Intravenous diltiazem and CYP3A-mediated metabolism

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Aims To study whether intravenous diltiazem, a calcium channel blocker commonly prescribed for hypertension and stable angina, is an inhibitor of the CYP3A enzymes by using oral lovastatin, an HMG Co-A reductase inhibitor, as a substrate.

Methods Ten healthy volunteers were studied in a randomized two-way crossover design. The two arms were 1) administration of a 20 mg dosage of lovastatin orally and 2) administration of a 20 mg dosage of lovastatin orally 1 h after an intravenous loading dosage and constant infusion of diltiazem. Blood samples were collected up to 25 h in order to quantify lovastatin and diltiazem concentrations in the separated serum. Lovastatin and diltiazem concentrations were quantified by GC-MS and h.p.l.c., respectively.

Results Intravenous diltiazem did not significantly affect the oral AUC, $C_{\max}$, $t_{1/2}$, or $t_{\max}$ of lovastatin.

Conclusions These data suggest that the interaction of lovastatin with diltiazem does not occur systemically and is primarily a first-pass effect. Thus, drug interactions with diltiazem may become evident when a patient is moved from intravenous to oral dosing.

Keywords: calcium channel blockers, CYP3A, diltiazem, drug interactions, lovastatin

Introduction

Intravenous diltiazem is widely used for acute heart rate control in patients with supraventricular tachyarrhythmias [1, 2]. Rapid onset of action and a high degree of efficacy in slowing ventricular rate make diltiazem preferable to digoxin for treatment of atrial fibrillation and atrial flutter in emergency settings [2, 3].

In vivo and *in vitro* studies have demonstrated that diltiazem is an inhibitor of cytochrome P450 3A4 (CYP3A4) [4–7]. Several clinical studies have shown that coadministration of oral diltiazem with orally administered substrates of CYP3A4 will increase the serum concentrations of those agents, e.g. cisapride, cyclosporin, triazolam [8–10]. The effect of intravenous diltiazem on the metabolism of orally dosed substrates is poorly understood [11, 12].

Lovastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor that inhibits the rate-limiting step in the biosynthesis of cholesterol [13]. Approximately 25% of the inhibition of HMG-CoA reductase activity in plasma is inhibited by lovastatin while the remainder has been attributed to one or more active metabolites, which appear to be formed by CYP3A enzymes [14, 15]. Our laboratory has previously shown that oral diltiazem inhibits lovastatin oral clearance [16].

The effect of diltiazem may be predominantly via inhibition of intestinal rather than hepatic CYP3A4 and therefore, we postulate that intravenous diltiazem will have a lesser effect on CYP3A mediated metabolism than oral dosing of diltiazem. Herein, we report a detailed study with lovastatin that supports this hypothesis.

Methods

Clinical protocol

Ten healthy, nonsmoking volunteers (five males and five females) provided a written informed consent approved by the Indiana University institutional review board. The

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sample size in our study could detect a 60% difference between groups with at least 80% power and a significance level of 0.05. All volunteers were within 15% of ideal body weight, with a mean weight of 75 kg (range 59–93 kg) and mean age of 29.4 years (range 24–34 years). The history and physical examination, ECG, haematological and biochemical tests showed no abnormal findings. None of the volunteers had a previous history of alcohol abuse, and none of the women was taking oral contraceptives. Women of childbearing potential had negative urine pregnancy screens before each phase of the study. Alcohol and medications (except paracetamol (acetaminophen)) were not allowed for 7 days prior to and for the duration of the study.

The study was conducted on an inpatient basis. A randomized two-way crossover design was applied with 2 weeks of washout between study arms. The two arms of the study were (1) administration of a single 20 mg dosage of lovastatin orally (2) administration of a 20 mg dosage of lovastatin orally 1 h after a constant infusion (10 mg h^{-1}) of diltiazem that was preceded by a diltiazem intravenous loading dosage (20 mg) infused over 2 min. The constant infusion of diltiazem lasted for 13 h. The recommended loading dosage for intravenous diltiazem is 0.25 mg kg^{-1} , increasing to 0.35 mg kg^{-1} in refractory cases, and the recommended infusion rate is $5\text{--}10 \text{ mg h}^{-1}$ [17].

Blood samples for determining lovastatin serum concentrations were obtained at 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after dosing. Diltiazem concentrations were assayed in the previous mentioned samples in addition to samples obtained at 1.25, 1.75, 3.5, 5, 7, 9, 13, and 25 h following initiation of the constant diltiazem infusion. The serum samples were stored at -20°C until assayed.

Drug assays

Diltiazem concentrations in serum samples were quantified by a high performance liquid chromatography (h.p.l.c.) method that has been reported previously [16]. The intraday and interday coefficients of variation were 10% or less. Serum concentrations of lovastatin were determined by a method that used gas chromatography-mass spectrometry, which has been described in detail previously [16]. The intraday and interday coefficients of variation were less than 10%.

Data analysis

The area under the serum concentration-time curve (AUC) up to the last measured sample was determined by a combination of log trapezoidal and linear trapezoidal methods [18]. The maximum concentration (C_{max}) was the maximum observed concentration. The time of the

Figure 1 Mean lovastatin serum concentrations with time for the study arm that received lovastatin alone (●) and for the study arm that received lovastatin in the presence of intravenous diltiazem (○). Lines are drawn to connect the points. Standard deviations are depicted for each mean value.

maximum concentration is t_{max} . All data are expressed as mean values $\pm$ standard deviation and were analysed by the two sided Student's t -test for paired values at a significance level of $P \leq 0.05$ or by ANOVA at the same significance level.

