The mechanism of cyclosporine toxicity induced by clarithromycin

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Aims Recently a number of case reports have described the interaction of clarithromycin with cyclosporine A, resulting in cyclosporine toxicity. This interaction is presumed to take place via the hepatic cytochrome P450 enzyme system.
Methods Following a case of cyclosporine toxicity and acute renal failure in a transplant patient started on clarithromycin, we investigated the effect of oral clarithromycin on the hepatic P450 system in five healthy normal male volunteers, by means of the erythromycin breath test.
Results Cytochrome P4503A (CYP3A) activity was reduced in all subjects by a mean level of 26% following clarithromycin treatment. This would result in a significant reduction in cyclosporine clearance in patients receiving clarithromycin.
Conclusions As clarithromycin was shown to inhibit CYP3A activity in all subjects tested, we recommend that a high degree of caution be exercised when clarithromycin is administered to patients receiving cyclosporine therapy or other drugs known to be eliminated by CYP3A-mediated metabolism.

Keywords: clarithromycin, cyclosporine A, cytochrome P450, CYP 3A, erythromycin, breath test, acute renal failure, simvastatin, rhabdomyolysis

Introduction

Recently, it was reported that the novel macrolide antibiotic clarithromycin interacts with cyclosporine, resulting in cyclosporine toxicity [1]. Following a case of cyclosporine toxicity with acute renal failure in a clarithromycin treated transplant patient (see below), the effect of oral clarithromycin on the hepatic cytochrome P450 (CYP) 3A subfamily of enzymes was investigated in five healthy male volunteers using the erythromycin breath test. As CYP3A enzymes are known to metabolise cyclosporine [2], it was proposed that these enzymes may by inhibited by oral clarithromycin.

Case report

A 54 year old woman who received her second cadaveric renal allograft in October 1986 was maintained on cyclosporine 225 mg (4.5 mg kg^{-1}), prednisone 10 mg and azathioprine 75 mg daily for 7 years, with a serum creatinine in the range of 180–215 μmol l^{-1} and an average G.F.R. of 30 ml min^{-1} 1.73 m^2. Cyclosporine serum concentrations were stable at 100–160 ng ml^{-1}. In addition to these immunosuppressive agents the patient received simvastatin 10 mg daily for hypercholesterolaemia. Clarithromycin was started at a dose of 500 mg twice daily following a *Mycobacterium haemophilum* infection of her hand and wrist.

Three weeks later the serum cyclosporine concentration was 1200 ng ml^{-1} and serum creatinine 340 μmol l^{-1}. The patient was admitted to hospital with an acute onset of muscle pain and an elevated CPK (12954 u l^{-1}).

The rhabdomyolysis was presumed to be due to an increased serum concentration of simvastatin as a result of either CYP3A inhibition by clarithromycin, or competetive inhibition of CYP3A by the high levels of cyclosporine [3–5]. The simvastatin was stopped. The cyclosporine dose was reduced to 150 mg daily, prednisone to 5 mg day^{-1}, and clarithromycin to 250 mg twice daily with resolution of symptoms. Serum cyclosporine concentration and graft function returned to baseline levels.

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Methods

Five healthy male volunteers underwent an erythromycin breath test which was performed as described by Watkins *et al.* [6]. One week later, each volunteer received clarithromycin 4×500 mg orally (500 mg 12 hourly for 48 h) and the erythromycin breath test was repeated. The erythromycin breath test was performed as follows: 4 μCi of [^{14}C]*N*-methyl erythromycin (New England Nuclear, Boston, MA) (=84 μg of erythromycin) was added to a syringe containing 2.5 ml of 5% dextrose, and the solution injected intravenously into the subject as a bolus. Subjects exhaled through a glass pipette (at intervals of 3, 10, 20, 30, 40, 60, 75, 90, 105 and 120 min) to create bubbles in a CO_2 trapping solution (=4 ml 0.5 M benzethonium hydroxide (Sigma Chemical Co. St Louis MO) in methanol: ethanol (1 : 1 v/v) containing phenolphthalein as an indicator) When trapping of 2 mmol of CO_2 had occurred (as indicated by the disappearance of the pink colour), the specific activity of ^{14}C was determined by scintillation spectometry. The fraction of the administered ^{14}C exhaled per minute was calculated, allowing for an endogenous CO_2 production of 5 mmol CO_2 m^{-2} min^{-1}. The results were expressed as a fraction of administered ^{14}C exhaled in 120 min.

