have been widely used and considered secure, with a well-established good safety profile. However, it is important to acknowledge that the process of comprehensive data collection on interactions and the real-world incidence of adverse reactions (ADRs) can be extremely challenging [152, 154, 183, 196].

These kind of compounds are preferentially applied by intravenous injection, but also administered by intra-abdominal, intra-arterial and intrathecal routes [152, 183]. Iodinated radiocontrast media (IRCM) classification is related with the charge of the iodinated molecule (ionic and non-ionic), the molecular structure (monomeric and dimeric) and the osmolarity (hyperosmolar, low osmolarity and iso-osmolarity). Although high osmolarity molecules were associated more frequently with hypersensitivity, the majority of serious reactions seemed to be osmolarity-independent [197]. The mechanisms underlying the ADRs associated with iopromide are not fully understood but may be related to the chemical properties of iopromide. Some studies suggest that iopromide has higher osmolality compared to other non-ionic contrast media, resulting in a higher particles concentration in solution that lead to more significant changes in blood chemistry and a greater risk of adverse reactions. Additionally, iopromide higher viscosity may enhance tissue irritation and inflammation [198, 199]. Another potential factor is the immunogenic nature of iopromide's molecular structure, which increases the likelihood of hypersensitivity reactions.

Hypersensitivity reactions occur when the immune system overreacts to a foreign substance like iopromide and can range from mild to severe, including anaphylaxis [22, 190, 200]. Overall, it is important to emphasize that the mechanisms underlying iopromide frequent adverse reactions are complex as they may involve multiple and intertwined factors. These factors can vary depending on the individual patient's health status, immune system response, among other related factors.

Immediate hypersensitivity reactions (occur in the first hour) and non-immediate reactions (occur from one hour up to ten days) are idiosyncratic, unpredictable and can appear in response to minimal amounts administered without nephrotoxic effect. They may also be allergic, mediated by IgE/T lymphocytes or by non-specific mechanisms of vasoactive mediator release. Acute non-nephrotoxic adverse reactions occur in 0.2%-0.7% administrations of iodinated contrasts, with serious reactions even rarer. Serious reactions can be subdivided into hypersensitivity and chemotoxic reactions. Chemotoxic reactions are associated with the chemical properties of contrasts, are dependent on dose and infusion rate, transient and self-limited, but overall serious [22, 139, 150, 194, 197, 201]. Renal adverse reactions are rare and usually occur in patients at high risk, for example, with a clinical condition related to renal failure. Unless they are on dialysis or it becomes clinically necessary, those patients should not be administered with iodine-based contrast agents [22].

Iopromide is a derivative of non-ionic, water-soluble tri-iodinated isophthalic acid, with a molecular weight of 791.12 Daltons. Its commercialisation started in 1989, trade name Ultravist®, whose marketing authorization holder is the pharmaceutical company Bayer® [45]. Iopromide is used for diagnosis as it opacifies the vessels or body cavities, allowing the radiographic visualization of the internal structures. Iopromide safety profile is currently based on data obtained

from pre-marketing studies (> 3.900 patients) and post-marketing studies (> 74.000 patients), as well as data from spontaneous reports and literature [8, 94, 152, 154, 189, 196, 202-205]. The most frequent adverse reactions are headache, nausea and vasodilation. The most serious ADRs identified include, according to the Summary of Product Characteristics, "*laryngospasm, bronchospasm, wheezing, dyspnea, and status asthmaticus; angioedema, subglottic edema and signs of airway obstruction; anaphylactic shock; cardiovascular collapse with peripheral vasodilation, hypotension, tachycardia, dyspnea, cyanosis, sweating, pallor, ventricular fibrillation and cardiac arrest; CNS stimulation or depression with agitation, convulsions, coma and death*", however, the incidence of ARs in real-world are usually uncertain or the significance of their occurrence is underestimated.

In Portugal, the National Pharmacovigilance System was created in 1992, and holds an essential role in the ongoing evaluation of the benefit/risk balance of medicines. The system is mostly based on the spontaneous ADR reporting method, which is an effective resource for early detection of rare or unexpected ADR [206]. Spontaneous ADR reporting in Portugal is performed by different stakeholders, including HCPs and patients, by filling online or paper forms. The spontaneous reporting by HCPs remains an effective resource for ADR detection; still, under-reporting remains a reality, with consequent limitations in the risk evaluation and detection and delays in risk signal generation. It is estimated that only 6% of all adverse reactions are reported [4]. Notably, the patient involvement in the Pharmacovigilance System since 2012 led to less underreporting along with reporting different ADRs and covering blind spots of pharmacovigilance as over-the-counter and herbal drugs, but also giving important information on the impact of ADRs on daily life [39, 167, 168, 207, 208]. The major limitation regarding the effectiveness of spontaneous ADR reporting system is underreporting of suspected ADRs, with consequent limitations in assessing the risk of drug and delay signal detection,

potentially causing serious health repercussions. The identification of attitudes and knowledge of HCPs related with under-reporting in Portugal has become essential to understand the reasons underpinning ADR under-reporting.

In this study, we aimed to investigate and characterize the occurrence of adverse events associated with the usage of iopromide contrast agent between August 2012 and October 2019 in a private radiology unit in Portugal.

Methods

An observational, retrospective and descriptive study was carried out. The study took place at a private Image Center in the Central Region of Portugal between November 2019 and June 2020, with the period studied between August 2012 and October 2019. The authors have accessed, under authorisation, to the records of adverse events and procedures after the event. A total of 77.449 computed tomography were registered in the clinic during the period, and from those, 15.640 cases where iopromide was used as a contrast agent.

Descriptive and inferential statistics were used to analyse and present collected data. The necessary statistical tests were used, namely, Pearson's Chi-square ($\chi 2$) test was performed to detect significant differences between variables. Significance was based on a two-sided $\chi 2$-test, and significance was set at $p<0.05$. The anonymised data were entered and analysed using IBM® - Statistical Package for the Social Sciences (SPSS) software version 27.0 for Windows.

Data analysis

A database was constructed to collect clinical data from the records. The database includes information on the date of the CT scan, sex, age of the patient, type of exam, the adverse event registered, treatment and time until discharge. The adverse events were classified with the Ring and Messmer Scale [209, 210], as described: acute adverse events to contrast agents were classified according to their clinical severity using the Ring and Messmer Scale into four degrees (I-IV)) [211].

The Ring and Messmer four step (I–IV) grading scale is the most widely accepted tool for describing the clinical severity. This four-step (I–IV) grading scale is used to describe clinical phenotypes, in which Grades I and II adverse events are not life-threatening and are more likely to be non-allergic, although they may still be IgE-mediated. Grades III and IV are life-threatening conditions, also called 'anaphylaxis', which are usually IgE-mediated (Table 1) [209-212].

Statistical analysis

Descriptive statistics were used to analyze and present collected data. Pearson's Chi-square ($\chi 2$) test was performed to detect significant differences between variables. Significance was based on a two-sided $\chi 2$-test, and significance was set at $p<0.05$. The anonymized data were entered and analyzed using IBM® - Statistical Package for the Social Sciences (SPSS) software version 27.0 for Windows.

Table 1. Classification of Immediate Allergic Reactions (Ring and Messmer Scale) [209-211].

Grade	Common symptoms
I	Generalised cutaneous and/or mucocutaneous symptoms (urticaria, angioedema, pruritus, erythema, rash, papules).
II	Mild systemic symptoms (rhinorrhea, dysphonia, dizziness, nausea, abdominal pain, tachycardia, hypotension, arrhythmia). Symptoms of the precedent grade can occur.
III	Severe systemic reactions (dyspnea, stridor, laryngeal oedema, dysphagia, dysarthria, vomiting, diarrhoea, confusion, feeling of imminent death). Symptoms of the precedent grade can occur.
IV	Cardio-respiratory failure (shock, altered consciousness, loss of sphincter continence, cyanosis, cardio-respiratory arrest). Symptoms of the precedent grade can occur.

Results

Of the 15.640 CTs scans with the iopromide contrast media, 105 patients developed adverse events, of which 64 were female (61.0%) with an average age of 58.24 ± 15.51, range 18-99, median of 59 and mode of 66 years old.

Table 2 offers an overview of the sample's characteristics. It includes the total number of computed tomography (CT) scans, the number of CT scans with Iopromide administration, and the incidence of events observed during the evaluated period. The table also provides information on the percentage of patients aged 65 years or older, the age range, the average age, the median age, and the mode (most frequently occurring age).

Table 2 - Sample characterization

Characteristics	Value
Total Computed Tomography (CT scans)	77.449
CT scans with Iopromide administration	15.640
Incidence of events in the evaluated period	0,67%
Patients > 65 years of age or older	43,6%
Age range	Min. 18 - Max. 89
Average age	58,24 years (± 15,51)
Median	59 years
Mode	66 years

Table 3 provides a characterization of the sample based on gender, age, and severity of adverse events. It reports the total number of patients with adverse events (105) and further breaks down the data by sex and age group.

The table shows the number and percentage of female (61.0%) and male (39.0%) patients, as well as the distribution across different age groups.

It also highlights the distribution of adverse events according to the severity established by Ring and Messmer, indicating the number and percentage of cases falling into each severity grade (I, II, III, IV).

Table 3 – Characterization of the sample by gender, age and severity of adverse events

Total patients with adverse events (n=105)	
Sex	
Female	64 (61.0%)
Male	41 (39.0%)
Age	
18-20	2 (1.9%)
21-30	2 (1.9%)
31-40	8 (7.6%)
41-50	8 (7.6%)
51-60	20 (19.0%)
61-70	20 (19.0%)
71-80	14 (13.3%)
81-90	4 (3.8%)
Data not available	27 (25.7%)
Severity according to Ring and Messmer Scale	
Grade I	74 (70.5%)
Grade II	6 (5.7%)
Grade III	16 (15.2%)
Grade IV	9 (8.6%)

Most events were classified in Grade I (n=74, 70.5%) accordingly to Ring and Messmer Scale, as underscored in Table 3. Age groups with more cases were from patients with 51-60 and 61-70 years, with 20 cases each (19%).

Table 4 provides information on the general effects and degree of severity of the adverse events observed. It categorizes the adverse

events into four grades (I, II, III, IV) and describes the corresponding general effects, common signs/symptoms, and the degree of severity for each grade. Grade I include generalised mucocutaneous signs such as erythema, urticaria, and angioedema, with a mild degree of severity occurring in 70.5% of cases. Grade II involves multi-organ manifestations such as tachycardia, cough, dyspnea, hypotension, and digestive signs, with a moderate degree of severity observed in 20.9% of cases. Grade III represents severe life-threatening multi-organ manifestations including arrhythmia, cardiovascular collapse, bronchospasm, tachycardia or bradycardia, and digestive signs. Grade IV represents the most serious level of adverse events, namely cardiopulmonary arrest or cardiac arrest, accounting for 8.6% of cases. As described in Table 1, symptoms of the precedent grades can occur when the seriousness increase (eg: erythema occur in all the grades – see Table 4)

Table 4 – General effects and degree of severity

Grade	General Effects	Common Signs/symptoms	Severity	%
I	Generalised mucocotaneous signs	Erythema Urticaria Angioedema	Mild	70,5%
II	Multi-organ manifestations	Tachycardia Cough, dyspnea Hypotension Digestive signs	Moderate	20,9%
III	Severe life threatening multi-organ manifestations	Arrhythmia Cardiovascular collapse Bronchospasm Tachycardia or bradycardia Digestive signs		
IV	Cardiopulmonary arrest	Cardiac arrest	Serious	8,6%

Table 5 presents the symptoms according to the severity scale established by Ring and Messmer. The severity scale is divided into four grades (I, II, III, IV), and the table shows the number of occurrences for each symptom within each grade.

