Lack of interaction between nefazodone and cimetidine: a steady state pharmacokinetic study in humans

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The steady-state pharmacokinetic interaction between nefazodone and cimetidine was evaluated in a three-period crossover study consisting of three treatments of 1 week duration with a 1 week washout between treatments. The 18 healthy, male study subjects received: nefazodone hydrochloride 200 mg twice daily (every 12 h) for 6 days; cimetidine 300 mg four times daily for 6 days; and 200 mg nefazodone hydrochloride twice daily + 300 mg cimetidine four times daily for 6 days. On day 7 of each treatment, only the morning dose was administered. Serial blood samples were collected for pharmacokinetic analysis after drug administration on day 7 of each treatment; blood samples for trough levels ($C_{\min}$) to assess attainment of steady state, were also collected just prior to the morning doses on days 2–7 of each study period. Plasma samples were assayed for cimetidine, and nefazodone and its metabolites hydroxynefazodone and *m*-chlorophenylpiperazine by specific, validated h.p.l.c. methods. Statistical analyses of $C_{\min}$ data indicated that, regardless of treatment, steady state was achieved for cimetidine by day 2 and for nefazodone and its metabolites by day 3 of multiple dosing, and that there were no significant differences in $C_{\min}$ levels between treatments. When nefazodone and cimetidine were co-administered for 1 week, no change in steady-state pharmacokinetic parameters for cimetidine, nefazodone or hydroxynefazodone was observed compared with each drug dosed alone. However, steady-state $C_{\max}$ and AUC(τ) values for *m*-chlorophenylpiperazine, a minor metabolite of nefazodone, were higher ($\approx 37\%$) when nefazodone and cimetidine were co-administered. The results indicate that therapeutic doses of nefazodone and cimetidine may be co-administered chronically without adjusting the usual dosage regimen of either drug.

Keywords nefazodone cimetidine drug interaction

Introduction

Nefazodone, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl-5-ethyl-2,4-dihydro-4-(2-phenoxy-ethyl)-3*H*-1,2,4-triazol-3-one hydrochloride (NEF, Serzone®), is a new selective serotonin reuptake inhibitor anti-depressant drug [1]. The pharmacokinetics of nefazodone have been shown to be non-linear and considerable inter-subject variability has been observed in the pharmacokinetic parameters [2]. Nefazodone is extensively metabolized [3] to hydroxynefazodone (HO-NEF) and *m*-chlorophenyl-

piperazine (*m*CPP). Since cimetidine has been reported to inhibit the cytochrome P-450 mediated metabolism of many drugs [4] and since nefazodone undergoes extensive oxidative metabolism, it is possible that both nefazodone and cimetidine could inhibit the metabolism of each other and thus dosage adjustment may be necessary for achieving optimum therapeutic response during concurrent therapy with nefazodone and cimetidine.

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Methods

Study design and drug analysis

This was an open-label, randomized, multiple-dose, three-period complete crossover study consisting of three treatments of 1 week duration with a 1 week washout between treatments. After being advised of the nature and risks of the study and giving written informed consent, 18 healthy male volunteers were enrolled. The protocol and informed consent form were approved by the local Institutional Review Board. The ages of the volunteers ranged from 19 to 40 years (mean 27.4 years); heights from 170 to 193 cm (mean 179.3 cm); weights from 60 to 94.5 kg (mean 76.1 kg). Subjects were required to abstain from drug use of any kind for 1 week prior to the study, and from any agent known to induce or inhibit drug-metabolizing enzymes for 1 month prior to the study. None of the subjects was administered drugs other than cimetidine and nefazodone during the study.

The three treatments were: nefazodone hydrochloride 2×100 mg capsules twice daily (every 12 h) for 6 days; cimetidine 1×300 mg tablet (Tagamet®) four times daily (each day, the first three doses were administered 6 h apart and dose 4 was administered 4 h after dose 3) for 6 days; concomitant administration of nefazodone 2×100 mg capsules twice daily and cimetidine 1×300 mg tablet four times daily for 6 days. On day 7 of each treatment, only a single morning dose was administered. During combined dosing nefazodone was administered first followed by cimetidine within 5 min. Each dose was administered with about 200 ml of water. The subjects did not eat for 2 h before and after each scheduled dose on days 1–6 of each study period; subjects also fasted overnight for 10 h prior to and for 2 h after dosing on day 7 of each study period. Serial blood samples were collected in tubes containing tripotassium EDTA predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h after the morning dose on day 7 of each study period. Blood samples for determining trough ($C_{\min}$) levels were obtained on days 2–7 of each study period in the morning immediately prior to dosing to assess the attainment of steady state. The plasma was stored frozen at or below -20°C until assay.

