Letters to the Editors

Tacrolimus/cerivastatin interaction study in liver transplant recipients

With advances in immunosuppressive treatment, graft loss due to acute and chronic rejection has declined such that a variety of metabolic disturbances are now assuming increasing importance in long-term survival of liver transplant patients. Accelerated atherosclerosis has thus become a crucial factor in patient survival after liver transplantation [1], and lipid-lowering drug therapy with 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase inhibitors has significant potential to alleviate cardiovascular complications in those patients [2–4].

The use of HMG-CoA reductase inhibitors in transplant recipients has been limited by reports of myotoxicity, including severe rhabdomyolysis in transplant patients when treated concomitantly with statins and the immunosuppressive agent cyclosporin [5]. These indicate a drug–drug interaction potential and elevated systemic exposure during cyclosporine cotreatment has been reported for all HMG-CoA reductase inhibitors investigated to date. The mechanisms for the drug interactions of cyclosporin with statins are complex, but cyclosporine-induced inhibition of cytochrome P-450 (CYP) 3A metabolic pathways, interference with active transport processes at the level of p-gylocoprotein or other carrier systems are the most probable explanations [6–8].

The HMG-CoA reductase inhibitor cerivastatin has several pharmacokinetic characteristics rendering it rather insensitive to drug interactions, e.g. complete absorption (>98%), high bioavailability (60%) due to moderate first-pass extraction, dual metabolic pathway (demethylation: metabolite M-1; hydroxylation: M-23), short plasma elimination half-life of 2–3 h, and biliary (70%) and renal (30%) route of elimination of the formed metabolites [9]. Regarding CYP-mediated metabolic clearance, cerivastatin shows high affinity to CYP 2C8, which catalyses the formation of metabolites M-1 and M-23 almost to the same extent. affinity for CYP 3A4 is considerably lower; CYP 3A4 contributes only to the formation of M-1. Nonspecific or specific CYP 3A4 inhibitors such as cimetidine, erythromycin, itraconazole, and mibefradil do not show clinically relevant interactions with cerivastatin [10]. Nevertheless, single and multiple dosing of once-daily 0.2 mg cerivastatin sodium in kidney transplant recipients led to a 3- to 5-fold increase in plasma concentrations of cerivastatin and its metabolites, whereas the cyclosporin steady-state concentrations remained unaffected. Cyclosporin-affected carrier-mediated active transport processes in and out of cerivastatin's main site of distribution and biotransformation – the liver – thus decreasing both metabolic clearance and volume of distribution, has been speculated as the underlying mechanism [8], similarly as done previously to explain the striking cyclosporin/pravastatin interaction [7].

Regarding interactions between statins and tacrolimus, the only data reported so far have been a pronounced interaction observed for simvastatin in tacrolimus-treated rats [10], similar to that described for cyclosporin [11]. Tacrolimus itself has been described to be primarily a CYP 3A4 substrate, and respective metabolic interactions e.g. with erythromycin, azole antifungals or nefazodone, have been reported [13–16].

As part of a study programme to address the role of cerivastatin in ameliorating acute cellular rejection in liver transplantation, we have studied the pharmacokinetic profiles of eight patients with steady-state tacrolimus levels after liver transplantation, following administration of a single 0.2 mg dose of cerivastatin sodium.

After approval of the study protocol by the Ethics Committee of Addenbrooke's Hospital, Cambridge, eight liver transplant recipients (four female/four male Caucasians; mean age: 51 years [range: 20–60 years]; mean weight: 67 kg [range: 49–84 kg]) provided written informed consent to participate in this single-centre, open-label study. The patients were on steady-state tacrolimus immunosuppressive treatment (tacrolimus dose range 6–15 mg daily in a divided dose; median 8 mg daily) with trough plasma levels between 5 and 20 $\mu g l^{-1}$ and stable graft function 8–52 weeks post-transplantation. The most common comedications were, in all patients, azathioprine (50–75 mg), prednisolone (5–10 mg) and ranitidine (300 mg), and nystatin (400.000 units) in six patients. Following screening and enrolment visits, study participants received a single oral dose of 0.2 mg cerivastatin sodium (supplied by Bayer AG, Leverkusen, Germany) together with 180 ml tap water under fasted conditions in the morning. Standard tolerability assessments, complete biochemistry and haematological profiles, urinalysis and measurement of vital signs (blood pressure, heart rate) and ECG were undertaken throughout the study.