Table 5 – Symptoms according to severity scale

Symptoms	**Severity according to Ring and Messmer Scale**				
	Grade I	**Grade II**	**Grade III**	**Grade IV**	**Total**
Papule	54	2	3	1	60
Itching	38	1	2	1	42
Erythema	22	1	3	1	27
Urticaria	13	0	0	1	14
Vomit	0	0	8	3	11
Rash	5	1	2	0	8
Stridor	0	0	6	2	8
Angioedema	5	1	2	0	8
Congestion	0	3	3	1	7
Breathing difficulty	0	1	3	3	7
Nauseas	0	1	2	2	5
Cough	0	2	2	1	5
Syncope	0	0	0	3	3
Cyanosis	0	0	0	2	2
Abdominal pain	0	0	0	2	2
Heart attack	0	0	0	2	2
Dysphagia	0	0	1	0	1
Total	**137**	**13**	**37**	**25**	**212**

Hypersensitivity events were immediate, the majority of cases featured by mild degree events with skin involvement, where the most common were papules (n=60), pruritus (n=42), erythema (n=27) and urticaria (n=14). Severe events are mainly represented by vomiting (n=11), stridor (n=8), breathing difficulties (n=7) and syncope (n=3). The exam that showed the most adverse eventss were the abdominal-pelvic computed tomography (CT). As for the severity of symptoms, 74 cases (70.5%) presented events of grade I, 6 (5.7%) grade II, 16 (15.2%) grade III and 9 (8.6%) grade IV. The analysis of risk factors revealed that there is no statistical relationship between severity and sex (p=0.143) as well as between severity and different age groups (p=0.172). The most used drugs to reverse adverse events were hydrocortisone and clemastine. Regarding discharge, 74.3% of patients left the clinic within 60 minutes after the symptoms switched, with four patients (3.8%) being transferred to the emergency department.

Table 6 focuses on the treatment of adverse events according to the severity scale. Similar to Table 5, it displays the number of occurrences for each treatment modality within each severity grade. Treatments listed include hydrocortisone, clemastine, methylprednisolone, adrenaline, and metoclopramide.

Table 6 – Treatment of adverse event according to Severity scale

Symptoms	**Severity according to Ring and Messmer Scale**				
	Grade I	**Grade II**	**Grade III**	**Grade IV**	**Total**
Hydrocortisone	63	5	14	5	87
Clemastine	62	4	12	5	83
Methylprednisolone	28	2	3	5	38
Adrenaline	0	1	2	2	5
Metoclopramide	1	1	4	1	7
Total	**154**	**13**	**35**	**18**	**220**

Discussion

Currently, the incidence of IRCM adverse reactions is difficult to accurately assess, which can potentially lead to an underestimation. This is due to the progressive developments of IRCMs, the difficulty in diagnosis and the absence of a mandatory registration that exposes these reactions, making them underdiagnosed and underreported. [213]. During the development of this study, data from reports of iopromide were requested to the Portuguese National Competent Authority, INFARMED I.P., to compare with our original data. During the same period, only 413 reports were collected in Portugal and only 31 in the region where the study was performed, contrasting with the 105 adverse events found in our study. This observation underlines the low reporting of adverse reactions to the pharmacovigilance national system. Other studies point that the main relative risk factors for developing hypersensitivity reactions are associated with a previous history of reactions with contrast media, bronchial asthma, drug allergy, food allergy and the female sex [35, 214].

In the adult population, when comparing the data published in the bibliography with the results obtained in this study, it was found that mild acute adverse reactions occur in 0.7-3.1% and 0.6%, respectively. The overall incidence of adverse events in our cases were 0.67%. Regarding immediate serious adverse events, the percentage in this study was calculated based on the total number of Grade IV events (n=9) divided by the total number of cases during the study period (n= 15640), resulting in an incidence of 0.058%. In similar studies, the overall incidence of hypersensitivity events was similar, with the range reported by other studies, for example, Zhang et al (0.16%–0.21%) [94], Sodagari et al (0.48%) [202], Kim et al (0.02%–0.05%) [203] and Endrikat et al (0.62%) [152]. In pediatric patients, Dillman et al. reported a rate of 0.18% of acute allergy-like reactions in this population [204]. Studies reporting serious adverse drug

reactions in large databases have described cases with rate of 0.01%[154], 0.02% [8, 205], 0.03% [189] and 0.04% [196] so the results presented in this study are quite higher (0.058%, n=9).

The safety profile of the contrast agent was established during the clinical trial; however, it is important to acknowledge the limitations of clinical trials, which often involve a relatively small number of participants and are conducted over a specific time period, making them less representative of real world evidence. Clinical trials also tend to have controlled and artificial conditions, which may not fully reflect the complexities and variations encountered in routine clinical practice. While the incidence of adverse events was determined in the clinical trial, it is essential to recognize that real-world evidence of drug usage can differ significantly. Factors such as misuse, medication errors, and several drug interactions (including drug-drug, drug-food, and drug-disease interactions) can influence the safety and effectiveness of the medication. Moreover, calculating the incidence of adverse drug reactions based on clinical trial data may not provide an accurate representation. Adverse drug reactions are primarily reported through spontaneous reporting systems, since this voluntary basis, introduces biases and potential underreporting, making it challenging to estimate the true number of new cases and the actual number of patients using a drug. These limitations should be considered when interpreting the study findings.

Previous studies showed that immediate reactions are predominantly skin symptoms, self-limited and of mild severity, [36] which is in accordance with the obtained results, with papules (57.1%) and pruritus (40.0%) being the most common symptoms among patients. Regarding discharge, only 4.8% of the patients needed to be transferred or left the clinic after twenty-four hours, with the remaining situations resolving without the need for further intervention or follow-up. Finally, Grade I adverse events (70.5%), were the most prevalent

and had a specific and limited course. Serious adverse events mainly involved respiratory and cardiovascular systems. Concerning medication, it is essential to assess the adverse reactions to choose an appropriate treatment. Due to the lack of randomized controlled studies, ethical issues and the constant development of the IRCMs used in clinical practice, it does not exist a gold standard recommendation to intervene medically, so different interventions may be used according to the clinical specificity of each case itself. In the event of a slight reaction, universal monitoring measures should be taken and, if necessary, a second-generation antihistamine drug, preferably non-sedative, can be administered. If it is impossible to use the oral route, for example, clemastine (the dose in adults is 2 mg IV or IM) may be a therapeutic choice. Comparatively, in this study, mild adverse events were resolved with the administration of an antihistaminic (clemastine) and a corticosteroid (hydrocortisone), to reduce the risk of developing cutaneous and also respiratory symptoms [37, 201]. In the moderate to mild reaction, the approach should be appropriate to the patient's clinical severity. In this study, in addition to the administration of hydrocortisone and clemastine, there was, in most cases, the need to also administer adrenaline, metoclopramide or methylprednisolone (Table 6).

Polypharmacy is a common phenomenon, particularly among elderly patients who often have multiple comorbidities requiring pharmacological management. The use of iopromide, along with other medications, can lead to potential drug interactions that may impact its effectiveness or increase the risk of adverse events. For example, interactions between iopromide and medications such as metformin and interleukin-2 have been described, as well as in the treatment and diagnosis of thyroid diseases with thyrotropic radioisotopes, which can be compromised due to reduced radioisotope uptake. Interleukins are associated with an increased prevalence of delayed hypersensitivity / anaphylactoid reactions after iodinated contrast agent administration.

These reactions include flu-like symptoms, fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, oliguria, and joint pain. Regarding metformin, in patients with acute kidney failure or severe chronic kidney disease, biguanide elimination can be reduced leading to accumulation and the development of lactic acidosis. This can lead to renal impairment onset or aggravation in patients treated with metformin, with an increased risk of developing lactic acidosis. Lastly, radioisotopes used in the diagnosis and treatment of thyroid disorders with thyrotropic radioisotopes may be impeded for up to several weeks after administration of iopromide due to reduced radioisotope uptake [215]. These interactions can have implications for the treatment and diagnosis of thyroid diseases with thyrotropic radioisotopes, as reduced radioisotope uptake may occur. In this context, we found that adverse events were more commonly observed in the elderly population, particularly among individuals aged 51-60 and 61-70 years. This finding is consistent with the higher prevalence of polypharmacy in older age groups, leading to an increased risk of adverse drug reactions due to potential drug-drug interactions, altered pharmacokinetics, and physiological changes associated with aging. Moreover, the cumulative burden of multiple medications can place additional stress on the body's organ systems, potentially exacerbating the risk of adverse events. It is important to acknowledge that obtaining comprehensive data on polypharmacy and interactions can be only done in post-marketing surveillance, which is particularly important among elderly patients who often have multiple comorbidities.

In any degree of severity, surveillance must be maintained for at least thirty minutes after the resolution of symptoms and adjust the time to remain in the clinic depending on the resolution of adverse events. Before leaving the clinic, patients should receive important information. This includes being informed about the nature of the reaction they may experience. They should also receive clear

instructions on what to do if symptoms reappear, such as going to an emergency department and alerting health professionals about the test they underwent, and the contrast used. Lastly, if they need to undergo another iodinated contrast test in the future, they should be advised to inform the medical staff about any previous adverse reactions they have had. When there is an indication of an earlier reaction or risk factors for the development of adverse reactions, the way to prevent it from a re-occurrence is to administer pre-medication with corticosteroids and antihistamines as prophylaxis for an eventual reaction [37].

Strengths and Limitations

The strength of this article lies in its robustness, from the substantial number of contrast administrations and recorded adverse events within the study period. The extended duration of the study allows for a more comprehensive and reliable assessment of the occurrence and characteristics of adverse events associated with contrast agent usage.

First, the absence of causality assessment for the observed adverse events to determine whether all events can be classified as adverse drug reactions is a major limitation. It is important to acknowledge that without such assessment, we cannot definitively attribute all events to the use of the contrast agent. However, it is worth noting a strong time relationship between the administration of the contrast agent and the occurrence of adverse events. This temporal association suggests a potential link, but further causality assessment would be required to establish a definitive relationship between the contrast agent and the adverse events.

The study has certain limitations that are primarily related to the quality of the information recorded by the center when an adverse reaction occurs. The registration of adverse events during the use of

iopromide was conducted on a voluntary basis by the nursing team. However, it is important to acknowledge that some adverse events may not have been properly registered for various reasons, including complacency, diffidence, indifference, ignorance, ambition to publish, fear of legal consequences related to the ADR, insecurity and lethargy, as referenced in Inman's work and confirmed in several publications about pharmacovigilance in Portugal [5, 63, 159, 216]. This highlights the potential for underreporting of adverse events, which should be taken into consideration when interpreting the findings of this study. Another limitation of the study is associated with the unavailability of a specific reporting form for adverse events. Instead, adverse events were recorded in a notebook that was designated for this purpose. However, the reports were not standardized, as each healthcare professional recorded the information, they deemed most important to describe the case. As a result, in some instances, crucial details might have been missing from the recorded data. To address this limitation, a potential outcome of this study could be the introduction of a dedicated form for registering and reporting adverse events in the clinic where the study was conducted. Implementing such a form would promote consistency in data collection, ensuring that all relevant information is captured uniformly for future studies and enhancing the clinic's ability to effectively monitor and address adverse events associated with iopromide usage.

