

transplantation, which may ameliorate the reappearance of DIL. Initial positive ANA became negative after stopping cysteamine, but is again positive after reintroduction of cysteamine. Disappearance of ANA, prior to introduction of immunosuppression, is critical evidence supporting cysteamine's role in DIL. Complement levels improved after stopping cysteamine and introducing immunosuppressant medications but have fallen following reintroduction of cysteamine. DIL in our patient was atypical as there was an associated APS, unusual in classical DIL. However, APS secondary to DIL has been described in patients treated with quinidine and penicillamine.

This is the first reported case of DIL and APS secondary to cysteamine therapy. Clinicians should exclude autoimmune abnormalities in patients with cystinosis, especially if patients report non-specific, unusual or unexplained symptoms.

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# Hypotension, as consequence of the interaction between tacrolimus and mirtazapine, in a patient with renal transplant

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## Abstract

The prevalence of psychiatric disorders in dialyzed patients is estimated around 5–20% of the cases. This explains the high use of antidepressant drugs in these patients.

We present the case of a 68-year-old woman with a history of renal failure, with chronic hemodialysis and a depressive syndrome in treatment with Mirtazapine. In November 2008, the patient received a renal graft.

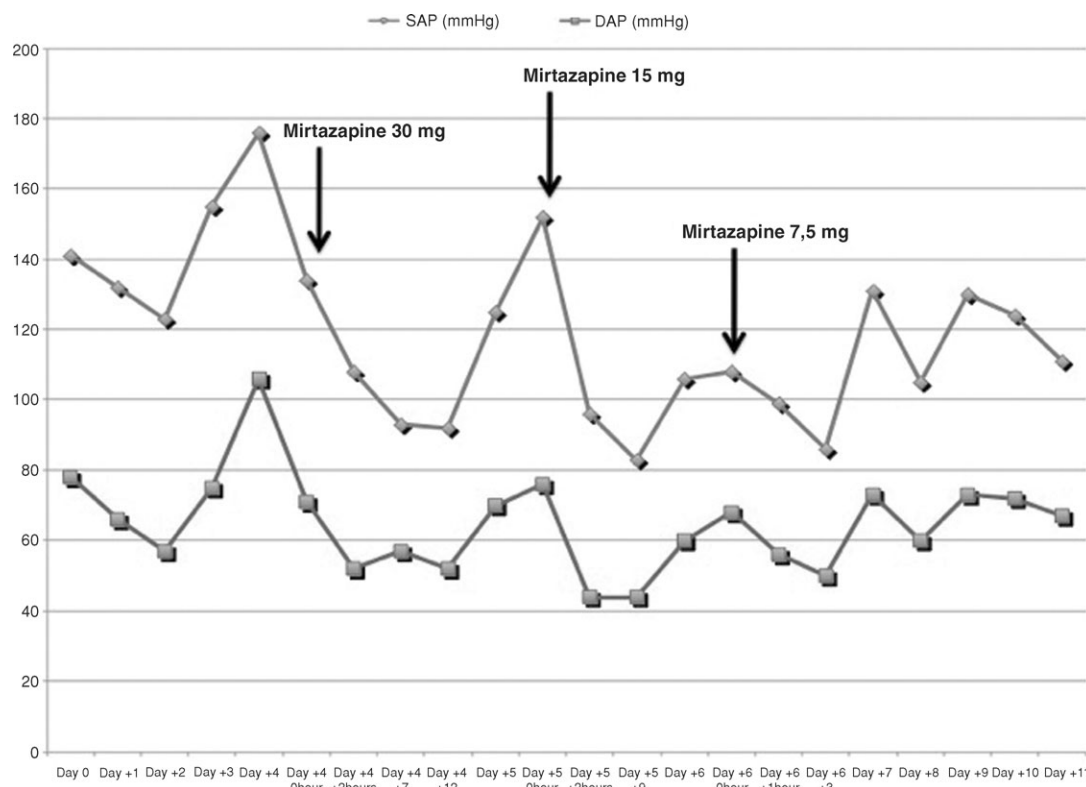
An immunosuppressant treatment was started with Basiliximab, Tacrolimus, Mycophenolate Mofetil, and corticosteroids. The patient did not present renal immediate renal function. Four days after the transplant, the treatment with Mirtazapine was re-applied, with an asymptomatic hypotension after 2 hours, and without surgical complications. Tacrolimus blood levels were higher than 15 ng/ml.

In our opinion, hypotension was a consequence of the interaction Mirtazapine-Tacrolimus in a patient without immediate renal function. This situation has not been described in the literature before, and hypotension could have had negative consequences in the evolution of the graft.