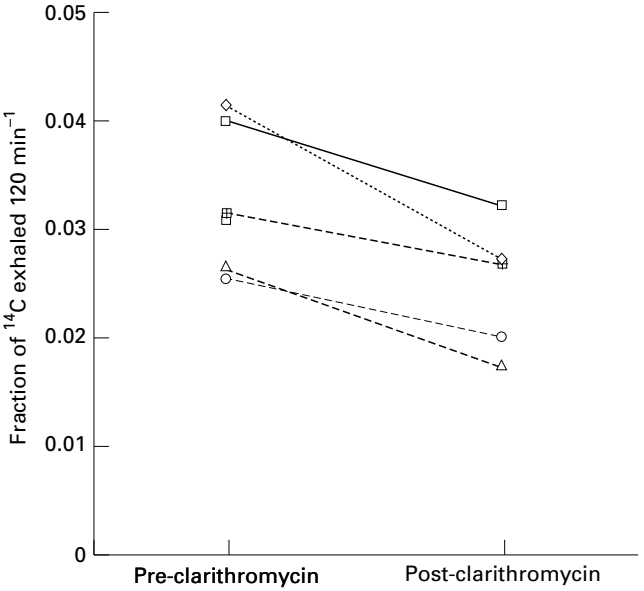

Figure 1 The effect of clarithromycin on cytochrome P450 3A activity as measured by the ^{14}C-erythromycin breath test in five healthy volunteers

Results were compared using the paired-sample Student's *t*-test.

Results

The baseline range of exhaled $^{14}CO_2$ was 0.0252–0.0412 of total administered ^{14}C/120 min, consistent with the known inter-subject variation of CYP3A activity in healthy individuals [11]. Following administration of clarithromycin, a reduction in the AUC of exhaled $^{14}CO_2$ was observed in all five subjects with a mean reduction of 26.2% (range 16.3% to 35.9%, $P=0.0075$) (Figure 1). The mean pre- and post clarithromycin fractions of exhaled $^{14}CO_2$ were 0.0327 and 0.0241 of exhaled $^{14}CO_2$/120 min respectively, with a mean difference of 0.0086 of exhaled $^{14}CO_2$/120 min (95% confidence intervals 0.38–1.33).

Discussion

The hepatic *N*-demethylation of [^{14}C *N*-methyl] erythromycin, as measured by exhaled $^{14}CO_2$, is known to represent a well-validated, indirect measurement of hepatic CYP3A activity [6]. The erythromycin breath test is based on the observation that the enzyme CYP3A appears to catalyse exclusively the *N*-demethylation of erythromycin, and that the carbon atom in the removed methyl group should largely appear in the breath as carbon dioxide.

Moreover, the erythromycin breath test has been shown to correlate well with cyclosporine clearance in renal transplant recipients [7]. Erythromycin is well recognised as an inhibitor of CYP3A-mediated drug metabolism due to the formation of a metabolite that complexes the CYP in an inactive state [8]. Because cyclosporine is predominantly metabolized by CYP3A, the observed interaction between erythromycin and cyclosporine is well documented [9]. Based on the high degree of structural similarity between erythromycin and clarithromycin (both possessing a sterically unhindered alkylamine group that undergoes CYP-mediated biotransformation), it is feasible that clarithromycin inhibits hepatic CYP3A by a similar mechanism. This is supported by studies in hepatic microsomes from dexamethasone-treated rats that demonstrated both clarithromycin and its *N*-desmethyl metabolites complex with CYPs [10].

In the present study, CYP3A activity was reduced in all subjects by a mean level of 26% following clarithromycin treatment. As cyclosporine clearance largely depends on CYP3A enzyme metabolism, we would expect significant reduction in cyclosporine clearance in patients receiving clarithromycin [11–13]. Indeed, the degree of CYP inhibition by clarithromycin on orally administered drugs such as cyclosporine may well have been underestimated in the present study as it has been established that CYP 3A subfamily enzymes are also expressed in small bowel mucosa [14, 15]. The effect on first-pass metabolism of inhibition of mucosal enzymes would not be detected by the erythromycin breath test, because the substrate for this assay was administered intravenously. As clarithromycin was shown to inhibit CYP 3A activity in all subjects tested, we recommend that a high degree of caution be exercised when clarithromycin is administered to patients receiving cyclosporine therapy or other drugs known to be eliminated by CYP 3A-mediated metabolism.

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