Another limitation is that no data regarding the frequency of premedication usage and its correlation with adverse events was available for this study. However, the inclusion of such data would provide valuable insights into the effectiveness of premedication in preventing adverse reactions. Specifically, it would be informative to analyze the number of patients who received premedication, the number of those who still developed adverse events despite premedication, and the severity of those events. Additionally, comparing these findings to the group of patients who did not receive

premedication would further enhance our understanding of the impact of premedication on adverse reactions.

Conclusion

In conclusion, the study reveals the presence of serious adverse events associated with iopromide usage, as described in the Summary of Product Characteristics. However, the incidence of ADRs in real-world settings is often uncertain or underestimated. This study also highlights the low reporting of adverse events to the national pharmacovigilance system, indicating the need for improved reporting practices. The study findings also emphasize the significant underreporting of adverse reactions associated with iopromide usage, when compared with the data obtained from the Portuguese National Competent Authority, INFARMED I.P., revealing a remarkably low number of adverse reaction reports in comparison to the adverse events identified in this study. The overall incidence of adverse events in the study cases was 0.67%, with a calculated incidence of 0.058% for immediate serious adverse events. These findings align with similar studies reporting comparable incidence rates of hypersensitivity reactions. Notably, the incidence of adverse events in this study was higher than those reported in large-scale databases, emphasizing the importance of vigilance when using iopromide. Most frequent symptoms were local, as skin adverse events, including papules, pruritus, and erythema. Common medication used to reverse adverse events were frequently hydrocortisone, clemastine and methylprednisolone. Improved reporting practices and a more comprehensive approach to capturing adverse events are crucial to obtaining a more accurate understanding of the risks and safety profile of iopromide. The key points to reduce the incidence of adverse reactions is to have a good clinical history and the identification and correct classification of adverse reactions to the drug, thus being able to reverse them in the most adjusted way.

Declarations

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Conflicts of interest: The authors declare no conflict of interest.

Ethics approval: This is a retrospective study using data already captured in a database; for this type of study no formal consent is required.

Consent to participate: Not applicable.

Consent for publication: The authors have obtained the written consent for data use and publication from the clinic where the data was collected. The document was approved by the clinic before publication.

Availability of data and material: The datasets presented in this study are available on request from the corresponding author.

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Authors' contributions Conceptualization: J.J. and R.M-C.; Methodology, J.J., C.M and R.M-C.; writing—original draft preparation, J.J., writing—review and editing, J.J., C.M and R.M-C.; All authors have read and agreed to the published version of the manuscript.

4. All-round approaches to increase adverse drug reaction reporting: a scoping review

All-round approaches to increase adverse drug reaction reports: a scoping review

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RESUMEN

Introducción

La medicación es la tecnología más eficaz para reducir la mortalidad y la morbilidad. Las reacciones adversas a medicamentos (RAM) son un problema de salud pública bien reconocido y una de las principales causas de muerte y hospitalización. La seguridad de los medicamentos solo puede establecerse una vez que han estado en el mercado durante varios años. Mantener las reacciones a medicamentos bajo vigilancia a través de sistemas de farmacovigilancia (PV) es indispensable. Sin embargo, el subregistro es un problema importante que socava la eficacia de los informes espontáneos.

Objetivos

Nuestro trabajo presenta una revisión sistemática sobre el uso de sistemas de información para la promoción de la notificación de RAM. Este trabajo tiene como objetivo describir las estrategias que utilizan los profesionales de la salud y los pacientes para promover la notificación de las RAM.

Métodos

Esta revisión de alcance se realizó de acuerdo con el marco de Arksey y O'Malley. Una búsqueda en PubMed (MEDLINE), Scopus y Cochrane Database, desde el inicio hasta 2020. Se incluyeron artículos centrados en la notificación espontánea de RAM. Los estudios publicados revisados por pares, de cualquier región del mundo, realizados con un diseño cualitativo, cuantitativo o de métodos mixtos y centrados en las preguntas de investigación, fueron elegibles para su inclusión. El informe siguió la lista de verificación Elementos de informe preferidos para revisiones sistemáticas y extensión de meta-análisis para revisiones de alcance (PRISMA-ScR). Dos revisores independientes realizaron la extracción y síntesis de datos estandarizados.

Resultados

Seis estrategias mejoraron la recopilación de informes de RAM, a saber, incentivos económicos, intervenciones educativas para profesionales de la salud y pacientes, atención de los medios, uso de redes sociales en la búsqueda proactiva de RAM y aplicaciones para teléfonos inteligentes y campañas. Estas estrategias permitieron la evolución en PV, permitiendo la detección temprana de RAM graves por parte de la industria y los reguladores. La creación de estrategias que permitan la implicación de los pacientes destacó su papel en la VP.

Conclusión

El camino futuro en la seguridad de los medicamentos depende únicamente de la PV proactiva por parte de todos los intervinientes, donde los pacientes juegan un papel vital en la notificación de RAM. La implementación de métodos innovadores es esencial para fomentar la notificación de RAM.

Palabras clave

“farmacovigilancia”; “reacción adversa a medicamentos”, “sistemas de notificación de reacciones adversas a medicamentos”; "medicamento"; “Informes de ADR”

Abstract

Introduction Medication is probably the single most effective technology to reduce mortality and morbidity. Adverse drug reactions (ADRs) are a well-recognized public health problem and a major cause of death and hospitalization. The safety of drugs cannot be established until it has been on the market for several years. Keeping drug reactions under surveillance through pharmacovigilance (PV) systems is indispensable. However, underreporting is a major issue that undermines the effectiveness of spontaneous reports. Our work presents a systematic review on the use of information systems for the promotion of ADR reporting. The aim of this work is to describe the strategies using to promote ADRs reporting, by health professionals and patients.

Methods A scoping review was performed with research articles and online multimedia used with the purpose of promoting ADRs reporting.

Results Six strategies improved the collection of ADRs reports, namely economic incentives, educational interventions for health professionals and patients, media attention, the use of social networks in the proactive search for ADRs, and applications for smartphone and campaigns. These strategies allowed evolution in PV, enabling the early detection of serious ADRs by industry and regulators. The creation of strategies that enable patients' involvement highlighted their role in PV.

Conclusion The future path in drug safety is solely dependent on proactive PV by all intervenient, where patients play a vital role by ADRs reporting. The implementation of innovative methods is essential to encourage ADRs reporting.

Keywords "pharmacovigilance"; "adverse drug reaction", "adverse drug reaction reporting systems"; "medicine"; "ADR reporting"

Introduction

Nowadays, medication is acknowledged as crucial in health care, becoming the most effective technology used to reduce mortality and morbidity. However, the ageing of population by the increase of average life expectancy, accompanied by a predominance of degenerative and chronic diseases, the increasing consumption of medicines, namely elderly, bespeak the occurrence of adverse drug reactions (ADRs) as an inevitability[217].

ADRs are a leading cause of morbidity in developed countries as well as increase in the number of hospital admissions (2.4%-6.5%, many of which preventable), representing a substantial burden on health-care resources[218]. For instance, some countries spent 15% to 20% of their hospital budgets to treat ADRs complications[219]. Taken these factors, the concerns in drug safety have steeped the bar of safety by various stakeholders, more significantly by the regulatory authorities [220].

It is considered that a large proportion of serious ADRs are detected only after drug approval since many of them are rare and/or manifest only in the long term[27]. In this way, the continuous surveillance of medicine, after its marketing authorization, is assumed to be essential. Therefore, the detection of drug risks as well as the ability to defend the marketed product against inappropriate use constitutes the essential expertise and skills which are attained by a sound role of pharmacovigilance (PV)[221]. PV aggregates skills for the detection, evaluation, understanding, and prevention of ADRs or any other drug-associated problem as the ultimate purpose are minimizing risks and maximizing the benefits of medicinal products[222].

The World Health Organization (WHO) has an international drug monitoring program, responsible for the exchange of information between countries, which promotes PV[221]. Through the Uppsala

Monitoring Centre (UMC), PV is promoted through the exchange of information and policies between countries. This Centre is responsible for international drug monitoring and managing technical and scientific aspects of the WHO PV network [223]. In January 2023, , 155 countries were part of this international program as effective members and 21 as associates, which covers about 99% of the world's population [223].

The ADRs received by the WHO are stored in the Vigibase® database for the spontaneous reporting, which contains the reports sent by the various member states enrolled in the program. Currently the databse have over 30 million reports.[41]. In Europe, supervision and promotion of PV are ensured by the European Medicines Agency (EMA)[224], and ADRs are registered in a database called EudraVigilance®, where all reports of ADRs by national regulatory authorities are sent of each to the countries of the European Union[225].

One of the limitations of PV is the low rate of ADR reporting. In many countries, PV systems have started collecting information exclusively from health professionals[18]. Due to poor adherence and insufficient information collected, new strategies were adapted to increase information about ADRs. Due the inexperience of the ADR reporting systems by patients it was necessary to raise awareness and promote the dissemination of these systems in order to boost the participation by patients in PV and reduce underreporting by professionals[226].

In 2010, through directive 2010/84/EC, patients were able to report directly to their country's national PV system, leading to an increase in the number of ADR reports[227]. This directive contributed to the early detection of ADRs, a better understanding of the impact on the patient's life, and the capture of subjective elements in ADR narratives, promoting consumer rights and equity[228-230]. In addition, reporting by patients makes a valuable contribution to detecting new signs or strengthening pre-existing signs and provides information about the

conditions of drug use[8]. Since then, several studies have shown that the contribution of patients goes beyond a quantitative contribution, providing a new dimension of PV[39].

Health professionals and patients have several methods to report ADRs to competent authorities. The most common are online or paper forms, but there are other options like by letter, mobile phone, or in some countries through smartphone applications[39, 228]. Each country adapted the most effective way, in order to increase the number of reports according to the resources and capacities available[8]. In a study carried out in 50 countries, 44 had spontaneous reporting systems for patients, with reports from these representing about 9% of the total reports received in these countries, with the remainder coming from health professionals[229]. In another international study with 144 countries, about 31.2% had implemented a reporting system specially designed for patients, which highlighted the simplified reporting forms, with appropriate language for patients and support texts for filling out the reporting form[39]. A positive impact on PV has also been observed in all countries that have implemented patient reporting systems, such as the description of the severity of ADRs[39] and the increased understanding of the impact of ADRs on the patient and the safety awareness of the population[228].

Currently, there are several measures that promote the collection of ADRs, both for health professionals and for patients. Of these, economic incentives stand out[231]; educational interventions for professionals and patients[232]; media attention[42]; use of social networks in the proactive search for ADRs[232, 233], or smartphone applications[232].

