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An interaction between tacrolimus and pristinamycin resulting in an elevated tacrolimus level

We report a case of interaction between tacrolimus and pristinamycin. A 62-year-old man, Mr TM, presented with a 2-day history of increased pain and left knee swelling after a twisting injury. This occurred 1 year after renal transplantation for end-stage kidney disease from membranous glomerulonephropathy, complicated by an episode of acute rejection requiring intravenous immunoglobulin, plasma exchange, pulsed glucocorticoids and antithymocyte globulin. His allograft function had ultimately stabilized (Cr 140 $\mu\text{mol/L}$) on an immunosuppressive regimen including 5 mg tacrolimus twice daily, 720 mg mycophenolate sodium (Myfortic) twice daily and prednisolone 10 mg daily. Other relevant medical history includes epilepsy controlled with stable doses of lev-
etiracetam, carbamazepine and sodium valproate as well as multiple venous thromboembolic events including pulmonary emboli despite inferior vena cava filter, thus requiring anticoagulation with Enoxaparin.

Haemarthrosis was diagnosed after aspirating frank blood (erythrocytes $243\,200 \times 10^6/\text{L}$, $3080 \times 10^6/\text{L}$ leucocytes, negative gram stain). Initially managed conservatively, together with cessation of anticoagulant therapy, Mr TM deteriorated, becoming tachycardic, hypotensive and delirious. Septic screen yielded a positive aerobic blood culture with methicillin-resistant *Staphylococcus epidermidis* (MRSE); thus IV flucloxacillin 2 g 6-hourly and vancomycin 1 g daily (when level $<20\text{ g/L}$) were commenced to treat for septic arthritis. A washout of his affected knee was performed but cultured no organisms. Mr TM improved with antibiotic therapy following the procedure, until fevers developed on Day 4 post washout and antibiotics escalated to ticarcillin/clavulanate 3.1 g 6-hourly and vancomycin.

Trough tacrolimus levels were monitored regularly; these remained stable between 4.8 and 5.2 $\mu\text{g/L}$. Maintaining intravenous access was an ongoing difficulty; thus IV antibiotics were converted to oral pristinamycin 1 g 8-hourly and amoxicillin/clavulanic acid 875/125 mg twice daily after remaining afebrile for 5 days. Following six doses of pristinamycin, the trough tacrolimus level was significantly elevated at 20.9 $\mu\text{g/L}$. The next two doses of tacrolimus were withheld, and intravenous antibiotics reinstituted. Tacrolimus level 24 h later, although trending lower, remained elevated at 9.1 $\mu\text{g/L}$. We recommenced tacrolimus at Mr TM's usual dosing and subsequent levels normalized.

Reviewing the literature, for many years, pristinamycin and cyclosporin have been known to interact. [1, 2] This interaction is attributed to the metabolism of both medications. Pristinamycin is a streptogramin antibacterial synergistically combining a macrolide (Pristinamycin I) with a depsipeptide (Pristinamycin II) [3], and its use is becoming increasingly common, particularly for methicillin-resistant pathogens. It is an inhibitor of cytochrome P450 3A4, while calcineurin inhibitors such as cyclosporin are metabolized by CYP3A4 [3, 4]. This combination results in elevated cyclosporin blood concentrations and potential toxicity.

Tacrolimus was approved by the Therapeutic Goods Administration in September 1998 for use in kidney transplantation. Its use has been steadily increasing; however, its

drug interaction profile is less well known, relative to cyclosporin. As a calcineurin inhibitor, it is also metabolized by CYP3A4 [5] leading to significant potential for interactions with pristinamycin and other CYP3A4 inhibitory medications. In our case, there were no other medications or dietary changes in the days between his normal and elevated tacrolimus levels to explain these changes. Mr TM did not suffer any adverse effects from this transient increase in serum tacrolimus concentration.

From this case, we recommend frequent monitoring of calcineurin inhibitor levels in patients while changing other medications, especially antibiotics in view of the increasing use of both tacrolimus and pristinamycin.

Conflict of interest statement. None declared.

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