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BRIEF REPORT

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Tacrolimus (FK506) malabsorption: management with fluconazole coadministration

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This paper is dedicated to the memory of our esteemed colleague and friend, Alex P. Mowat, who died last year

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Abstract We report the use of fluconazole to control primary immunosuppressive management with tacrolimus in a 9-year-old liver transplant recipient. Progressive increases in the doses of both cyclosporin (up to 20 mg/kg/day) and, subsequently, tacrolimus (up to 60 mg/day) failed to maintain immunosuppressive levels of both agents. After excluding poor compliance, drug interactions and analytical problems and identifying poor bioavailability (< 2.6 %) and rapid clearance (4.2 l/h), fluconazole (100 mg/day) was initiated to inhibit tacrolimus metabolism and consistent therapeutic blood levels of tacrolimus were achieved. However, graft function had deteriorated irrevocably and retransplantation was performed. Simultaneous use of tacrolimus (5 mg/day) and fluconazole (100 mg/day) maintained immunosuppression after transplantation. Three weeks later, obstruction of the Roux loop caused deteriorating liver function and tacrolimus blood levels fell. After correction at laparotomy, stabilisation was achieved and discharge was possible on 5 mg tacrolimus b.i.d. plus fluconazole (100 mg).

Key words Tacrolimus, malabsorption, fluconazole · Prograf, malabsorption, fluconazole · Fluconazole, malabsorption, tacrolimus · Malabsorption, tacrolimus, fluconazole

Introduction

The absorption of tacrolimus is variable but considered to be independent of bile flow [6], unlike that of cyclosporin [8]. Therapeutic blood levels of 5–15 μg tacrolimus per liter whole blood can usually be maintained with oral doses ranging from 0.05 to 0.3 mg/kg per day. We report a case of a 9-year-old boy who developed chronic rejection in his first graft because of an inability to maintain therapeutic blood levels of tacroli-

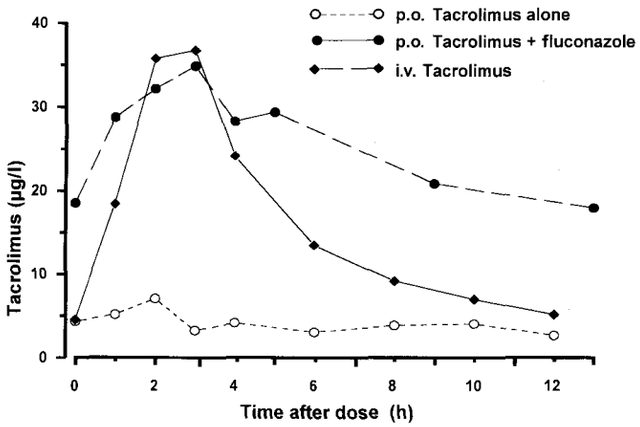

Fig. 1 Tacrolimus blood levels during pharmacokinetic investigations. Blood levels were measured using a microparticle enzyme-linked immunoassay after administration of 10 mg oral tacrolimus alone (o····o), 1 mg i.v. tacrolimus (◆—◆) 3 weeks later or 5 mg oral tacrolimus during concomitant therapy with 100 mg fluconazole four months later (●····●)

mus despite doses up to 120 mg/day (4 mg/kg per day). Inadequate immunosuppression had also been experienced previously using high doses of both conventional and microemulsified cyclosporin (Sandimmun and Neoral, respectively). However, adequate blood levels of tacrolimus were achieved with coadministration of oral fluconazole, and the patient maintained satisfactory immunosuppression after retransplantation.

Case history

An 8-year-old boy with linear growth just below the 50th percentile underwent liver transplantation for liver cirrhosis associated with alpha-1-antitrypsin deficiency (PiZZ). One course of high-dose steroids was administered for acute rejection diagnosed on the 6th post-operative day, and the patient was discharged after 2 weeks on oral cyclosporin (8 mg/kg per day; blood levels 150–300 µg/l by a specific monoclonal fluorescence polarisation immunoassay), azathioprine (1.5 mg/kg per day) and prednisolone (reducing from 30 to 5 mg/day during the next month). He was also receiving ganciclovir prophylaxis as the recipient of a cytomegalovirus-positive graft.