Collectively, this work scrutinizes forefront evidence of the different methods used to increase the collection of ADRs, surveying the different strategies used by countries to increase the collection of

reports, describing the tools used to improve participation in the systems of PV by professionals or by patients.

Material and Methods

This review was prepared using the scoping review methodology described by Arksey and O'Malley [234] in order to identify the different methods used to increase the collection of ADRs. To ensure the thorough completion of this scoping review, the guidelines set forth by the Joanna Briggs Institute[235, 236] were utilized to impart clarity and rigor to the review process. The results of this scoping review were reported using the PRISMA-ScR checklist, which ensured a transparent and methodological approach was taken[237].

Search Strategy

The search strategy aimed to find published and unpublished studies. A pilot search by PubMed was undertaken to identify articles on the topic. The text words contained in relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for the PubMed search engine. The search strategy, including all identified keywords and index terms, was adapted for each included information source. No geographical or cultural limitation or year of publication limits for the studies included was applied.

The following databases were searched from inception onwards on acceptance of this protocol: PubMed (MEDLINE), Scopus and Cochrane Database, chosen as they are the recommended databases to provide a comprehensive, but manageable search. The literature search was supplemented by scanning the reference lists of included studies and searching grey literature sources, such as Google Scholar, as well as conference proceedings and abstracts published by journals and

organizations, including but not limited to the ISOP and ISPE annual congresses.

A revised search was created and PubMed® and Google Scholar® databases were searched using the keywords “Pharmacovigilance”, “ADRs”, “medicine” and “spontaneous reporting”.

Literature Screening and Information Selection

Articles published between 2005 and 2020, in English that addressed the issue of ADR reporting were selected. First, titles and abstracts were screened independently by three reviewers for relevance. Articles prior to 2005, which do not focus on the subject under study, and whose analysis of the title and abstract do not present relevant information for the review were excluded. For this review, information present in digital means of communication (webpage, social media, etc.) of the Competent National Authorities was also included in order to obtain information about the methodologies used in promoting the reporting of adverse reactions by patients. 46 publications were found in PubMed® and 8 in Google Scholar®. Figure 1 demonstrates the bibliographic selection process. After obtaining the articles according to this methodology, the bibliographic references were analyzed to identify other relevant studies. After a deeper analysis of the abstracts of the articles, those that did not reveal importance for the study were excluded. However, some of the excluded articles had important references that were used later. All duplicate articles were also excluded. As a result of this methodology, 24 articles were obtained, and some information was present in digital media (web page, social media, etc.), which represents the sample for this review. All the results are organized in the following Table 1 organized by strategy, placing the most relevant information about the theme, and grouping

the information of the respective strategy by author, year and reference, country, and collection method.

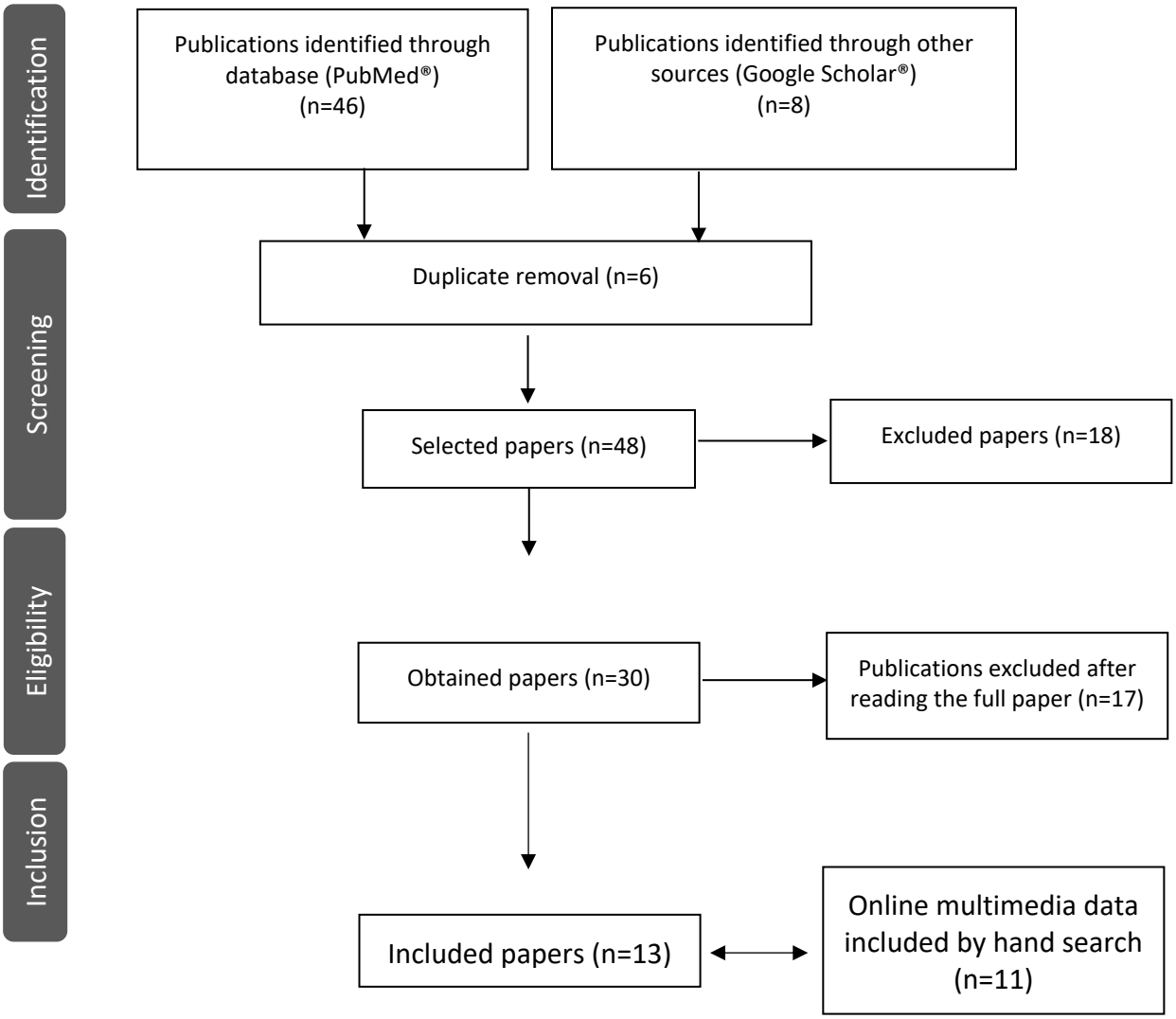

Figure 1: Screening process and included and excluded articles.

Literature Screening and Information Selection

Quantitative and qualitative data were extracted from articles included in the review by two independent reviewers using a data extraction tool developed by the reviewers as indicated by the methodology for scoping reviews proposed by the Joanna Briggs Institute[18].

The data extracted were grouped by strategy to improve Patient reporting and details from Author, Country and Type of information as

well as the main outcomes details and key findings relevant to the review´s objective were presented. Any disagreements that arise between the reviewers were resolved through discussion, or with a third reviewer. The results are presented in Table 1.

Critical appraisal

Since the objective of this scoping review is to provide an overview of the available literature on a specific topic or research question. Unlike traditional systematic reviews, scoping reviews do not focus on critically appraising the quality of individual studies or synthesizing the results in a meta-analysis. The primary objective of a scoping review is to identify the breadth and depth of the available evidence and to identify gaps in the research. Given this objective, critical appraisal of individual studies is not necessary for a scoping review. Instead, the focus is on identifying all relevant studies and providing a descriptive overview of the evidence, rather than evaluating the quality of the individual studies. Thus, the lack of critical appraisal in a scoping review is appropriate and justified given the objectives and goals of this type of review.

Results

Economic incentives

Economic incentives aimed to increase the number of ADR reports through a bonus, with physicians and patients[238, 239]. In the studies presented, there was an increase in the number of reports with the offer of an incentive compared to the previous year and the number of serious reports, observing its use in combination with other

strategies[53]. As an advantage, they have high adherence by health professionals[239], however not all countries have the resources to implement this measure, in the studies presented only countries such as Sweden[238], China[33] and the Iran[53] implemented this strategy. Additionally, this kind of approaches can increase the frequency of fraud and stimulate the false reporting.

Educational interventions

In the studies included in this review, there was observed an increase in the number of reports after educational interventions[53, 240-242], with multiplication of the report rate and improvement in quality[241, 242], quantity[39] and relevance[39, 242], with ADRs reporting not mentioned in the summary of product characteristics[241]. Furthermore, there was an increase in the number of reports after the intervention period, with a subsequent decrease[242]. On the other hand, the combination of interventions, namely, active educational interventions carried out by telephone interviews[39, 239], workshops[39, 53], group sessions[242], educational seminars[53], meetings[53, 240, 242], lectures[53], conferences, training and passive interventions such as educational material [240, 242], ADR reporting form[242], campaign promotion and e-mails[53] was suggested to have better results in both short and long term, maintaining the number of reports for longer period[53].

Educational interventions allowed the knowledge in drug safety and promotion of spontaneous reports, improving quality, quantity and relevance, but presented as a disadvantage the decrease in the number of reports of ADRs after the intervention period[39, 241, 242].

Media attention

The media revealed a powerful approach to increase ADRs reporting, as people are increasingly costumed with social media like social networks. Their purpose is to raise awareness of the importance of communicating suspected ADRs[52], disseminating information material and campaigns on major social networks such as LinkedIn®, Instagram®, Facebook®, Twitter®, Youtube® and Snapchat®, reaching many views worldwide[54]. In the studies observed, there was a peak in reports after the transmission of possible ADRs in two drugs, offering the possibility for patients and health professionals to be able to report ADRs that cause an impact on the patient's daily life. However, the massive increase in reports is verified, but only in the short term[40, 42].

The use of the various measures referred to is again related with the level of development and resources of each country. Developed countries preferentially use social networks and existing applications for smartphones, as they are easier to access[232]. WHO, through the international drug monitoring program, allows the exchange of information between countries regarding campaigns, educational material and videos on PV, which can later be adapted to the reality of each country. Sweden, where the WHO-UMC is located, is an example of proactivity in PV, promoting campaigns[51], educational interventions[241], publications in the media[54], publication of scientific posters[54-56] and international journals on PV[238, 241], and in the development of the smartphones application[43, 49]. In addition to Sweden, the United Kingdom, Croatia and the Netherlands, at European level, are also involved in various PV activities, such as campaigns[58, 243], programs broadcast in the media[40, 42], and also have applications for smartphone for ADRs reporting [43, 44, 49, 56, 59].

Social networks

Social networks are a promoting measure in PV and proactive search for ADRs, with a higher number of ADRs detected through these than by the commonly used methods and in a shorter period[48]. According to data observed in this study, Facebook offered more detailed and better-quality information compared to Twitter®[46]. WEB-RADR is based on a data mining process, which has been successfully applied[47, 55]. Social networks can offer information about medicines, allow the detection of signs of efficacy of medicines not available in traditional sources, enable the detection of subjective and sentimental reactions, with low cost and high agreement regarding to traditional methods[48]. On the other hand, there were presented some disadvantages as duplications, medical condition may not be precisely defined, the existence of privacy policies and the difficulty in detecting and normalizing medical events[46, 55]. With the technological advances social networks can be used as a source of information about ADRs in the future[44].

