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Case report

Renal Allograft Dysfunction Possibly Caused by Amiodarone Nephrotoxicity: a Case-Report

Nikolina Basic-Jukic[1], Lea Katalinic[1], Marijana Coric[2], Monika Kocman[1], Branimir Krtalic[1] and Petar Kes[1]

[1]Department of nephrology, arterial hypertension, dialysis and transplantation, [2]Department of pathology, University hospital center, Zagreb, Croatia

Abstract

Amiodarone is a potent inhibitor of CYP3A4 and can increase serum concentrations of drugs that are substrates of this enzyme system. Immunosuppressive drugs are also metabolized through the cytochrome metabolic pathway what may lead to important drug-drug interactions.
A 60-year-old female received her second allograft from the deceased donor and was treated with tacrolimus, mycophenolate mofetil and steroids. Amiodarone was introduced for treatment of paroxysmal atrial fibrillation four days after the transplantation. One month after the discharge she was readmitted to hospital for evaluation of the creeping creatinine. Biopsy showed borderline acute rejection. She received 3 boluses of 6-methilprednisolone but creatinine continued to rise. Repeated biopsy was without signs of rejection with mild interstitial fibrosis/tubular atrophy, mild global glomerulosclerosis and moderate arterial sclerosis. However, tubular vacuolization was prominent. After careful revision of her therapy we decided to replace amiodarone with sotalol. One week later her creatinine fell from 350 to 220 μmol/l and remained stable. This case illustrates possible amiodarone nephrotoxicity in a renal transplant recipient. We suggest that patients who need amiodarone in combination with tacrolimus be closely monitored by both cardiologists and nephrologists, with frequent determinations of tacrolimus trough levels and serum creatinine measurements.

Key words: tacrolimus, amiodarone, interaction, renal transplantation, nephrotoxicity

Introduction

Amiodarone is an important drug indicated for the treatment of supraventricular and ventricular arrhythmias, such as atrial or ventricular fibrillation. It is a potent inhibitor of CYP3A4 and may increase serum concentrations of drugs that are substrates of this enzyme system. Additionally, amiodarone may inhibit the P-glycoprotein efflux pump in the intestines thus enhancing absorption of certain drugs. Immunosuppressive drugs are also metabolized through the cytochrome metabolic pathway [1], what may lead to important drug-drug interactions. Several case reports have described QT interval prolongation after concomitant use of amiodarone and tacrolimus [2,3]. Also, amiodarone nephrotoxicity has been demonstrated in animal and observational studies [4-6].
We report a case of kidney allograft dysfunction possibly caused by amiodarone nephrotoxicity precipitated by tacrolimus.

Case report

A 60-year-old woman with end-stage renal disease caused by chronic glomerulonephritis without biopsy received her second allograft from deceased donor in July 2014. First transplantation was performed in 1996, and graft functioned until 2005 when she had restarted with hemodialysis. Immunosuppression consisted of Thymoglobulin induction, tacrolimus (0.1 mg/kg), mycophenolate mofetil 2x1 g and steroids. Amiodarone was introduced 4 days after the transplantation for treatment of paroxysmal atrial fibrillation. She was discharged from the hospital with serum creatinine 212 umol/l 15 days after transplantation, in the sinus rhythm. Other drugs included pantoprazole, bisoprolol, valgancyclovire, trimetoprim-sulphometoxazol, vit D3, furosemid, minoxidil and moxonidine. She was readmitted to the hospital one month later for evaluation of allograft dysfunction with the "creeping" serum creatinine reaching 330 μmol/l. Tacrolimus trough level was 8.2 μg/L. Trimetoprim-sulphometoxazol was immediately omitted. Viruses were negative. Biopsy showed borderline acute rejection with negative C4d. Donor specific antibodies were negative. CML and ADCML were both positive, however, with evident cytotoxicity in the control test of autologous serum what may be consequence of drugs toxicity. She received 3 boluses (500 mg each) of 6-metilprednisolone with no effect. Serum creatinine continued to rise with

no changes indicative for acute rejection on repeated biopsy. Pathohistological finding included mild interstitial fibrosis/tubular atrophy, mild global glomerulosclerosis and arterial sclerosis. However, tubular vacuolization was present (Figure 1) indicating possible toxicity.

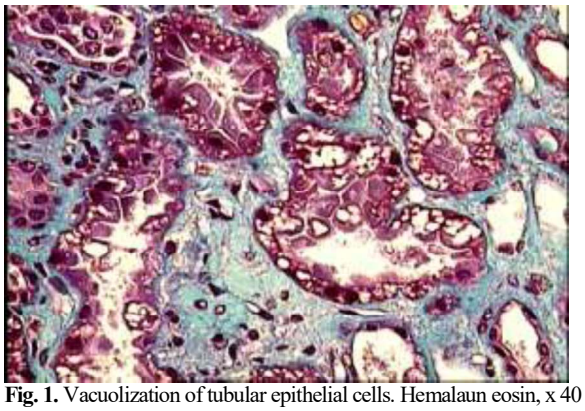

Fig. 1. Vacuolization of tubular epithelial cells. Hemalaun eosin, x 40

After careful revision of her therapy we suspected amiodarone nephrotoxicity and decided to replace amiodarone with sotalol for rhythm control. Seven days after removing amiodarone, serum creatinine fell from 350 to 220 µmol/l and remained stable during the follow-up of three years.

Discussion

We describe a case of a kidney transplant recipient with a possible amiodarone-tacrolimus interaction leading to amiodarone nephrotoxicity. Tacrolimus is metabolized by cytochrome CYP3A4 in liver and small bowel. It is also a substrate for P-glycoprotein, a drug transporter that decreases the absorption and increases excretion of substrates. Amiodarone inhibits both mechanisms and therefore may cause drug-drug interactions [1]. Amiodarone and tacrolimus interactions have been previously described [2,3]. Both are substrates at CYP3A for enzyme metabolism and could potentially be implicated in increasing the concentration of the other agent through competition for metabolism sites.

To our knowledge, this is the first report demonstrating amiodarone-tacrolimus interaction beyond the QT interval prolongation with normal trough levels of tacrolimus. It seems that underestimated drug-drug interaction ultimately induced amiodarone nephrotoxicity.

Previous case reports recommend frequent serum tacrolimus concentration monitoring and prospective tacrolimus dose reductions when the two drugs are given in combination. The amiodarone-induced inhibition of tacrolimus metabolism resulted in significantly lower doses of tacrolimus necessary to achieve proper therapeutic serum concentrations [3]. Much less is known about effects of tacrolimus on possible elevation of amiodarone concentration, which may be clinically important while both animal and observational studies suggested that amiodarone may cause renal impairment by reducing renal blood flow or inducing tubular alterations [4-6].

In conclusion, given the importance of the amiodarone-tacrolimus interaction, we suggest that patients who need amiodarone in combination with tacrolimus be closely monitored by both cardiologists and nephrologists, with frequent determinations of tacrolimus trough levels and serum creatinine measurements. If possible, an alternative agent for control of hearth rhythm in renal transplant recipients treated with tacrolimus should be discussed with cardiologists.

Conflict of interest statement. None declared.

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