Blood plasma samples were collected before and 1, 2, 3, 4, 6, 8, 12, and 24 h after administration of the investigational product. They were analysed for cerivastatin and its metabolites M-1 and M-23 by liquid-liquid extraction followed by h.p.l.c. with fluorescence detection [17]. The limit of quantification was 0.2 $\mu g l^{-1}$ for the parent compound and 0.1 $\mu g l^{-1}$ for the metabolites. Urine samples were collected 0–4, 4–8, 8–12 and 12–24 h

postdose. Analysis of the metabolites was carried out by h.p.l.c. with fluorescence detection; the limit of quantification was 1.0 $\mu g l^{-1}$.

Tacrolimus whole-blood concentrations were determined 24 h before, immediately predose and 24 h post cerivastatin sodium dosing using the commercial competitive-binding microparticle immunoassay II from Abbott Diagnostics, run on the Abbott IMx® analyser (Abbott Laboratories, North Carolina/IL, USA).

Maximum plasma concentration (C_{max}), time to peak (t_{max}), terminal half-life ($t_{1/2}$), area under the curve (AUC) and amounts excreted in urine (Ae_{ur}, for metabolites only) were calculated using standard noncompartmental methods. All data were reported using descriptive statistics. Tacrolimus trough concentrations predose and 24 h postdose were compared via paired *t*-test after logarithmic transformation.

Cerivastatin single-dosing was safe and well tolerated. No adverse events were reported, and no clinically relevant treatment related changes in laboratory parameters were observed.

Tacrolimus steady-state trough levels were not affected by cerivastastin co-administration with geometric mean (gsd) values of 10.6 (1.18) $\mu g l^{-1}$ immediately before, and 10.8 (1.17) $\mu g l^{-1}$ 24 h after cerivastatin dosing. The ratio post-/predose was 1.04 with a 95% confidence interval of 0.98 to 1.11, i.e. cerivastatin does not interact with the CYP 3A4 substrate tacrolimus, in line with cerivastatin's general lack of cytochrome P450 inhibitory or inducing potential [10].

Mean cerivastatin and metabolites M-1 and M-23 AUC and C_{max} values were 50% higher in liver transplant recipients on tacrolimus treatment when compared with data obtained in healthy subjects [8, 9]. Elimination half-lives ($t_{1/2}$) of cerivastatin and metabolites and amounts of metabolites M-1 and M-23 excreted in urine (Ae_{ur}) remained unaffected; thus accumulation of the drug under multiple-dosing is not anticipated (Table 1, Figure 1).

In summary, the first pharmacokinetic interaction study in transplant recipients on tacrolimus treatment receiving cerivastatin sodium demonstrated only a moderate elevation of systemic drug exposure, which would not prohibit the use of cerivastatin in this patient population.

With respect to a mechanistic explanation for this interaction, the parallel increase in plasma concentrations of cerivastatin and its metabolites and the apparent lack of effect on half-lives, similarly as observed for cerivastatin in cyclosporin-treated kidney transplant recipients [8], together with the known insensitivity of cerivastatin clearance to CYP 3A4 inhibition in general [10], do not support a metabolic inhibitory interaction induced by tacrolimus. Consequently, an analoguous interaction mechanism to that proposed for statins and cyclosporin may be present, i.e. inhibition of active hepatic transport processes, especially biliary excretion [7, 8, 12]. However, the tacrolimus/cerivastatin interaction exhibits a much less profound effect on cerivastatin plasma concentrations than that induced by cyclosporin, and it will be interesting to see how tacrolimus compares with cyclosporin in transplant patients treated with other statins.