Smartphone apps

The strategy of collecting ADRs through smartphone applications is recent, with the first application being launched in July 2015, in the United Kingdom and later in the Netherlands and Croatia[56]. In the analyzed articles, it was observed that the submission time is shorter through these when compared to traditional methods and the submissions were more complete[59, 232]. Additionally, the applications allowed the subscription of news about the medicines that the patient takes[44, 49, 56], able to be used in several countries, free download, and important for ADRs reporting with other quality for both PV and signal detection[49]. As benefits, they have easy accessibility

to reporting forms[56], help drug manufacturers and regulators to detect safety signs early, being able to intervene early[44] and reduce the time spent on paper reports[49]. However, they have the disadvantages of the large volume of reports received, patients may not correctly assess causality, very limited signal detection and unclear regulation[233].

Educational campaigns

The campaigns aim to involve the public in PV actions and supervise the safe use of drugs[58], recognizing and reporting suspected ADRs[51]. They are practiced through billboards, press advertisements, radio, online images, posters in waiting rooms and leaflets[58]. It was observed in one of the campaigns, coordinated with the media, to promote the recognition and of ADRs reporting, which reached 27 countries, reaching 2.3 million people on social networks, with 1,852 new reports of ADRs during their occurrence[51]. Thus, the campaigns make it possible to raise awareness among patients and health professionals about the importance of reporting an ADR, allow obtaining additional information about the medications and positively influence the prevention of side effects, without offering any disadvantages[58].

Table 1- Schematic matrix of interventions to improve ADRs reporting.

Strategy	Author (year), Reference	Country	Method	Main outcomes
Economic incentives	Bhatia A *et al* (2005), [239]	India	Research Article	- Lack of awareness and resources were the most important factors leading to underreporting; - The establishment of more ADR reporting and monitoring centers, awareness workshops, a multidisciplinary team approach to ADR reporting, and legalized monitoring of products by pharmaceutical companies were suggested for increasing ADR collection; - 66% of private physicians and 75% of physicians in government hospitals wanted incentives to be offered for reporting ADRs.
	Bäckström M *et al* (2006), [238]	Sweden	Research Article	- In the intervention area there was an increase in the number of ADRs reported by 59% compared to the same time period in the previous year; - Increase in the number of serious ADR reports; - 15% of study participants expressed the opinion that economic incentives could be a positive.
	Chang F *et al* (2017), [231]	China	Research Article	- In 2009, a bonus of 20 RMB (Chinese currency) was awarded for each spontaneous reporting of ADRs and a fine of 50 RMB for any withheld reporting; - Pre-intervention period: average of 29 ADR reports; 1st period: 277; 2nd period: 666; - The monthly number of notified ADRs was stable in the three periods: 3.56 ± 3.60 / month, 21 ± 13 / month in the first intervention period and 56 ± 20 / month in the second intervention period; - 128 (pre-intervention), 753 (1st), 2001 (2nd) reports of ADRs, where 40% were new ADRs.
	Khalili M *et al* (2020), [53]	Iran	Research Article	- 9 studies assessed the impact of financial rewards and incentives; - One study used this intervention: 4.8-fold increase in ADR reports; - In the rest, prizes and financial incentives were used in combination with other interventions (electronic registration, sending reminders and/or feedback and educational interventions), the ADR reporting rate increased from 1.2 to 23.0 times.
Educational interventions	Herdeiro MT *et al* (2008), [242]	Portugal	Research Article	- Increased of ADRs reporting: 275.63 *per* 1,000 pharmacists/year; - Multiplication of the report rate of ADRs: severe, 10 times; unexpected, 4 times; high causality, 9 times; and new drug reports, 9 times. - Reporting stimulated by a 1-hour educational intervention; - Number of reports from pharmacists increased 5.9 times; - Improved reports regarding quality and relevance.
	Johansson M *et al* (2009), [241]	Sweden	Research Article	- Increase in the number of reports: 89 (2006) to 111 (2007); - 25% increase in the number of reports compared to 2006 (P = 0.037); - Reports of high quality before and after the intervention were 36 and 48%, respectively, in the intervention group and 40 and 36%, respectively, in the control group; - 16 reports concerned ADRs not mentioned in the SmPC (intervention group); - Increase in the number of reports, but it was not possible to detect an isolated effect of the intervention;

Table 1- (Cont.).

Strategy	Author (year), Reference	Country	Method	Main outcomes
Media attention	Hunsel FV *et al* (2009), [42]	Netherlands	Research Articl	- Peak of ADR reporting after program transmission; - Patients: 265 reports on statins with 780 ADRs (average of 3 ADRs per report); - Health Professionals: 833 reports with 1609 ADRs (average of 1.5 ADRs per report); - Patient reports provided more information about the impact on daily life.
	Rolfes L *et al* (2016), [40]	Netherlands	Research Article	- 1800 reports (2013-2015) after the Thyrax packaging were transformed from glass to blister (93% from patients); - 1167 people who notified responded to the ears; - Patients who reported possible ADRs showed a significant decrease in health-related quality of life; - Increase in the number of reports compared to the period between 2006 and 2010; - 85% of reports sent after attention in the media, national television coverage and communication in newspapers - Patients considered the impact of an ADR on their quality of life an important issue and reported it more frequently than health professionals.
	UMC (2017), [52]	Middle East	Magazine-Uppsala Reports 77: Project Report Me kuwait;	- Aimed to teach how to report ADRs and increase the awareness of health professionals about the urgency of reporting ADRs; - Short videos, information cards and brochures on medication safety; - More than 2,600 followers on LinkedIn, around 1,300 on Instagram and a growing presence on Facebook, Twitter, Snapchat and YouTube; - Featured on TV shows and local newspapers; - 8 reports were received, in spite the absence of an official PV structure in the country.
	Santoro F *et al* (2019), [54]	Sweden	Poster-UMC	- Campaign with 32 drug regulators from the EU, Latin America, Australasia and the Middle East;; - Sharing campaign materials on social networks; - The animations reached 1.4 million people on Twitter, Facebook, LinkedIn, Instagram and YouTube; - Have been viewed more than 360,000 times.

Table 1- (Cont.).

Strategy	Author (year), Reference	Country	Method	Main outcomes
Social networks	Marinela Z *et al* (2011) [48]	Serbia	Research Article	- In seven months, 21 ADRs were reported: 4 ADRs (19%) defined, 11 (52%) probable and 6 (29%) possible; - Strong causal relationship with medications, suggesting high sensitivity of this instrument for reporting ADRs; - High yield of reported ADRs (2%) when compared to other interventions aimed at the general public; -Low cost of intervention.
	UMC (2017), [57]	Europe	Magazine-Uppsala Reports 75	- 21 European National Competent Authorities and their national PV and regional monitoring centers launched an ADR awareness campaign on social media; - Disseminated messages with the objective of encouraging the increase in the report of suspected ADRs; - 13% increase in report of ADRs (1,056 reports) - The messages reached 2,562,071 people through social networks: Twitter, Facebook; LinkedIn and YouTube; - 337,781 people viewed the animation - NAMMD saw a 350% increase for ADRs from all sources, with a 67% increase (700 reports) in direct reports from consumers and healthcare professionals.
	Pierce CE *et al* (2017), [46]	Boston	Research Article	- 935,249 publications collected from Facebook and Twitter (03/2009-10/2014); - 98,252 identified with Proto-AE; - 13 selected for evaluation of drug-adverse event causality, leaving 6 with interest that described possible and probable cases; - Of the 10 safety signs identified by the FDA, 2 were associated with the 13 publications; - Increased number of posts on Twitter due to advertisements in pharmacies, references to financial reports and links to articles or literature related to drugs; - Facebook posts offered high quality, with more detailed information;
	Gattepaille LM *et al* (2018), [55]	Sweden	Poster-UMC	- Method of recognition of ADRs on Twitter, developed in WEB-RADR; - Through the method, 316 tweets from ADRs were selected - Accuracy of 36% and a sensitivity of 23% - major difficulties in the method: detecting and normalizing medical events and transferability of models outside the universe of main data to external datasets is low.
	Dietrich J *et al* (2020), [47]	Germany	Research Article	- Benchmark database used after collecting publications on Twitter; - 57,473 sampled tweets, which mentioned 1 of the 6 selected drugs; - Publications about ineffectiveness, nervous system/psychiatric disorders or problems of use; - 1.8% of tweets were identified as positive adverse event, through the database; - Contained 1396 drug-event combinations, comprising 292 different MedDRA® Preferred Terms; - 83.9% drug-event combinations were confined to 4 MedDRA® organ classes; - 18.5% of tweets contained indicative information, comprising 25 different Preferred Terms; - 95% of tweets contained a maximum of 2 adverse events; - Of the tweets with an adverse event, 88.3% (n=932) refer to the 3 most mentioned drugs (methylphenidate, zolpidem and levetiracetam).

Table 1- (Cont.).

Strategy	Author (year), Reference	Country	Method	Main outcomes
Smartphone apps	Taavola H *et al* (2017), [56]	Sweden	Poster- UMC	- WEB-RADR developed an application, based on a simplified report form; - Allowed subscription to news about the patient's medication; - Launched in the UK (07/2015), Croatia (05/2016) and the Netherlands (01/2016); - 144 reports were received from the United Kingdom, 37 from Croatia and 106 from the Netherlands; - Significantly higher proportion of reports through apps in the UK (28%) and Croatia (32%); - The proportion of at least moderate quality reports was high in both groups in all countries, but relatively lower in app reports: 83% vs 92% in the UK; 78% vs 78% in Croatia; and 85% vs 98% in the Netherlands;
	Montastruc F *et al* (2017), [232]	France	Research Article	- VigiBIP allowed the communication of data or photographs of ADRs; - 4102 reports, 133 (4.7%) through VigiBip and 3909 (95.3%) through other methods; - Patients and health professionals report more through VigiBip
	Donovan BO et al (2019), [59]	UK	Research Article	- Yellow Card registered largest number of reports received (8,272), in 2018; - 2708 (88.5%) people used the internet to report ADRs, 98 (3.2%) the telephone and 247 (8.1%) paper forms; - 2015 presented a huge growth in Internet reporting, from 13% to 88%, compared to 2005;
	UMC (2020), [49]	International	Megazine- Upssala Reports 82	- Med Safety app (WEB-RADR App) recognizes ADRs; - Watchlist of drugs of interest and sharing of news articles on social networks; - Important for reporting ADRs along with other methods; - Access to the latest information on drug safety; - More than 5000 downloads
	WEB-RADR, [43]	International	Website- WEB-RADR	- Use of social networks and new technologies for PV purposes; - Development of applications that allow reporting ADRs, provide updated information and news alerts; - Launched specific applications for each country: United Kingdom (MHRA), Netherlands (Lareb) and Croatia (Halmed); - Med Safety app was created and launched in Burkina Faso, Zambia, Armenia, Ghana, Ethiopia and Botswana;
	IMI, [44]	Europe	Website- IMI	- HALMED launched the application (WEB-RADR) in Croatia; - More than 10,000 downloads; - Health professionals, health care providers, and patients directly report ADRs and receive reliable information about medications; - Helps drug manufacturers and regulators to detect new safety signals and intervene early; - Implemented to support malaria programs (Burkina Faso and Zambia), with a positive impact; - 12 more countries expressed interest in the application and have already adopted it in some contries.