Over the next 5 weeks, the boy's cyclosporin requirements progressively increased to 12 mg/kg per day despite constant comedication. Ten weeks after surgery, liver biopsy showed acute cellular rejection of moderate severity (AST 476 IU/l, bilirubin 101 µmol/l, ALP 563 IU/l). This was managed with a cycle of high-dose intravenous methylprednisolone (500 mg/day for 3 days), with a repeat course given after a second biopsy revealed ongoing cellular rejection. Cyclosporin blood levels were low throughout this period (< 50 µg/l) despite doses of 20 mg/kg per day of oral Sandimmun. A trial period of dosage with Neoral also failed to achieve therapeutic levels and immunosuppression was changed to tacrolimus. Despite progressive dose increases up to 30 mg tacrolimus per day, blood levels remained below the limit of accurate quantitation (4 µg/l). A systematic search for the cause of poor blood levels ex-

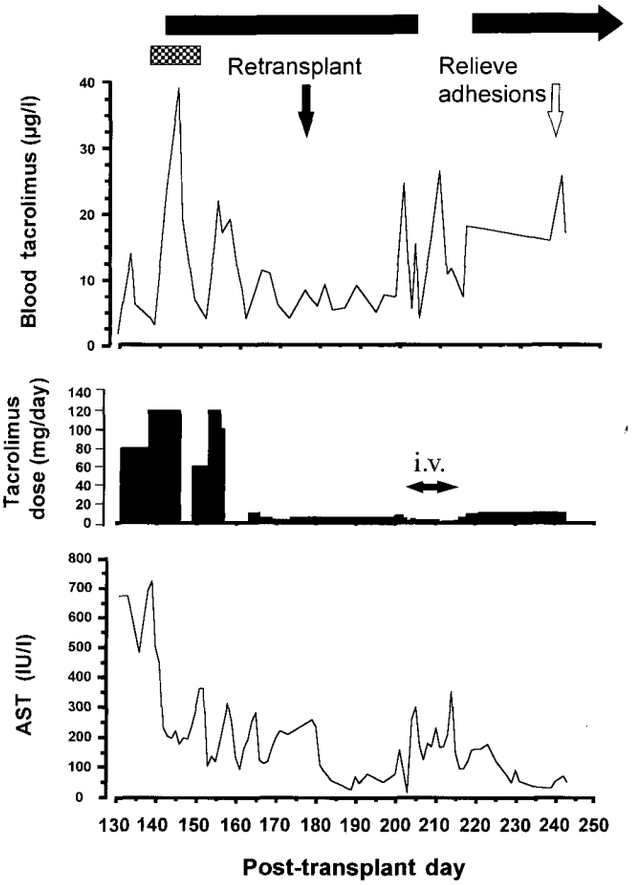

Fig. 2 Clinical course during fluconazole usage. Tacrolimus blood levels and dosage and serum asparatate aminotransferase activities are shown during management with fluconazole (*solid bar*) and erythromycin (*chequered bar*). A period of intravenous (i.v.) tacrolimus administration is shown, as well as the times of retransplantation and relief of adhesions, designated by *vertical arrows*

cluded analytical problems, poor compliance, drug interactions and an effect of food. Pharmacokinetic studies after oral administration of 10 mg tacrolimus (Fig. 1) showed blood levels not exceeding 7.0 µg/l and just above the limit of detection of the tacrolimus microparticle enzyme immunoassay defined in our laboratory (2 µg/l). Data from a 1 mg i.v. infusion (Fig. 1) showed a maximum blood level (C_{max}) of 36.7 µg/l, clearance of 4.2 l/h, terminal elimination half-life of 4.8 h and a bioavailability of oral tacrolimus below 2.6 % (literature values 5 %–67 % [6]). Graft function continued to deteriorate (AST 229 IU/l, bilirubin 545 µmol/l, ALP 686 IU/l) but biliary obstruction was excluded with a percutaneous transhepatic cholangiography (PTC). A course of high-dose steroids was ineffective and liver biopsy showed changes consistent with chronic rejection and viral hepatitis, for which ganciclovir was initiated.