Table 1 Pharmacokinetic parameters (geometric means (gSD), [range]) of cerivastatin and its metabolites M-1 and M-23 following a single oral dose of 0.2 mg given to eight liver transplant recipients on individual tacrolimus treatment compared with previous data obtained in healthy subjects [8, 9].

	AUC ($\mu g l^{-1}$ *h*)	C_{max} ($\mu g l^{-1}$)	$t_{1/2}$ (*h*)	Ae_{ur} # [%]
Cerivastatin				
Liver transplant patients	19.8 (1.54)	3.2 (1.48)	2.8 (1.23)	n.m.##
($n=8$)	[11.7, 43.8]	[2.3, 6.7]	[1.9, 3.5]	
Healthy male subjects	15.3 (1.33)	2.4 (1.34)	3.2 (1.22)	n.m.##
($n=29$) [9]				
Metabolite M-1				
Liver transplant patients	2.2 (1.55)	0.24 (1.64)	3.6 (2.18)	2.26 ± 0.99
($n=5$)	[1.12, 3.40]	[0.13, 0.58]	[1.5, 11.9]	[0.57, 4.04]
Healthy male subjects	1.2 (1.06)	0.16 (1.38)	3.4 (1.35)	2.33 ± 1.44
($n=12$) [8]				
Metabolite M-23 data				
Liver transplant patients	6.6 (1.43)	0.63 (1.32)	4.9 (1.92)	7.59 ± 2.37
($n=8$)	[4.1, 11.1]	[0.40, 0.91]	[1.8, 14.0]	[3.95, 10.1]
Healthy male subjects	3.2 (1.38)	0.32 (1.22)	5.1 (1.60)	7.51 ± 3.50
($n=12$) [8]				

arithmetic means ± s.d.;

n.m. = not measured (as cerivastatin is not excreted unchanged in urine).

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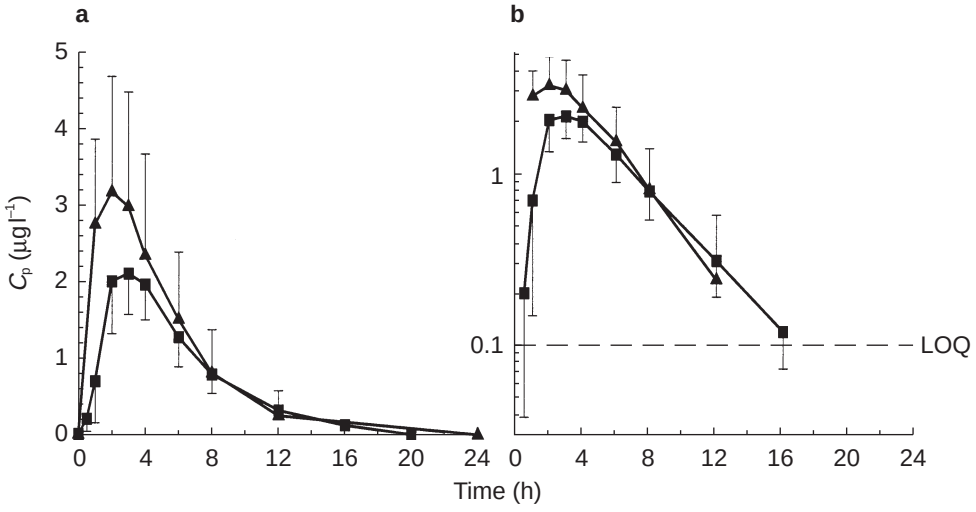

Figure 1 Cerivastatin plasma concentrations (geometric means (gSD)), on a linear (a) and semilogarithmic (b) scale, following a single dose of 0.2 mg cerivastatin sodium to eight liver transplant recipients on individual tacrolimus treatment (▲) compared with previous data obtained in healthy subjects (■) [9].