Table 1- (Cont.).

Strategy	Author (year), Reference	Country	Method	Main outcomes
Educational campaigns	HALMED (2013), [58]	Croatia	Website-HALMED	- Promoted the importance of reading the information leaflet and reporting ADRs; - Positively influence in the prevention of side effects; - Annual continuous education of pregnant women, health professionals and the public about the risks of self-medication during pregnancy and lactation; - Motivation of patient involvement in medication and monitoring the safe use of medication; - Reduction of unnecessary and inappropriate use of antibiotics; - Intensive public education on the rational and appropriate use of antimicrobial drugs in the treatment of milder respiratory infections;
	MHRA (2018), [243]	UK	Website-MHRA	- Involved 32 drug regulators - The Yellow Card app allow additional questions about drug exposure during pregnancy.
	UMC (2018), [51]	International	Magazine - Uppsala Reports 78	- Coordinated with the media to promote recognition and reporting of suspected ADRs; - Participation of 27 countries - Reached 2.3 million people on Twitter, Facebook, LinkedIn and YouTube; - 1,852 new reports of ADRs during the campaign; - Increase of 11% compared to the two months before the campaign.

Legend:

BoMRA- Botswana Medicines Regulatory Authority; **EMA**- European Medicines Agency; **FDA-**Food and Drug Administration; **FAERS-**FDA Adverse Event Reporting System; **ICSR-** Individual Case Safety Reports**; IMI**-Innovative Medicines Initiative; **WHO**- World Health Organization ; **MedDRA**- Medical Dictionary for Regulatory Activities; **MHRA**-Medicines and Healthcare products Regulatory Agency; **NAMMD-**National Agency for Medicines and Medical Devices of Romania; **ADR**- Adverse Drug Reaction; **PPU-** Porto Pharmacovigilance Unit; **PUSS**- Pharmacovigilance Unit of Setúbal and Santarém; **UMC-**Uppsala Monitoring Centre; **ARIIS**-Adverse Reaction and Incident Information System; **PNFS**-Portuguese National Pharmacovigilance System

Discussion

In spite of recent increased number of reports by patients, recent studies emphasize the need to raise awareness among patients and health professionals of the ongoing need to promote the reporting of ADRs[18]. In addition, it is crucial that competent authorities implement innovative methods to strengthen ADR reporting for overcome barriers such as the lack of active promotion due to scarcity of resources to support publicity campaigns and the inability to deal with an overload of reports[39].

This scoping review consisted in an innovative search screening that collected a panoply of different approaches for the encouragement of ADRs report. However, there was some limitations to highlight, such as the lack of articles on economic incentives within the inclusion criteria. This is due to the lack of economic resources in some countries to adopt this measure, and the reduced information on the use of social networks and smartphone applications in the consulted databases, due to the recent use of these two methods in PV. Here, we found six strategies to improve the collection of ADRs reports in PV, namely economic incentives, educational interventions for health professionals and patients, media attention, the use of social networks in the proactive search for ADRs, and applications for smartphone and campaigns.

The implementation by several countries of an ADR reporting system for patients allowed them to spontaneously report an ADR, providing a major advance in PV, increasing the number of ADR collections and early detection of signs[39]. Patients are more likely to report severe reactions[18], provide more information about the impact on quality of life, and report more frequently than healthcare professionals[40].

Advances in reporting methods and more proactive promotion of PV, such as the use of smartphone applications, online forms for reporting

- as is the case with the ADR reporting portal, massive use of social networks, dissemination campaigns and educational interventions, make reporters be more aware about the problems related to the use of the drug, accompanying by the growing number of adverse reactions reported annually [41]. Through these means, the various tools that enable reporting are disclosed, providing the patients involvement in an active way, where many are unaware of the existence of a PV system in the country, where only young people and people with higher education had some knowledge about the report possibilities[18].

Each country adopted the best strategies to encourage spontaneous ADRs reporting, considering the characteristics of its population, available resources, and the development of PV system. In some countries, it has been observed that media attention to certain ADRs increased populations attention and awareness of PV, indicating that dissemination had a positive impact on the collection of ADRs[39, 40, 42]. In 2014, the launched of WEB-RADR project that worked on the development of a smartphone application allowing the report of suspected ADRs to regulators in the European Union, enabling direct and instantaneous reports for patients and health professionals, and a means for regulators to communicate with interested parties the latest information on PV[39, 43, 44]. This application is already in use in several European countries, such as the United Kingdom, the Netherlands and Croatia [56], with more than 10 thousand downloads[44]. According to WEB-RADR project, is possible to detect, extract, standardize and analyze information related to social networks, which can be used as a source of information about ADRs in the future[44]. With advances in technology, social networks and smartphone applications are increasingly being used, which suggests that in the future they will be the most successful methods for reporting adverse reactions[44].

The use of social networks is a method with high sensitivity [45] and quality[46], a greater number of ADRs detection and high agreement compared to traditional methods, which allows more detailed information[47] and above all is a low-cost method[48]. Smartphone applications have a simplified reporting form, make it possible to subscribe to news about the medications that the patient is taking, present the latest information on medication safety and are capable of being used in several countries[44, 49].

WHO, through the international drug monitoring program, allowed the exchange of information between countries regarding campaigns, educational material and videos on PV, which can be later adapted to the reality of each country[50]. Sweden, where the WHO-UMC is located, is an example of proactivity in PV promoting campaigns[51, 52], educational interventions[53], publication of scientific posters[54-56] and international journals on PV[49, 51, 52, 57], and also in the development of the smartphone application[43, 49]. In addition to Sweden, the United Kingdom, Croatia and the Netherlands, at European level, are also involved in various PV activities, such as campaigns[58], programs broadcast in the media[40, 42], and also have applications for smartphone for report of ADRs[43, 44, 49, 56, 59].

Collecting ADRs reports and efficiently using that information remains an ongoing challenge. The potentially reporting population needs regular interventions, if possible combined with other interventions, so that patients know how to recognize, assess causality, and correctly report an ADR. Furthermore, adequate programming support must also be available to ensure the implementation of strategies with proven efficacy.

Conclusion

Raising awareness among patients and health professionals is crucial for promoting the ADRS reporting. This review collects and synthesize the different approaches used by several counties in order to increase the reports of ADRs. The implementation of innovative methods such as economic incentives, educational interventions, media attention, and the use of social networks and smartphone applications is necessary to improve the collection of ADRs reports in PV. Therefore, patients play a vital role and are increasingly involved in the drug safety process since they were able to report ADRs in an increasing number of countries.

Several countries have adopted different strategies to encourage spontaneous ADRs reporting, and international organizations like WHO are involved in promoting PV through exchange of information and campaigns. Clearly, the implementation of innovative methods such as economic incentives, educational interventions, media attention, and the use of social networks and smartphone applications is necessary to improve the collection of ADRs in PV. The use of social networks and smartphone applications are increasingly being used as successful methods for reporting ADRs.

The future path and providence of drug safety is solely dependent on proactive PV throughout the involvement of all intervenient.

CHAPTER 4

DISCUSSION

IV. DISCUSSION

An adverse drug reaction (ADR) refers to any undesirable and unintended outcome experienced by a person as a result of taking a medication. These reactions can include both expected and unexpected effects, ranging from therapeutic to non-therapeutic consequences. While all individuals who take medication are potentially at risk of encountering ADRs, how each patient perceives this risk can differ significantly.

When individuals consume medications, they do so to improve their health or manage a particular condition. However, medications can sometimes lead to unwanted side effects that vary in severity and impact. These adverse reactions can manifest as physical symptoms, psychological effects, or changes in the overall well-being of the individual.

The occurrence of ADRs can depend on several factors, such as the specific medication being taken, the dosage, the duration of use, and individual variations in physiology and metabolism. Additionally, certain populations, such as the elderly or those with compromised organ function, may be more susceptible to experiencing ADRs.

Patient perception of the risk associated with ADRs can greatly influence their decision-making process and overall medication adherence. Some individuals may be aware of potential side effects and be prepared for them, while others may have limited knowledge or misconceptions about ADRs. Moreover, previous experiences with medications, either personal or through word-of-mouth, can shape an individual's perception of ADRs. Factors like anxiety, fear, and past negative experiences with medications can further contribute to a heightened perception of the risks involved[25-27].

The current study highlights a concerning perception of risk among individuals and healthcare professionals. Many people hold a strong belief that medications are inherently safe and effective, assuming that extensive research and development processes guarantee their reliability while disregarding potential risks. Moreover, there is a misconception that medications prescribed by doctors are inherently more trustworthy. Another troubling finding is the belief that generic prescription medications are less effective compared to their brand-name counterparts.

Interestingly, the study indicates that individuals with higher levels of education tend to acknowledge that there is no substantial difference between prescription and over-the-counter medications. However, they still hold the belief that generic prescription medications are inferior to other available options in terms of effectiveness.

These perceptions of risk can have significant implications for medication adherence and patient health outcomes. When individuals trust medications without considering the potential risks, they may overlook or downplay adverse drug reactions and fail to report them to healthcare professionals. This can lead to underreporting of ADRs and hinder the identification of potential safety concerns.

To address these misconceptions, it is crucial to improve public education and raise awareness about the potential risks associated with medications, regardless of their prescription status or brand name. Healthcare professionals play a key role in fostering open and transparent communication with patients, discussing the benefits and risks of different treatment options, and addressing any concerns or misconceptions they may have.

Additionally, promoting accurate information about generic medications and dispelling the belief that they are inherently less effective can help individuals make more informed decisions about their treatment options. Providing evidence-based resources and

empowering patients to actively participate in their healthcare decisions can contribute to a more balanced perception of medication risks.

The participant's understanding of the Portuguese Pharmacovigilance System was also deemed adequate. However, when questioned about the reporting process used by the organisations, the literacy levels stay the same, preventing patients from actively reporting ADR. The prospect of using an integrated reporting system for ADR identification and management is something that 46,2% of respondents, despite their partial awareness of the reporting system, are aware of it. Younger and older age groups represent the age group with little information on the Portuguese Pharmacovigilance System. Higher qualified individuals are unquestionably more knowledgeable about ADR and the critical necessity to report them.

Healthcare professionals play a crucial role in addressing patient perceptions and concerns about ADRs. Effective communication between patients and healthcare professionals can help alleviate anxieties and provide accurate information regarding the likelihood and severity of potential adverse effects. By fostering a trusting and open dialogue, healthcare professionals can empower patients to make informed decisions about their treatment plans, including weighing the potential benefits against the risks of ADRs.

The perception of risk can significantly impact patient behaviour [28], as patients who perceive a high risk of ADRs may choose not to take their medications or hesitate to start new medications. This can have a negative impact on their health and may result in the use of alternative therapies that are not evidence-based. Looking for the factors that can influence the risk perception of patients, it is possible to highlight the age, previous experiences, culture and beliefs and fear and anxiety [28].