Results

The mean lovastatin concentrations in the control and intravenous diltiazem treatment is shown in Figure 1. Table 1 lists the pharmacokinetic parameters for lovastatin in the control and intravenous diltiazem groups. There was no statistically significant difference between the two groups when comparing AUC, C_{max} , and t_{max} . In addition

Figure 2 Mean diltiazem serum concentrations with time. Diltiazem was administered as an intravenous loading dosage of 20 mg infused over 2 min, followed by a 10 mg h^{-1} constant infusion for the next 13 h. The line is drawn to connect the points. Standard deviations are depicted for each mean value.

Table 1 Pharmacokinetics of lovastatin alone and lovastatin during diltiazem treatment.

Volunteer	AUC (ng ml ⁻¹ h)		t _{1/2} (h)		C _{max} (ng ml ⁻¹)		t _{max} (h)	
	L	L + DTZ	L	L + DTZ	L	L + DTZ	L	L + DTZ
1	48	110	*	13	4.3	24.8	2.5	2.5
2	58	102	*	28	7.2	13.5	2.5	2.5
3	42	58	12	*	4.3	3.3	4.0	12.0
4	29	29	27	37	1.8	2.8	4.0	2.0
5	75	22	8	4	19.6	3.6	2.5	3.0
6	47	61	9	39	6.4	6.3	2.5	2.5
7	72	114	33	*	4.6	6.8	0.8	8.0
8	19	39	6	20	2.4	3.1	4.0	6.0
9	129	144	9	20	15.8	19.6	3.0	3.0
10	125	126	35	7	15.2	8.2	1.5	6.0
Mean	64	81	17	21	8.2	9.2	2.7	4.8
s.d.	37.2	43.8	12.2	13.0	6.31	7.67	1.08	3.25
C.I.	-39, 6		-26, 5		-8, 6		-4, 0	

L = lovastatin L + DTZ = lovastatin during diltiazem treatment. * unable to estimate $t_{1/2}$. C.I. = 95% confidence interval for differences.

there were no treatment, sequence, and period effects based on results from a three-way ANOVA.

The mean diltiazem concentrations, which ranged from 73 to 140 ng ml⁻¹ (0.18–0.34 μ M) throughout the infusion, are illustrated in Figure 2.

Discussion

The cytochrome P450 (CYP) enzymes in the 3A subfamily, originally identified as the major xenobiotic monooxygenase in the liver, are also abundant in mature enterocytes of the small intestine [19]. High enzyme levels in enterocytes are thought to account for the significant first-pass metabolism of many CYP3A substrates [19–21]. It follows that inhibition of CYP3A in the gut would decrease first-pass metabolism, with a corresponding increase in peak concentrations, AUC, and half-life [21]. Such a mechanism has been proposed for the interaction of oral diltiazem with cyclosporin and lovastatin during which oral coadministration of the drugs increased the AUC dramatically [16]. Presumably, with oral dosing, high concentrations of diltiazem and other inhibitors accumulate in the gut villi and effectively inhibit CYP3A4 metabolism, thereby causing enhanced parent compound bioavailability.

Paine and associates compared the metabolism of intraduodenally and intravenously administered midazolam in patients during the anhepatic phase of liver transplantation [22]. The fraction of midazolam that was metabolized after passage through the intestinal mucosa was 43%; in contrast, only 8% of intravenous drug passing through the splanchnic vascular bed was metabolized [22]. These data strengthen the assumption that the gut makes only a small contribution to systemic drug clearance, and

further implies that metabolizing enzymes in the intestinal villi are exposed to minimal amounts of intravenous drug. Hence, if a given interaction is truly a first-pass effect isolated to the gut wall, one would not expect to see the same effect on oral substrate metabolism with administration of the inhibitor intravenously.

This hypothesis is consistent with a previous study that characterized the inhibition of lovastatin by diltiazem [16] and by the accompanying clinical study that showed that intravenous diltiazem did not inhibit lovastatin metabolism. These studies support the assertion that the primary site of oral diltiazem inhibition is at the luminal wall of the intestine and that drug interactions with diltiazem may become evident when a patient is moved from intravenous to oral diltiazem.

This study also validates the supposition that the gut villi are minimally exposed to intravenous drug. If significant amounts of diltiazem were diffusing from the blood stream into the gut villi, CYP3A4 inhibition with consequent elevation of plasma drug concentrations would be expected. An absence of this finding is the expected result, and there are three possible explanations for this. First, CYP3A4 has been localized in terminally differentiated enterocytes towards the villus tip, which probably have limited perfusion [22]. Second, diltiazem is highly protein bound, meaning there is little concentration gradient to drive drug across the gut epithelium and into the villi. Third, the diltiazem infusion may have been too short to allow diffusion of adequate amounts of diltiazem to the villi. The recommended dose of intravenous diltiazem is 25 mg kg⁻¹, and the recommended infusion rate is 5–10 mg h⁻¹ [17]. In the present study the effect of intravenous diltiazem on oral lovastatin was evaluated by administering a loading dose of 20 mg that was followed

with an infusion of 10 mg h^{-1} for 13 h. This regimen resulted in plasma concentrations of diltiazem, $0.18\text{--}0.34 \text{ }\mu\text{M}$, comparable to studies that had administered oral diltiazem for 2 weeks [16, 23]. Studies with long-term infusions of intravenous CYP3A inhibitors should be considered to determine if infusion time affects inhibition.

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