Cimetidine plasma concentrations were measured using a validated h.p.l.c./u.v. method that was based on two previously published assays [5, 6]. Nefazodone and its metabolites did not interfere with the assay of cimetidine as demonstrated by assaying some plasma samples from subjects who had been administered nefazodone alone. Nefazodone, HO-NEF and *m*CPP concentrations in plasma samples were determined using a validated robotic h.p.l.c./u.v. assay method [7]. Cimetidine or its metabolites did not interfere with the assay of nefazodone or its metabolites as demonstrated by assaying some plasma samples from subjects who had been administered cimetidine alone. Standard curves for nefazodone and its metabolites and cimetidine demonstrated good reproducibility and had correlation coefficients > 0.995 . Predicted QC concentrations were within

15% of normal values and the between and within day variability (% RSD) of predicted QC concentrations was $\leq 8.3\%$ confirming the accuracy and precision of the analytical runs and study sample stability.

Pharmacokinetic and statistical analysis

Plasma concentration vs time data for cimetidine and nefazodone and its metabolites were analyzed by non-compartmental methods [8]. The AUC for a dosing interval was designated as $\text{AUC}(\tau)$. $\text{AUC}(\tau)$ for NEF, HO-NEF and *m*CPP was AUC from 0–12 h and for cimetidine, AUC from 0–6 h after the morning dose on day 7.

The attainment of steady state in each treatment group for each analyte was evaluated with a randomized block ANOVA to determine if day 2 through day 7 $C_{\min}$ values varied over time. If statistically significant differences were observed among days, then Tukey's multiple comparisons procedure [9] was used to determine on which day steady state was achieved. The steady-state (day 7) pharmacokinetic parameters (peak concentration ($C_{\max}$), half-life ($t_{1/2,z}$), $\text{AUC}(\tau)$, and $C_{\min}$) were analyzed by an ANOVA appropriate for this three-period complete crossover study. Steady-state $t_{\max}$ values were compared using Wilcoxon's signed rank procedure [10]. With the exception of Levene's test, all tests of significance were performed at the $P = 0.05$ level.

Results and Discussion

Concomitant administration did not affect the plasma levels of cimetidine, nefazodone or hydroxynefazodone, but *m*-chlorophenylpiperazine plasma levels were elevated by co-administration of cimetidine and nefazodone (Figure 1).

The mean pharmacokinetic parameter values of cimetidine, nefazodone, hydroxynefazodone and *m*-chlorophenylpiperazine are listed in Table 1. Statistical analyses of the $C_{\min}$ data collected on study days 2–7 revealed that steady state was achieved by day 2 for cimetidine and by day 3 for nefazodone and its metabolites whether nefazodone and cimetidine were administered alone or concomitantly. For cimetidine, the small differences in mean steady-state $C_{\min}$, $C_{\max}$, $t_{\max}$, $t_{1/2,z}$ and $\text{AUC}(\tau)$ values between treatments were not statistically significant. For nefazodone and hydroxynefazodone, although mean steady-state parameters tended to be slightly increased ($C_{\min} \approx 25\%$, and $C_{\max}$, $t_{1/2,z}$ and $\text{AUC}(\tau)$, all $< 10\%$) when nefazodone was co-administered with cimetidine, no statistically significant differences were obtained. The mean steady-state $C_{\min}$ for *m*CPP was about 50% higher when nefazodone and cimetidine were co-administered. This difference was not statistically significant, probably because of the high variability of the data. However, co-administration of nefazodone and cimetidine did result in significantly

Figure 1 Mean steady-state plasma concentration-time profiles for cimetine (CMET), nefazodone (NEF), hydroxynefazodone (HO-NEF) and *m*-chlorophenylpiperazine (*m*CPP) after administration of cimetine and nefazodone alone (○) or concomitantly (●).

higher ($\approx 37\%$) mean $C_{\max}$ and $AUC(\tau)$ values for *m*CPP. As was observed for cimetine, nefazodone and hydroxynefazodone, the half-life and $t_{\max}$ values for *m*CPP did not change significantly when cimetine and nefazodone were coadministered.