Consumer experience is essential because it gives ADR reports significance and value and makes it possible to identify potential new reactions. As a result, healthcare professionals need to gradually gain more authority to recognise probable ADRs, report them, and fully inform patients of the side effects of medications and the Portuguese Pharmacovigilance System. [5,29] The behavioural influence of health professionals on patients can be great. Thus, patient-centered communication is a key issue for the patient to exert an active role in the decision-making process of healthcare systems.[18,19,30] Among several hot topics to fulfill, issues comprising the recognition of the regulatory requirements and the education on applicable standards and responsibilities regarding product safety are widely encouraged.[30,31] Communication channels must be improved to translate patients' concerns about ADRs into effective awareness by routine reporting within pharmacovigilance systems.[32]

In the context of deprescribing medications, healthcare practitioners must have a comprehensive understanding of risk perception. This understanding can help identify individuals who may benefit from dosage reduction or discontinuation of certain medications. By utilizing deprescribing techniques to critically evaluate medications, clinicians can enhance patient safety and improve overall health outcomes by reducing the likelihood of adverse drug reactions. By considering risk perception, healthcare practitioners can assess how patients perceive the potential risks and benefits associated with their current medication regimen. This evaluation involves understanding patients' concerns, beliefs, and attitudes toward their medications, including any apprehensions they may have about adverse effects or long-term use.

Based on this understanding, healthcare professionals can identify patients who might be at a higher risk of experiencing adverse drug reactions or who could potentially benefit from reducing or stopping specific medications. By engaging in shared decision-making with

patients, clinicians can discuss the potential benefits and risks of deprescribing, taking into account individual patient preferences and priorities.

Deprescribing involves a careful review of medications to determine if they are still necessary or if alternative treatment options may be more suitable. This process aims to simplify medication regimens, reduce polypharmacy (the use of multiple medications), and minimize the potential for drug interactions and adverse effects.

By implementing deprescribing strategies, healthcare practitioners can improve patient safety by mitigating the risks associated with medication use. This approach requires ongoing monitoring, regular reassessment of treatment plans, and effective communication with patients to ensure their understanding and cooperation. [33]

The studies underscore the inadequate awareness among patients regarding adverse drug reactions (ADRs) and national reporting systems. It is crucial to prioritize future initiatives that aim to improve public outreach for patient safety and involve pharmacovigilance systems.

There is a significant need to educate patients about ADRs, ensuring they have access to accurate and comprehensive information. Many individuals may not be fully aware of the potential risks associated with the medications they are taking or the importance of reporting any adverse effects they experience. Enhancing public outreach efforts can help bridge this knowledge gap and empower patients to make informed decisions about their healthcare.

Furthermore, involving pharmacovigilance systems is essential for gathering comprehensive data on ADRs and monitoring medication safety at a national level. These systems play a critical role in detecting and evaluating potential risks associated with medications. By actively engaging patients and healthcare professionals in reporting ADRs,

pharmacovigilance systems can capture a broader range of data, leading to improved patient safety.

Although imaging-related medications (contrast agents), commonly used to improve visualization of biomedical imaging, are generally considered to be safe, they occasionally result in adverse events in patients. While the ideal imaging agent provides enhanced contrast with little biological interaction, it has been perceived a significant rate of adverse reactions to iopromide, a low osmolar non-ionic monomeric contrast medium containing iodine [23]. Yet, the risk of under-reporting, particularly in the national healthcare private biomedical imaging system, continuously hinder the early detection, assessment and prevention of ADR or any other medicine-related problem.

As stated in the second article, the included research's huge sample sizes improved the validity of the results and made it possible to uncover even rare ADRs. The article also highlighted a few risk variables linked to ADRs to iopromide, offering guidance to CMs.

The existence of certain conflicting results, which may be related to variations in study designs, demographics, or methodology, was one of the study's shortcomings. Most of the trials in the study focused on short-term or acute adverse reactions, which might not accurately reflect the long-term safety profile of iopromide. Finally, even though the evaluation acknowledged links between specific risk factors and ARs, additional confounding factors that were not considered or adjusted in these studies could affect the results.

The occurrence of IRCM side effects is currently difficult to identify, which may cause reality to be underestimated. This is because IRCMs develop slowly, are challenging to identify, and are not required to register, which exposes these reactions and leads to underdiagnosis and underreporting. [34] The main relative risk factors for developing hypersensitivity reactions are associated with a previous history of

reactions with contrast media, bronchial asthma, drug allergy, food allergy, and the female gender [35].

Previous studies showed that immediate reactions are predominantly skin symptoms, self-limited and of mild severity[36], which follows the obtained results, with papules (57.1%) and pruritus (40.0%) being the most common symptoms among patients. Finally, grade I reactions (70.5%) were the most prevalent and had a specific and limited course. Serious reactions mainly involve the respiratory and cardiovascular systems. Concerning medication, it is essential to assess the adverse reactions to choose an appropriate treatment.

Since there is no gold standard suggestion due to a lack of randomised controlled research, ethical concerns, and the ongoing development of the IRCMs used in clinical practice, various therapies may be adopted depending on the clinical distinctiveness of each case. In this study, mild reactions were resolved by administering an antihistaminic (clemastine) and a corticosteroid (hydrocortisone) to reduce the risk of developing cutaneous and respiratory symptoms. In some cases, it was necessary to reinforce it with methylprednisolone due to the persistence of symptoms[37].

There is a growing body of research that highlights the discovery of previously unrecognized adverse drug reactions associated with contrast media, which are commonly used in medical imaging procedures. One such example is the emergence of nephrogenic systemic fibrosis as a novel side effect in recent years. This underscores the importance of closely monitoring and studying the adverse effects of contrast media.

The identification of new adverse drug reactions associated with contrast media calls for increased attention and vigilance in monitoring their potential risks. Nephrogenic systemic fibrosis, in particular, has been recognized as a significant side effect that warrants careful consideration and investigation.

To ensure patient safety, it is crucial to conduct comprehensive surveillance and monitoring of adverse effects related to contrast media. Healthcare professionals, regulatory agencies, and researchers should collaborate to establish effective pharmacovigilance systems that track and analyse adverse events associated with these agents.

By closely monitoring the adverse effects of contrast media, healthcare professionals can gain a deeper understanding of their potential risks and take necessary precautions. This knowledge can inform clinical decision-making, patient counselling, and the development of guidelines to minimize the occurrence and severity of adverse reactions.

Furthermore, healthcare professionals should stay updated with the latest research findings and participate in continuous education and training programs. This will enable them to effectively recognize and manage adverse reactions related to contrast media, thereby improving patient outcomes and reducing potential harm[38].

Despite the recently increased number of patient reports, recent studies emphasise the need to raise awareness among patients and health professionals of the ongoing need to promote the reporting of ADRs[18]. In addition, competent authorities must implement innovative methods to strengthen ADR reporting to overcome barriers such as the lack of active promotion due to the scarcity of resources to support publicity campaigns and the inability to deal with an overload of reports.[39]

The scoping study for the third article included an innovative search screening that gathered various strategies for promoting ADRs report. Nevertheless, there were certain drawbacks to point out, such as the absence of articles on financial incentives under the inclusion requirements. This is because some nations need more financial means to implement this measure and because social networks and smartphone applications have only recently been used in PV, there is

less information about their usage in the checked databases. Here, we identified six methods to enhance the collection of ADR reports in PV, including financial incentives, patient and healthcare professional education initiatives, media attention, the use of social media for proactive ADR search, and smartphone apps and campaigns. The implementation by several countries of an ADR reporting system for patients allowed them to spontaneously report an ADR, providing a major advance in PV, increasing the number of ADR collections and early detection of signs[39]. Patients are more likely to report severe reactions[18], provide more information about the impact on quality of life, and report more frequently than healthcare professionals[40].

The use of smartphone applications, online reporting forms, such as those on the ADR reporting portal, widespread use of social media, dissemination campaigns, and educational initiatives, along with improvements in reporting procedures and more proactive promotion of PV, make notifiers more aware of the issues associated with the use of the drug and are accompanied by an increase in the number of adverse reactions reported each year.[41] Through these means, the various tools that enable reporting are disclosed, providing the patient’s involvement in an active way; where many are unaware of the existence of a PV system in the country, only young people and people with higher education have some knowledge about the report possibilities[18].

Every country has devised its own set of policies to encourage the spontaneous reporting of ADRs based on factors such as population characteristics, available resources, and the level of advancement of their PV systems. In some nations, the media's coverage of ADRs has played a crucial role in generating public interest and awareness regarding PV, thereby facilitating the collection of ADR reports. Recognizing the unique needs and circumstances of their populations, countries have implemented tailored strategies to promote ADR

reporting. These strategies consider factors such as healthcare infrastructure, technological capabilities, and the level of healthcare accessibility. By aligning their policies with these specific considerations, countries can optimize the effectiveness of their PV systems and encourage healthcare professionals and patients to report ADRs. Media coverage of ADRs has proven to be influential in increasing public interest and knowledge about PV. When ADRs receive extensive media attention, it generates awareness among the general population regarding the importance of reporting such incidents. This heightened awareness contributes to a greater number of ADR reports being submitted, providing valuable information for PV activities. The distribution of information through media channels has proven beneficial for the collection of ADR reports. It catalyzes public engagement, encouraging individuals to share their experiences and report any suspected adverse reactions they have encountered. Media coverage can also educate the public about the potential risks associated with medications, empowering patients to make informed decisions and actively participate in the monitoring of medication safety. It is important to acknowledge that each country's approach to promoting ADR reporting should be tailored to its specific context and requirements. By understanding the population's characteristics, allocating appropriate resources, and continuously advancing their PV systems, nations can effectively enhance the spontaneous reporting of ADRs.[39, 40, 42] In 2014, the launched of WEB-RADR project worked on the development of a smartphone application allowing the report of suspected ADRs to regulators in the European Union, enabling direct and instantaneous reports for patients and health professionals and a means for regulators to communicate with interested parties the latest information on PV. [39, 43, 44] This application is already used in several European countries, such as the United Kingdom, the Netherlands, and Croatia [56], with over 10 thousand downloads.[44] According to the WEB-RADR project, it is possible to detect, extract,

standardise, and analyse information related to social networks, which can be used as a source of information about ADRs in the future[44]. With technological advances, social networks, and smartphone applications are increasingly being used, which suggests that they will be the most successful methods for reporting adverse reactions[44].

The use of social networks is a method with high sensitivity [45] and quality[46], a greater number of ADRs detection, and high agreement compared to traditional methods, which allows more detailed information[47] and, above all, is a low-cost method[48]. Smartphone applications have a simplified reporting form, making it possible to subscribe to news about the patient's medications, present the latest medication safety information, and use it in several countries.[44, 49]

The WHO international drug monitoring program allows the exchange of information between countries regarding campaigns, educational material, and videos on PV, which can be later adapted to the reality of each country[50]. Sweden, where the WHO-UMC is located, is an example of proactivity in PV-promoting campaigns[51, 52], educational interventions[53], publication of scientific posters[54-56], and international journals on PV[49, 51, 52, 57], and also in the development of the smartphone application.[43, 49] In addition to Sweden, the United Kingdom, Croatia, and the Netherlands, at the European level, are also involved in various PV activities, such as campaigns[58], programs broadcast in the media[40, 42], and also have applications for smartphone for a report of ADRs.[43, 44, 49, 56, 59]

The collection of ADR reports and the effective use of that data continue to be challenged. Patients must get frequent interventions, ideally in combination with other interventions, in the potentially reporting population to recognise, determine the cause, and properly report an ADR. Additionally, sufficient programming support must be made accessible to guarantee the application of proven effective solutions.