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Effect of grapefruit juice on the disposition of omeprazole

In a recent issue of this journal, Tassaneeyakul *et al.* reported the effect of grapefruit juice (GFJ) intake on the disposition of omeprazole and its primary metabolites following a single oral dose to 13 healthy volunteers, two of whom being poor metabolisers (PM) for cytochrome P450 (CYP) 2C19 [1]. As recalled by the authors, furocoumarins in GFJ have been implicated in several drug interactions involving CYP3A4 substrates, including felodipine, cyclosporin, midazolam, and saquinavir [2]. However, unlike stated in their introduction, other beverages have been shown to alter the disposition of some of these drugs. For example, juices prepared from the Seville (sour) orange, pummelo and sweetie fruit, and red wine contain many of the furocoumarins and flavonoids found in GFJ, including 6′, 7′ dihydroxybergamottin, that are known to inhibit various CYP and/or transporter activities *in vivo* and/or *in vitro* [3-7].

The authors reported that, as with water, GFJ had virtually no effect on the average area under the concentration-time curve (AUC), maximal plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and elimination half-life ($t_{1/2,z}$) of omeprazole and its CYP2C19-mediated metabolite, 5-hydroxyomeprazole (Table 1). In addition, while GFJ also had no effect on the t_{max} and $t_{1/2,z}$ of the CYP3A4-mediated metabolite, omeprazole sulphone, the average AUC and C_{max} for this metabolite were significantly reduced. These findings would suggest that omeprazole metabolism is primarily mediated by CYP2C19 when CYP3A4 is inhibited. However, because 5-hydroxyomeprazole is further metabolized to a CYP3A4-mediated sulphone, one might also have expected an increase in 5-hydroxyomeprazole AUC following GFJ intake.

The authors further reported no difference between extensive metabolisers (EM) and PM regarding GFJ effects on omeprazole pharmacokinetics. However, Figure 2b (lower right curve) provided incomplete data describing omeprazole sulphone disposition in the two CYP2C19 PM, making the calculation of the mean $t_{1/2,z}$ questionable. Moreover, despite the fact that the authors found a 5-fold higher omeprazole AUC in PM compared with EM, the data were pooled, which probably led to the wider-than-expected variability observed in both the AUC and C_{max} of omeprazole. This method of analysis likely precluded the expected significant increase with GFJ. Nevertheless, if the authors are correct, and because omeprazole is generally well-tolerated and omeprazole AUC was not even increased by GFJ, then the clinical relevance of this interaction remains unclear [2]. In addition, given the 5-fold higher omeprazole AUC in PM compared with EM, one would expect CYP2C19 to be the major metabolic pathway for this drug even in absence of CYP3A4 inhibition.

The decreased omeprazole sulphone C_{max} and AUC without an accompanying change in omeprazole $t_{1/2,z}$ following GFJ intake was indeed most likely the result of inhibition of intestinal CYP3A4-mediated first-pass metabolism. However, CYP2C19 has been recently detected in human small intestinal microsomes, with protein content and catalytic activity comparable with those measured in liver microsomes [8]. In addition, the authors stated from their unpublished data that this isoform can be inhibited by various furocoumarins found in GFJ. Thus, inhibition of intestinal CYP2C19 by GFJ cannot be ruled out in the present study, despite its lack of effect on 5-hydroxyomeprazole AUC and C_{max}. Again, pooling PM and EM data may have masked a difference in 5-hydroxyomeprazole AUC between water and GFJ intake. Likewise, inhibition of 5-hydroxyomeprazole secondary metabolism by the juice could have increased this metabolite's AUC but to a different extent between PM and EM, also masking a difference between the two treatment phases.

The contribution of intestinal metabolism, as well as transport, in limiting the oral bioavailability of drugs is difficult to assess in humans in the absence of a specific and reliable probe(s) for each pathway. This is particularly true for drugs like omeprazole that undergo complex primary and secondary metabolism prior to reaching the portal circulation [1]. Addressing this critical issue *in vivo* is of particular interest and will likely require taking into account each of the relevant intestinal enzymes and/or transporters [9] potentially involved in the interaction, as well as the physicochemical conditions in the intestinal lumen, to improve our understanding of the effect of the intestinal barrier on oral drug absorption.

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