Nefazodone undergoes almost complete oxidative metabolism by *N*-dealkylation and aliphatic and aromatic hydroxylation with subsequent elimination of conjugated and free metabolites in the urine and faeces [3]. Recently the cytochrome P450IIIA sub-family has been implicated in the hydroxylation of nefazodone (R. I. Shader, personal communication.) The elimination of *m*CPP in humans by metabolism to *p*-hydroxy-*m*CPP is subject to oxidative polymorphism of the debrisoquine/dextromethorphan type [11] and strongly implicates cytochrome P450IID6-mediated metabolism as the rate limiting step in the clearance of *m*CPP. When nefazodone is administered

with alprazolam or triazolam, clearance of these two triazolobenzodiazepines is significantly reduced [12, 13]. Cimetine inhibits the clearance of many drugs including alprazolam and triazolam [14, 15], warfarin [16], diazepam [17], phenytoin [18], nifedipine [19], propranolol [20], lignocaine [21] and theophylline [22]. It is considered to be a non-selective inhibitor of oxidative drug metabolism because it interacts directly with the haem iron of P450 isozymes through one of the nitrogen atoms in the imidazole nucleus [23]. However, the inhibitory potency of cimetine on drug metabolism by individual human liver cytochrome P450 isozymes *in vitro* has been shown to be highly variable [24]. This may be reflected in the present results since the disposition of nefazodone was not significantly affected by cimetine coadministration.

In conclusion, we consider that at therapeutic

Table 1 Mean ($\pm$ s.d.) pharmacokinetic parameters for cimetidine (CMET), nefazodone (NEF), hydroxynefazodone and *m*-chlorophenylpiperazine ($n = 18$ subjects/treatment)

Parameter	Study day	Cimetidine		Nefazodone		Hydroxynefazodone		<i>m</i> -Chlorophenylpiperazine	
		CMET	NEF + CMET	NEF	NEF + CMET	NEF	NEF + CMET	NEF	NEF + CMET
$C_{\min}$ (ng ml ⁻¹)	2	257 (97)	241 (117)	88.0 (107)	88.4 (62)	58.5 (48.0)	48.5 (29.1)	15.2 (13.9)	19.7 (13.5)
	3	261 (85)	288 (118)	109 (159)	152 (139)	56.1 (66.0)	83.1 (67.7)	12.0 (6.0)	24.1 (21.4)
	4	238 (115)	245 (94)	127 (170)	197 (177)	65.4 (71.3)	85.8 (80.0)	15.7 (16.8)	24.9 (23.9)
	5	211 (92)	260 (179)	125 (216)	170 (152)	63.0 (83.7)	76.0 (58.0)	18.1 (19.8)	25.1 (20.5)
	6	223 (103)	247 (95)	142 (206)	161 (141)	70.5 (85.2)	85.0 (72.5)	18.6 (19.2)	26.5 (24.4)
	7	281 (112)	298 (124)	120 (132)	165 (111)	62.5 (60.7)	81.1 (55.0)	16.6 (16.3)	27.2 (23.0)
	S-S ^a	243 (83)	265 (93)	129 (173)	162 (119)	62.1 (69.3)	77.3 (55.4)	16.5 (15.1)	24.6 (21.4)
$C_{\max}$ (ng ml ⁻¹)	7	1315 (365)	1323 (776)	1540 (985)	1646 (772)	406 (163)	423 (151)	42.4 (26.7)	57.8 ^d (35.4)
$t_{\max}^b$ (h)	7	1.5 (0.5–3.0)	1.5 (0.5–3.0)	1.0 (0.5–3.0)	1.5 (0.5–3.0)	2.0 (0.5–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.5 (1.0–6.0)
$t_{1/2}$ (h)	7	3.97 (4.00)	4.78 (4.67)	3.23 (1.07)	3.53 (1.38)	3.18 (1.10)	3.30 (1.27)	8.96 (6.14)	8.86 (4.61)
AUC (τ) ^c (ng ml ⁻¹ h)	7	4390 (1107)	4119 (1266)	7129 (5181)	7650 (4399)	2694 (1510)	2777 (1332)	329 (242)	453 ^d (332)