**Keywords:** haemodialysis; mirtazapine; renal transplant; tacrolimus

## Background

Depression follows arterial hypertension, as the chronic condition most frequently found in the general population. In the dialysis population, the prevalence of psychiatric disorders is unknown, but it is estimated to be around



**Fig. 1.** Evolution of the arterial systolic pressure (SAP) and of the arterial pressure diastolic (DAP) after the ingestion of mirtazapine. 234 × 169 mm (72 × 72 DPI).

5–10% [1]. The most important psychiatric problem in dialysed patients is depression, but its diagnosis is complicated by the difficulty in distinguishing between depression symptoms and those symptoms associated with chronic renal failure (CRF) [2]. Drugs are commonly used to treat the psychiatric disorders in dialysed patients. The main factors that need to be taken into account when choosing a drug and adjusting the dosage for patients with CRF are whether the drug metabolizes through the renal or the hepatic pathway, and whether it can be eliminated through dialysis or not.

We present the case of a patient on haemodialysis with depressive syndrome treated with mirtazapine who received a renal transplant. The interaction between tacrolimus and mirtazapine could have had deleterious effects on the post-transplant renal function.

## Case report

We present the case of a 68-year-old woman with CRF secondary to mesangiocapillary glomerulonephritis on chronic haemodialysis. The patient had a history of arterial hypertension and depressive syndrome, and she was receiving treatment with sevelamer, acetylsalicylic acid, omeprazole, pravastatin, levothyroxine, bromazepam and mirtazapine (30 mg/day). In November 2008, she received a renal graft. Immunosuppressant treatment was started with basiliximab, mycophenolate mofetil, retarded release

tacrolimus (0.2 mg/kg/day) and a single dose of corticosteroids. Ninety-six hours after the renal transplant, the antidepressant treatment was restarted with mirtazapine and bromazepam. After the renal transplant, the patient did not immediately recover renal function; thus, haemodialysis was required. The patient was haemodynamically stable directly after surgery, but 2 h after the administration of mirtazapine she presented an arterial pressure of 92/52 mmHg, and 7 h after administration, the pressure was 88/54 mmHg without associated symptoms. Haemorrhagic or infectious complications were ruled out. Given the suspicion of hypotension secondary to treatment with mirtazapine, we decided to progressively remove the drug. During its removal, we observed that after taking each dose of the drug, hypotension appeared, although with less intensity (Figure 1). Tacrolimus blood levels during the first 7 days after the transplant were higher than 15 ng/mL, which forced us to reduce the dose. The patient was hospitalized for 21 days, with good evolution of renal function and tacrolimus blood levels between therapeutic values.

A genetic study was performed, ruling out mutations in the CYP3A4 gene.

## Discussion

Mirtazapine is a new antidepressant drug. It is an antagonist of the pre-synaptic and serotonergic alpha-2 adrenergic receptors 5-HT<sub>2</sub> and 5-HT<sub>3</sub>, which produce an increase in

noradrenergic and serotonergic transmission. It is also an antagonist of peripheral histamine and  $\alpha$ -1 adrenergic receptors, which are responsible for sedation, and orthostatic hypotension can occur. After oral administration, its bioavailability is 50%, and it reaches its maximum plasmatic concentration after 2–3 h, with a high degree of binding with plasmatic proteins (85%) [3] and an elimination half-life of 20–40 h. It is metabolized almost completely by CYP2D6 and CYP3A4, and, to a lesser extent, by CYP1A2. *In vitro* studies reveal that it is a weak competitive inhibitor of CYP1A2, CYP2D6 and CYP3A4 [4].

Tacrolimus, an anticalcineurinic drug commonly used for immunosuppression in renal transplant patients, is metabolized through oxidation by CYP3A4. It is a known inhibitor of CYP3A4; therefore, its concomitant use with drugs that metabolize through pathways that depend on CYP3A4, such as mirtazapine, may affect the metabolism of the drug and significantly increase its levels.

In our case, the patient had received a renal transplant and was under treatment with tacrolimus. The introduction of mirtazapine was associated with episodes of hypotension. Our hypothesis is that the hypotensive effect of mirtazapine was boosted by the high levels of tacrolimus, and possibly by the lack of elimination of this drug through the renal pathway or through the haemodialysis membranes [3]. We believe that a certain degree of interference between the metabolism of tacrolimus and the metabolism of mirtazapine must exist, which has not yet been described.

In conclusion, we warn that the use of antidepressant drugs, specifically mirtazapine, in patients with a renal transplant who are being treated with anticalcineurinic drugs and do not immediately recover renal function, may endanger the evolution of the graft, due to the haemodynamic effects of the drug. We describe for the first time an interaction between mirtazapine and tacrolimus [5].

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