One week later erythromycin (250 mg t.i.d.) was introduced to inhibit the metabolism of tacrolimus (60 mg b.i.d.). Tacrolimus trough blood levels rose to 23.8 µg/l within 4 days but liver function continued to deteriorate (AST 690 IU/l, bilirubin 326 µmol/l; ALP 636 IU/l). A 10-day course of OKT3 was begun (3 mg/day) and

liver function improved rapidly (AST falling to 195 IU/l within 4 days), but the concomitant appearance of a skin rash and concerns about changes in gastrointestinal motility with prolonged erythromycin [3] prompted its withdrawal. Fluconazole (90 mg/day) was substituted because of its known safety during prolonged antifungal therapy. A rapid rise in blood levels of tacrolimus occurred (to 38.9 μg/l) and dosage was temporarily halted. After recommencement, tacrolimus trough blood levels could be maintained above 10 μg/l using a dosage of 60 mg b.i.d. together with fluconazole (100 mg/day; Fig. 2). AST values remained below 150 IU/l, but renal function began to deteriorate (serum creatinine rising progressively to above 250 μmol/l when continuous veno-venous dialysis was begun) and tacrolimus was withdrawn. A further deterioration in liver function prompted the patient's listing for retransplantation, which was performed 2 weeks later, 6 months after the first graft.

The Roux loop was reconstructed in an uneventful operation. The patient made a rapid recovery and over the next 3 weeks trough tacrolimus levels remained at 5–10 μg/l at a dosage of 5 mg/day with simultaneous fluconazole (100 mg/day). Mild acute cellular rejection was diagnosed at 3 weeks and treated with high-dose steroids (3 days) and ganciclovir (2 weeks). Liver function deteriorated further (AST 348 IU/l, bilirubin 54 μmol/l, ALP 523 IU/l) and he developed a persistent skin rash and pyrexia, eventually responsive to antibiotic therapy. A second biopsy showed ongoing cellular rejection with perivenular cell drop-out and mildly cholangiolytic portal tracts. Intravenous tacrolimus was commenced (1 mg b.i.d.), fluconazole was withheld and a PTC performed that suggested evidence of an obstructed Roux loop. Adhesions were responsible, causing kinking of the Roux loop at the level of the transverse mesocolon. This was corrected at laparotomy with an immediate improvement in hepatic function (AST 92 IU/l, bilirubin 51 μmol/l, ALP 367 IU/l). The patient reverted to oral tacrolimus (5 mg b.i.d. with fluconazole, 100 mg) and liver function continued to improve until discharge, 5 weeks after the second transplant (AST 31 IU/l, bilirubin < 20 μmol/l, ALP 268 IU/l). He has remained well for the last 12 months with stable tacrolimus levels while fluconazole therapy continues.

Discussion

In our patient, difficulties with achieving adequate blood levels, first of cyclosporin and then of tacrolimus, were likely to have been responsible for the progression to chronic rejection in the first graft. This could not be ascribed simply to poor bile production because the absorption of Neoral (with a lesser dependency on bile production than Sandimmun [4]) and tacrolimus (with relative independence from bile production [7]) was also inadequate, failing to provide therapeutic blood levels. Pharmacokinetic studies with tacrolimus showed that bioavailability was low (< 3 %) and that elimination was rapid. Factors known to interfere with tacrolimus and cyclosporin absorption include the administration of antacids [1, 10], while inducers of cytochrome P450 (CYP) 3A, such as antitubercular drugs, increase elimination of both drugs [1]. None of these drugs was prescribed to our patient. It is of note that significant inter-patient variability in the CYP3A-dependent rates of metabolism of both agents has been reported [9]. The inhibition of the metabolism of tacrolimus by erythromycin [2] and azole antifungal drugs [5, 7, 10] is well recognised and probably underlies the value of fluconazole in this case.

No adverse effects of combining fluconazole with high doses of tacrolimus were noted, except when tacrolimus blood levels rose rapidly initially and renal failure occurred. The need for fluconazole administration after both the first and second transplants suggests that hepatic metabolism was unlikely to be the sole factor responsible for low tacrolimus blood levels. The most likely alternative, or additional, explanation is the rapid intestinal metabolism of tacrolimus by CYP3A which is known to be present in enterocytes [11]. An additional likely complication in this patient was adhesions of the Roux loop. These may have caused sequestration of tacrolimus and prolonged its transit time and exposure to intestinal CYP3A, so limiting its bioavailability. Whether such adhesions, noted at the time of the second transplant, contributed to the initial malabsorption is unknown, but their subsequent surgical correction apparently improved tacrolimus absorption.

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