Erythromycin enhances the absorption of cyclosporin

Transplant patients on Cyclosporin A (CyA) therapy when co-administered with erythromycin have exhibited CyA toxicity, probably associated with the consistent marked elevation in CyA blood concentration (Hourmant *et al.*, 1985). The mechanism of this important interaction has been investigated and generally is believed to be caused by erythromycin inhibiting CyA metabolism (Gonwa *et al.*, 1986; Kessler *et al.*, 1986). In all studies to date, CyA has been given orally during erythromycin administration. If inhibition of metabolism does occur, the interaction should also be seen after intravenous CyA administration. We report on our evaluation of this possibility.

Six renal transplant patients on long-term CyA therapy received an oral dose of CyA (5 mg kg^{-1}) and a 3–6 h constant-rate intravenous infusion (3.5 mg kg^{-1}) on separate days before and during a 3 day course of erythromycin (500 mg four times daily) according to a randomised design. Blood samples were taken throughout and, after separation at 37°C, the plasma CyA was determined by high-pressure liquid chromatography (Gupta *et al.*, 1987) to define the pharmacokinetics of CyA.

The plasma CyA concentration-time data from a representative patient is displayed in Figure 1. It is clearly evident that during erythromycin administration there is a sharp increase in the plasma CyA concentrations following oral administration, but not following intravenous CyA administration, compared to the concentrations seen after CyA therapy alone. Similar results were seen in the other patients. Following the intravenous dose of CyA there was a small but statistically significant decrease ($P<0.05$, paired t-test) in clearance (alone 0.31 ± 0.16 l h^{-1} kg^{-1}; during erythromycin 0.27 ± 0.15 l h^{-1} kg^{-1}) and no change in terminal half-life (12.9 ± 2.8 h; to 13.0 ± 5.1 h). In contrast, following the oral dose of CyA there was a substantial increase in both the maximum concentration (884 ± 390 μg l^{-1} to 2480 ± 1230 μg l^{-1}; $P<0.001$) and area under the curve, AUC (6150 ± 2400 μg l^{-1} h to 13200 ± 8300 μg l^{-1} h $P<0.001$). From these observations we conclude that erythromycin primarily increases CyA absorption, with at best a marginal effect on its clearance. Indeed, by comparison of the oral with the corresponding intravenous CyA data, we calculate that the absorption of CyA has increased from 36 ± 12% to 60 ± 20%.

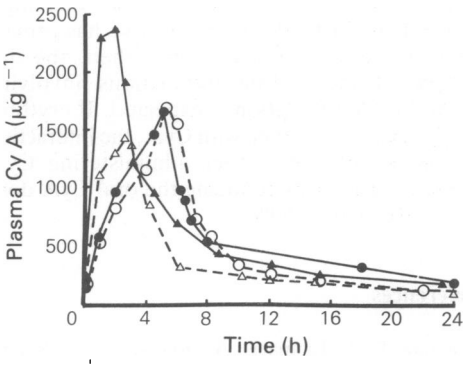

Figure 1 Plasma cyclosporin concentration in a renal transplant patient receiving either oral or intravenous administration of cyclosporin alone (△, ○) and during erythromycin administration (▲, ●).

The mechanism for this increased absorption is unclear. CyA has poor aqueous solubility and is incompletely absorbed. Perhaps erythromycin aids dissolution of CyA or facilitates its passage across the gut. It may be argued that the low oral bioavailability of CyA is due to extensive first-pass (pre-hepatic and/or hepatic) metabolism and that erythromycin reduces this effect, but there is little evidence to support this hypothesis. A significant first-pass hepatic loss of CyA may be discounted as CyA is a drug of only low to moderate clearance (0.30 l h^{-1} kg^{-1}) compared with hepatic blood flow (1.3 l h^{-1} kg^{-1}). Also, no pre-hepatic metabolism of CyA has been demonstrated.

Phenytoin lowers the blood concentration of CyA when given orally (Freeman *et al.*, 1984). The mechanism initially postulated was one of induction of CyA metabolism, but our analysis of both CyA and metabolite data associated with the study indicated that the data are better described by reduced absorption than by increased clearance (Rowland & Gupta, 1987). Had reduced absorption been due to increased pre-hepatic metabolism, one would have antici-

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pated a disproportional increase in the metabolite AUC, but this AUC was decreased in direct proportion to that of CyA.

If our hypothesis of altered absorption of CyA by erythromycin and phenytoin is correct, these interactions may be circumvented by ensuring CyA is normally well absorbed, but producing a product that achieves this objective has proved to be extremely difficult. Until then, the discovery of more drug interactions involving altered CyA absorption is expected. If erythromycin needs to be given with CyA, the interaction can be avoided by either administering CyA intravenously or by reducing the oral CyA dose by approximately 50%.

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Cyclosporin–verapamil interaction

There have been several reports (Pochet & Pirson, 1986; Grino *et al.*, 1986) of diltiazem increasing the concentration of cyclosporin in renal transplant patients. We have observed that verapamil also affects the concentration of cyclosporin.

A 30 year old man with end stage renal failure secondary to polycystic kidney disease was transplanted in September 1986. He was treated with cyclosporin and low dose azathioprine. One month after transplantation his renal function was stable (serum creatinine 0.16 mmol l^{-1}). The cyclosporin dosage was 150 mg twice a day, and whole blood predose cyclosporin concentrations, measured by RIA, were 200–400 $\mu g\ l^{-1}$. His renal function remained stable over the next 7 weeks but because of hypertension he was commenced on verapamil 40 mg twice daily. One week later the dose of verapamil was increased to 80 mg twice a day and he remained on this dose for 3 weeks.

After the first week of verapamil therapy his cyclosporin concentration increased from 350 $\mu g\ l^{-1}$ to 704 $\mu g\ l^{-1}$, and then to 1054 $\mu g\ l^{-1}$ with the increased verapamil dose. Verapamil was ceased and nifedipine 20 mg twice a day introduced. The whole blood cyclosporin level fell to 504 $\mu g\ l^{-1}$ 1 week after ceasing verapamil and 2 weeks later was 409 $\mu g\ l^{-1}$. Serum creatinine remained stable over those 7 weeks (Figure 1). Other drug therapy included ranitidine 150 mg day^{-1} and azathioprine 100 mg day^{-1} and was unchanged over this period.

As verapamil at concentrations up to 1000 ng ml^{-1} did not interfere in the cyclosporin assay,