Drug Interaction with Pristinamycin in a Kidney and Pancreas Transplant Patient

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Abbreviations: INR: International Normalised Ratio; P-gp: Multidrug Transporter P-Glycoprotein; CYP3A4: Cytochrome P450 Isoenzyme 3A4

Keywords: Drug interaction; Pristinamycin; Immunosuppressant therapy; Transplantation

Abstract

We report the case of a 49-year-old renal and pancreatic female transplant recipient, who presented a drug interaction between tacrolimus, warfarin and pristinamycin. Three days after oral pristinamycin 1000 mg bid administrations, the patient presented nausea, vomiting, abdominal pain and violent headaches that required hospitalization. Tacrolimus trough level was 5 times higher (34.9 µg/l) than the target required (5-8 µg/l) and the INR was 5.8 (therapeutic index between 2 and 3) despite a stable kidney function (serum creatinine 130 µmol/L) and no other organic disorders. Five days following discontinuation, drug monitoring revealed adequate tacrolimus plasma trough concentrations (8.9 µg/l) and the INR subsequently decreased.

Pristinamycin is an antibiotic effective against the majority of Gram positive bacteria. This drug is an inhibitor of the multidrug transporter P-glycoprotein (P-gp) that could lead to the accumulation of tacrolimus. Moreover, pristinamycin IA is the active metabolite of quinupristin/dalfopristin which, is known to be an inhibitor of cytochrome P450 3A4 (CYP 3A4). Our case supposes that pristinamycin is also an inhibitor of CYP 3A4 that can lead to an increase of tacrolimus levels.

This case report brings to light potential drug interactions of pristinamycin with narrow therapeutic index drugs such as tacrolimus and warfarin.

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Pristinamycin, an oral streptogramin antibiotic, has been used widely in France for nearly 50 years in the treatment of staphylococcal and streptococcal infections. It is extracted from Streptomyces pristinaspiralis [1] and has inhibitory activity against a broad range of gram-positive bacteria. It is formed by the pristinamycin IA and the macrocyclic lactone pristinamycin IIA. Each compound is bacteriostatic, but their association is synergic and bactericidal [1].

We report the case of a 49-year-old renal and pancreatic female transplant recipient, who presented a drug interaction between tacrolimus, warfarin and pristinamycin.

Following double kidney/pancreas transplantation in 2005, the patient was treated with a standard triple immunosuppressive regimen including prednisone (5 mg/d), azathioprine (75 mg/d) and tacrolimus (6 mg bid). She was also treated with warfarin for a venous thrombosis of the primitive ilac vein and the pancreatic graft vein. In July 2010, she received oral pristinamycin 1000 mg bid following a dog bite. Neither tacrolimus dose adjustment, nor INR or biological follow up were realised. Three days after pristinamycin initiation, the patient presented nausea, vomiting, abdominal pains and violent headaches that required hospitalization.

Upon her admission, the tacrolimus trough level was 5 times higher (34.9 µg/l) than the target required (5-8 µg/l) and the INR was at 5.8 (therapeutic index between 2 and 3) despite a stable kidney function (serum creatinine 130 µmol/L) and no other organic disorders. Tacrolimus and warfarin were discontinued. Five days after discontinuation, therapeutic drug monitoring revealed adequate tacrolimus plasma trough concentrations (8.9 µg/l) and the INR had subsequently decreased (1.3) (Figure 1). Warfarin anticoagulation and tacrolimus were then reinitiated with the same therapeutic index target. No other drug-drug interaction which could explain such an increase of tacrolimus and INR blood rates was detected.

Immunosuppressant pharmacotherapy is a critically important aspect of post transplant patient care in order to avoid graft rejection and to assure transplantation success [2]. The past 10 years have seen an important increase in the number of immunosuppressive agents and other medications used in transplantation, resulting in more complex medication regimens and greater potential for interactions and adverse effects [3]. Drug interactions with pristinamycin are still not well known due to limited pharmacodynamic and pharmacokinetic evaluations [4].

Phung-Ba et al. [5], have observed that pristinamycin IA could be an inhibitor of the multidrug transporter P-glycoprotein (P-gp). P-gp is a drug efflux pump that works as a biological barrier by extruding toxic substances and xenobiotics out of cells. This transporter can enhance the elimination of drugs out of the hepatocytes, renal tubules, and intestinal epithelial cells into the adjacent luminal space. It is known that P-gp regulates oral bioavailability and tissue distribution of tacrolimus. That is the reason why Pristinamycin IA, by inhibiting the efflux of tacrolimus out of cells, can increase tacrolimus blood levels.
Moreover, quinupristin/dalfopristin, a semi synthetic derivative hydrolysed to the active metabolite pristinamycin IIa, is an inhibitor of cytochrome P450 3A4 (CYP3A4) resulting in multiple drug interactions [6,7]. The effects of quinupristin/dalfopristin 7.5 mg/kg every 8 hours on tacrolimus pharmacokinetics was evaluated in liver transplant patients [6]. A mean increase in tacrolimus concentrations of 1.3-1.4 μg/L was observed over the 3-days study. The significance of this interaction is minor (therapeutic range 5-20 μg/L), but tacrolimus concentration monitoring should be considered with quinupristin/dalfopristin administration. At least, the drug-drug interaction between pristinamycin and cyclosporine is well documented [8,9]. It is postulated that pristinamycin inhibits the metabolism of cyclosporine via the inhibition of CYP 3A4 resulting in a raise of cyclosporine blood concentrations and an increased risk of toxicity [6,10]. According to this observation and knowing that tacrolimus is also metabolized by CYP 3A4 [11,12], our case report confirms the hypothesis that pristinamycin might also be an inhibitor of CYP 3A4 that can lead to an increase of tacrolimus levels. However, there are few data from clinical studies and evidence is weak for recommending tacrolimus dose adaptation when initiating a treatment with pristinamycin. Nevertheless, physicians should be aware of this possible drug interaction and prevent it by a close monitoring of immunosuppressive drugs.

At least, pristinamycin, as well as several antibacterial drugs, is associated with a strongly increased hemorrhagic risk during oral anticoagulant therapy with warfarin [13]. There is no clear explanation for why an interaction might be expected. It is suggested that antibacterial can displace warfarin from protein-binding sites leading to an increase in active concentrations. Other mechanisms include the reduction of intestinal bacterial production of vitamin K2 substances and hence the reduction of synthesis of vitamin-K dependant clotting factors [13]. Awareness of this drug interaction and more frequent monitoring of coagulation status during the initial stages of antibacterial drug therapy may minimize the risk of bleeding complications.

This case report brings to light potential drug interactions between narrow therapeutic index drugs such as tacrolimus or warfarin with pristinamycin. The use of pristinamycin must be carefully monitored in order to avoid concomitant drug accumulation and inappropriate high drug exposure that could lead to dramatic complications particularly in transplant patients.

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