CHAPTER 5

CONCLUSIONS

V. CONCLUSIONS

In conclusion, adverse drug reactions are unwanted and unpleasant side effects that can occur as a result of taking medications. While all medication users are susceptible to ADRs, the way individuals perceive this risk can vary greatly. Understanding and addressing patient perceptions of ADRs is essential for promoting medication adherence and ensuring patient well-being. Through effective communication and education, healthcare professionals can help patients make informed decisions about their treatment while mitigating concerns related to ADRs. Healthcare practitioners must be thoroughly trained, employ the proper communication style, and consider the patient's gender, age, and cultural background to explain hazards to patients successfully. Innovative strategies must be used to inform people about reporting processes and their significance. However, such discussion should be handled cautiously, in a small group, ideally one-on-one rather than in front of others. Alternatively, it may result in disorder and confusion among the patients, interrupting therapies due to the miscommunication of several people from various socioeconomic and racial backgrounds. Due to their traits, older populations are more likely to struggle to adhere to the ADR reporting technique. The national pharmacovigilance system, particularly the reporting process of suspicious reactions, should be made more widely known.

The ADRs linked to iopromide show how their frequency varies depending on various variables like age, gender, and underlying medical issues. Iopromide has a higher incidence of ARs than other contrast agents like iopamidol and iodixanol, according to some research. To fill in the research gaps and increase our understanding of the safety profile of iopromide, we needed more studies on the subject. These studies should include well-designed prospective

studies, randomised controlled trials, and investigations into long-term safety.

Despite all the available data, using iopromide carries some hazards, and its safety profile is not yet completely established. It can be challenging to appropriately interpret these reactions, given that older and those who take several medications have a higher frequency of unfavourable IRCM reactions. Taking a thorough clinical history, identifying adverse reactions, and classifying them correctly can all help reduce adverse occurrences.

Using iopromide CM is considered safe despite the possibility of minor adverse reactions and the extremely low frequency of significant adverse events. To produce a more representative profile, gathering data from additional hospitals and clinics is crucial. Overall, this study urges additional research to document the negative effects of CM treatment.

To encourage the reporting of ADRs, it is important to raise awareness among both patients and healthcare professionals. This study examines various strategies employed by different countries to enhance ADR reporting and synthesizes them. To effectively increase the collection of ADR reports within pharmacovigilance (PV) systems, innovative techniques such as financial incentives, educational interventions, media engagement, and the use of social networks and smartphone applications must be implemented. Notably, patients now have the opportunity to report ADRs in an expanding number of countries, signifying their crucial role and increasing involvement in the drug safety process. International organisations like WHO are actively interested in promoting PV through exchanging knowledge and campaigns. Several nations have established various techniques to boost spontaneous ADR reporting. Improving the collection of ADRs in PV calls for cutting-edge strategies, including financial incentives, educational interventions, media attention, and the usage of social

networks and smartphone applications. Social media platforms and smartphone apps are used more frequently as effective tools for reporting ADRs.

The future direction and assurance of medication safety rely solely on proactive PV practices that involve the active participation of all stakeholders. A considerable amount of work is yet to be done in order to exponentiate the benefits derived from patients reporting, both a contribution to and an expression of "health literacy" that has a considerable influence on evidence-based regulatory decisions to preserve and protect patients' health statuses.

Pharmacovigilance serves as a critical component of ensuring the safety and efficacy of medications throughout their lifecycle. It involves the systematic collection, analysis, and evaluation of data related to ADRs and other drug-related problems. By identifying and understanding potential risks associated with medications, PV aims to prevent harm and improve patient outcomes.

CHAPTER 6

REFERENCES

VI. REFERENCES

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APPENDIX

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REVIEW ARTICLE

All-round approaches to increase adverse drug reaction reports: a scoping review

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Abstract

Introduction Medicines are among the most effective technologies for reducing mortality and morbidity. Adverse drug reactions (ADRs) are a well-recognised public health problem and a major cause of hospitalisation and death. Even though the evaluation of the safety of drugs is performed throughout the entire life cycle of a given compound, the postmarketing phase still displays a chief role. In this sense, the surveillance of drug reactions through pharmacovigilance (PV) systems is indispensable. Yet, underreporting is a major issue that undermines the effectiveness of spontaneous reports. This work presents a scoping review on the use of information systems and strategies used to promote ADR reporting by health professionals and patients.

Methods A scoping review was conducted under Arksey and O'Malley's framework. A search on the PubMed (MEDLINE), Scopus and Cochrane databases was conducted from 2005 until 2022. Articles with a focus on the spontaneous reporting of ADRs were included. Peer-reviewed published studies from any region in the world conducted with a qualitative, quantitative, or mixed-methods design focused on the research questions were eligible for inclusion. The reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist. Two independent reviewers performed standardised data extraction and synthesis.

Results This work discloses six strategies aimed to improve the collection of ADR reports, namely economic incentives, educational interventions for health professionals and patients, media attention, the use of social networks in the proactive search for ADRs, applications for smartphones and campaigns. These strategies allowed PV systems evolution, enabling the early detection of serious ADRs by industry and regulators. Creating strategies that enable patients' involvement are highlighted across PV systems.

Conclusion The future path in drug safety solely depends on proactive PV approaches carried out by all stakeholders, where patients play a vital role in ADR reporting. The implementation of innovative methods is essential to encourage ADR reporting.

Introduction

Medicines are essential to healthcare systems and have emerged as one of the most efficient tools for lowering morbidity and mortality. However, due to the significant increase of average life expectancy, the predominance of degenerative and chronic diseases, and the rising consumption of medication, particularly among the elderly, adverse drug reactions (ADRs) are inevitable [1].

ADRs are a leading cause of morbidity in developed countries and are responsible for an increase in hospital admissions (2.4–6.5%, many of which are preventable), representing a substantial burden on healthcare resources [2], with some countries spending 15–20% of their hospital budgets to treat ADR complications [3]. These have raised safety concerns among various stakeholders, particularly regulatory authorities [4], prompting increased attention from healthcare professionals [5, 6] and patient organisations [7, 8] and patients to ensure safety in drug use.

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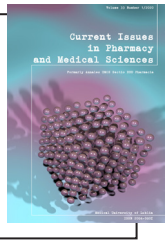

Assessment of risk perception of patients concerning adverse drug reactions

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ABSTRACT

Introduction. The use of medicines involves trade-offs between their therapeutic benefits and inherent risks. Several studies show that numerous adverse drug reactions (ADRs) could be avoided by increasing patients' awareness of medicine's risks. Even though drug labels enclose relevant information about risks and benefits, this information often requires patient education and overall health literacy to improve medication adherence, thereby preventing ADR frequency.

Aim. To describe patient awareness of ADR risks and the Portuguese Pharmacovigilance System.

Methods. A questionnaire comprising 27 questions was conducted at a health centre in Coimbra, Portugal. This study included ninety-one patients and healthcare professionals. Risk perception was scored as positive (≥2.5 points) or negative (<2.5 points). Results were analysed by SPSS v 27.0.

Results. This work highlights poor patient perceptions of risk with a rate of negative responses of 85,7%. Although some responders were aware of the possibility of reporting ADRs, only some participants were familiar with the Portuguese Pharmacovigilance System. Additionally, only five patients – out of the vast majority of those who had previously encountered ADRs – reported the event to INFARMED.

Conclusion. Patient low literacy regarding ADRs and the national reporting systems need to be urgently improved. Patient-centred communication strategies for recognising regulatory requirements and standards of product safety are important measures to achieve effective awareness through routine reporting within the Pharmacovigilance systems.

INTRODUCTION

According to Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010, an adverse drug reaction (ADR) is defined as a "noxious and unintended effect to a medical product" [1]. Such a directive was an outcome of the thalidomide tragedy in 1961, which accelerated the development of an international system aimed at improving drug safety while identifying ADRs previously unknown [2].

In July 2012, Directive 2010/84 was adopted in the several European countries that had committed to implementing an automatic reporting system where healthcare professionals and patients could share integrated notification channels towards active participation [3]. The Portuguese Pharmacovigilance System was earlier, and was put in place in 1992 under the regulatory frame of INFARMED. It was intended to accomplish three challenging goals: i) improve risk/benefit analysis, ii) provide early notice of ADRs' and iii) enable data analysis and accurate information divulgation [4]. Accordingly, every spontaneous report was to be analysed to identify and properly integrate public health concerns. Under the directive, healthcare professionals and patients are both encouraged to report to the Pharmacovigilance System [5-7]. Hospital reports are crucial because they often disclose risks in administration of new and innovative drugs, hence, allowing earlier detection of risk, and more accurate data analysis [8,9]. Still, ADRs elicited by over-the-counter drugs are equally relevant given their frequent misuse due to poor literacy.

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Decision: **initial accept**

Dear Prof. Joaquim,

I am pleased to inform you that your manuscript, entitled: Safety assessment of iopromide contrast media: a narrative review focusing on adverse events (CIPMS-00141-2023-02), has been initially accepted for publication in our journal.

To receive a full acceptance and to have the article published it is required from you to:

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Kind regards,
Editor-In-Chief
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jjj@estescoimbra.pt

De: em.jrsm.0.83daa8.8b3d8344@editorialmanager.com em nome de The International Journal of Risk and Safety in Medicine <em@editorialmanager.com>
Enviado: 7 de junho de 2023 10:23
Para: João Joaquim
Assunto: Your Submission JRS-230021
Anexos: JRS-230021_reviewer 30-May-2023.pdf

Ref.: Ms. No. JRS-230021
Safety assessment of iopromide – A seven years retrospective analysis of adverse reactions The International Journal of Risk & Safety in Medicine

Dear Prof. Joaquim,

Reviewers have now commented on your paper and we are pleased to inform you that your manuscript may be acceptable for publication in the International Journal of Risk & Safety in Medicine pending major revisions. For your guidance, reviewers' comments are appended below.

Please revise your manuscript according to the reviewers' suggestions and provide a point-by-point response to the reviews. Please also highlight the corrections in the text. Should English not be your mother language, we highly recommend that your manuscript is edited by a native English speaker.

Your revision is due by Jul 07, 2023.

To submit a revision, go to https://www.editorialmanager.com/jrsm/ and log in as an Author. You will see a menu item named "Submission Needing Revision". You will find your submission record there. When you submit a revision please ensure to upload the source files of the paper (LaTeX or MsWord) and not only a .pdf copy.

Yours sincerely,

Liliya Eugenevna Ziganshina, MD, PhD, DSci Editor-in-Chief The International Journal of Risk & Safety in Medicine

Reviewers' comments:

Reviewer #1:
1. Is the paper logical with a concise ordering of ideas?
- Yes, but I feel there are a number of areas where additional work is needed or could be made. It is a good topic with presumably solid quality and quite large data.

2. Does the paper describe sound research methods, analysis & interpretation? Are limitations to the study included and discussed?
- Yes, but some additional work is needed. This would both exclude some shortcomings of the paper as well as add value (for example incidence of events).

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies?
- NOT really they mention some earlier sources, but didn't compare results.

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin.
- Seems ok.

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit?