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Rashed Bakri
Cormac Breen
Douglas Maclean
John Taylor
David Goldsmith

Serious interaction between tacrolimus FK506 and chloramphenicol in a kidney–pancreas transplant recipient

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R. Bakri · C. Breen · D. Maclean
J. Taylor · D. Goldsmith (✉)
Renal Unit, 4th Floor TGH,
Guy's Hospital, London, SE1 9RT, UK
E-mail: david.goldsmith@kcl.ac.uk
Tel.: +44-20-79555000
Fax: +44-20-79554909

Dear Editors:

Calcineurin inhibition has been the cornerstone of renal and other solid-organ transplantation for the past two decades. Drug interactions with cyclosporine and tacrolimus are a significant problem, due to the involvement in the metabolism of cytochrome P450 systems in the liver and the small bowel. We describe here a serious interaction between tacrolimus and chloramphenicol, the latter being employed to counter a serious urine infection with vancomycin-resistant enterococci.

A 56-year-old man (168 cm, 66 kg, BSA 1.5 m^2) with a 22-year history of insulin-dependent diabetes mellitus and 18 months of peritoneal dialysis for end-stage renal failure, underwent a successful cadaveric kidney–pancreas transplantation (exocrine juices drained into the urinary bladder) in August 2000. Post-operative complications included caecal perforation, abdominal collection requiring laparotomy and ileostomy, pancreatic vessel thrombosis, urinary tract and chest infections, cytomegalovirus infection, and allograft rejection. These were all successfully overcome in the first 10 weeks after transplantation. Baseline immunosuppression was with prednisolone, tacrolimus and azathioprine, later with mycophenolate mofetil (MMF).

In early September 2000, the patient first developed a vancomycin-resistant enterococcal urinary tract infection (symptoms: fever, pyuria). Initial therapy included amoxycillin. Further infections ensued frequently, despite adequate bladder emptying. Other urinary pathogens included gentamicin-resistant and ceftazidime-resistant *Klebsiella* species, requiring a prolonged course of intravenous amikacin. Eleven weeks after transplantation there was a further vancomycin-resistant enterococcal infection with renal transplant dysfunction (the single diagonal arrow in Fig. 1). In vitro resistance was found with amoxycillin, co-amoxiclav, cefadroxil, cefuroxime, vancomycin and trimethoprim; sensitivities were limited to tetracycline and chloramphenicol. Oral administration of chloramphenicol 750 mg four times daily was started. Tacrolimus blood concentrations had been maintained between 5 and 11 μg/l for the previous 2 weeks on a constant dose of 4 mg oral b.d. Other drugs administered included warfarin, co-trimoxazole, ranitidine, atenolol, sodium bicarbonate, prednisolone and MMF.

Within 3 days of the start of medication with chloramphenicol, the tacrolimus blood concentration was >30 μg/l. This level was maintained for a further 7 days, with a small rise in plasma creatinine and a significant rise in plasma potassium (renal tubular acidosis). After 10 days of chloramphenicol therapy, the tacrolimus dose was reduced to

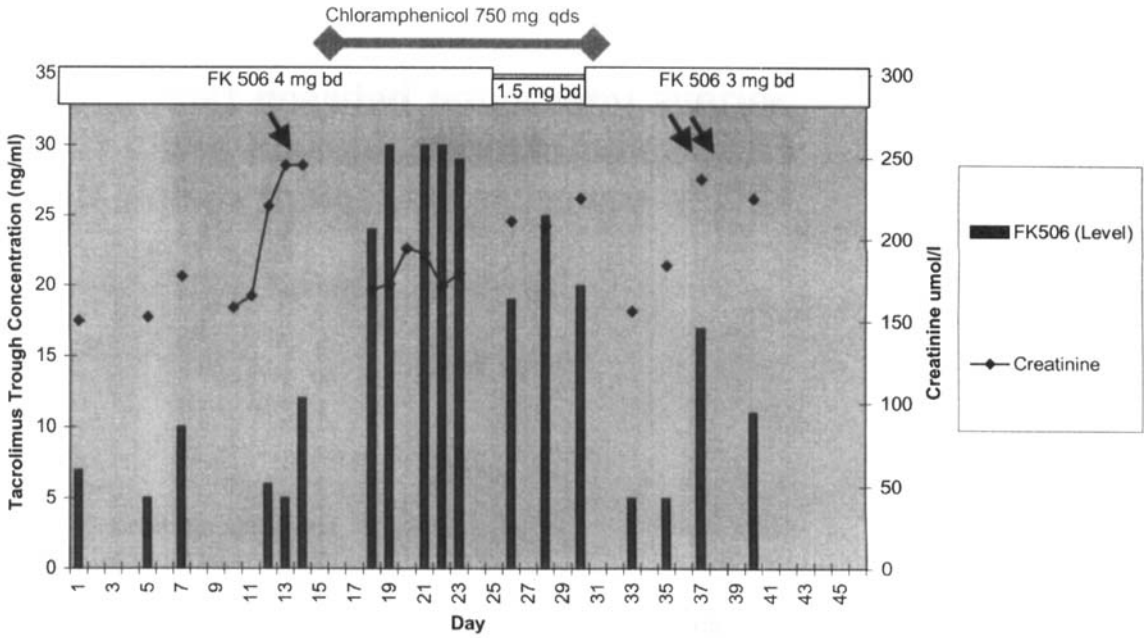

Fig. 1 Time course of tacrolimus (FK 506) levels and plasma creatinine with chloramphenicol administration and tacrolimus marked. *One black arrow* initial vancomycin-resistant enterococcal infection, *two black arrows* rejection episode

1.5 mg oral b.d., and the blood tacrolimus concentration fell to 18–25 μg/l. After 15 days, chloramphenicol administration was stopped and the tacrolimus dose was doubled to 3 mg oral b.d., but the blood levels fell to < 5 μg/l for several days and rose slowly thereafter, returning to the desirable range (8–15 μg/l). The patient had an acute cellular rejection episode with a significant rise in plasma creatinine (the two black arrows in Fig. 1) just after the tacrolimus blood levels had fallen to < 5 μg/l. This was successfully treated with pulsed methylprednisolone. The patient's prothrombin time also rose slightly while he was on chloramphenicol (2.0 to 3.5). These events are shown in Fig. 1 (plotting plasma creatinine, chloramphenicol administration, tacrolimus levels and doses).

Tacrolimus is one of two commercially available calcineurin inhibitors used mainly, but not exclusively, in the context of organ transplant-related immunosuppression (the other being cyclosporin A). Both of these agents are metabolised extensively by the cytochrome P_{450} 3A4 isoenzyme system in the small bowel and liver. Numerous drug interactions have been described, typically with those drugs that inhibit cytochrome P_{450}, including macrolide antibiotics, fluconazole, ketoconazole and diltiazem. Use of this fact has been made to reduce the significant cost of calcineurin inhibitor-based immunosuppressive drug regimens. The blood levels of calcineurin inhibitors are routinely measured to ensure that the drugs are used in their therapeutic window (excess levels are associated with an increased number of side effects, importantly, nephro- and neurotoxicity; low levels with inadequate immunosuppression and the risk of allograft rejection).

Vancomycin-resistant enterococcal urinary tract infections are emerging as one of a series of microbiological challenges to successful engraftment. Increased incidence and pathogenicity of this infection has been reported in bone marrow, liver, and kidney transplant patients. Anti-microbial therapies are limited, both by efficacy and by potential toxicities. Chloramphenicol, a broad-spectrum antibiotic developed in the 1960s, has fallen into opprobrium due to both dose-dependent and idiosyncratic bone-marrow suppression. Chloramphenicol has useful in vitro activity against many vancomycin-resistant enterococcal infections [2].

This is the third report of a serious interaction between chloramphenicol and tacrolimus [3, 4], and the first in a kidney–pancreas transplant recipient. A further case profiles a similar but less severe interaction between chloramphenicol and cyclosporin A [1]. The reason for the interactions has not been fully elucidated—chloramphenicol undergoes a wide variety of metabolic biotransformations in the liver, including conjugation, acetylation, hydrolysis and oxidation. Chloramphenicol has also been shown to inhibit the metabolism of chlorpropamide, phenytoin and warfarin (as also shown in this case), and some evidence exists to support its inhibition of the CYP2C11, CYP2C6 and CYP3A2 cytochrome P_{450} isoenzymes.

In summary, there is a rapid and severe interaction between chloramphenicol and tacrolimus, with greatly

increased tacrolimus levels during co-administration, and a rapid fall after chloramphenicol withdrawal. These major fluctuations in drug dosage and on immunosuppressive effectivity are serious and mandate very careful supervision and further investigation, as co-administration of these drugs is likely to increase in frequency.

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