^aSteady-state $C_{\min}$, which is the mean of $C_{\min}$ values on study days 3–7. ^bMedian (range) presented. ^cAUC over a dosing interval: 0–12 h for nefazodone and its metabolites, and 0–6 h for cimetidine. ^d $P < 0.05$.

doses, co-administration of nefazodone and cimetidine does not result in a clinically significant pharmacokinetic interaction. Therefore, dosage adjustment is not necessary for either drug when they are co-administered.

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References

- 1 Feighner JP, Pambakian R, Fowler RC, Boyer WF, D'Amico MF. A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. *Psychopharmacol Bull* 1989; **25**: 219–221.
- 2 Kaul S, Shukla UA, Barbhuiya RH. Nonlinear pharmacokinetics of nefazodone after escalating single and multiple oral doses. *J Clin Pharmacol* 1995; (in press).
- 3 Mayol RF, Cole CA, Luke GM, Colson KL, Kerns EH. Characterization of the metabolites of the antidepressant drug nefazodone in human urine and plasma. *Drug Metab Dispos* 1994; **22**: 304–311.
- 4 Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine. *Clin Pharmacokinet* 1987; **12**: 321–366.
- 5 Lorenzo B, Drayer DE. Improved method for the measurement of cimetidine in human serum by reverse phase high pressure liquid chromatography. *J Lab Clin Med* 1981; **97**: 545–550.
- 6 Kunitani MG, Johnson DA, Upton RA, Riegelman S. Convenient and sensitive high performance liquid chromatography assay for cimetidine in human plasma or urine. *J Chromatogr* 1981; **224**: 156–161.
- 7 Franc JE, Duncan GF, Farnen RH, Pittman KA. High-performance liquid chromatographic method for the determination of nefazodone and its metabolites in human plasma using laboratory robotics. *J Chromatogr* 1991; **570**: 129–138.
- 8 Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd Ed. Marcel-Dekker, New York, 1982.
- 9 Gill JL. *Design and analysis of experiments in the animal and medical sciences*. The Iowa State University Press, Ames, IA, 1978; pp. 179–182.
- 10 Box GEP, Cox DR. Analysis of transformations. *J Roy Stat Soc (Series B)* 1964; **26**: 211–252.
- 11 Buch AB, Shukla UA, Pittman K, Barbhuiya RH. Pharmacokinetics of nefazodone (NEF) in extensive (EM) and poor (PM) metabolizers of dextromethorphan. *Pharm Res* 1993; **10**: S-314.
- 12 Barbhuiya RH, Shukla UA, Kroboth PD, Greene DS. Co-administration of nefazodone and benzodiazepines: II. A pharmacokinetic interaction study with triazolam. *J Clin Psychopharmacol* 1995; (in press).
- 13 Greene DS, Salazar DE, Dockens RC, Barbhuiya RH. Co-administration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. *J Clin Psychopharmacol* 1995; (in press).
- 14 Abernethy DR, Greenblatt DJ, Divoll M, Moschitto L, Harmatz JS, Shader RI. Interaction of cimetidine with the triazolobenzodiazepines alprazolam and triazolam. *Psychopharmacol* 1983; **80**: 275–278.
- 15 Pourbaix S, Desager JP, Hulhoven R, Smith RB, Harvenge C. Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1985; **23**: 447–451.
- 16 Silver BA, Bell WR. Cimetidine potentiates the hypoprothrombinemic effect of warfarin. *Ann Intern Med* 1979; **90**: 348–349.
- 17 Klotz U, Reimann I. Delayed clearance of diazepam due to cimetidine. *New Eng J Med* 1980; **302**: 1012–1014.
- 18 Hetzel DJ, Bochner F, Hallpike JF, Shearman DJ, Hann CS. Cimetidine interaction with phenytoin. *Br Med J* 1981; **282**: 1512.
- 19 Khan A, Langley SJ, Mullins FG, Dixon JS, Toon S. The pharmacokinetics and pharmacodynamics of nifedipine at steady state during concomitant administration of cimetidine or high dose ranitidine. *Br J Clin Pharmacol* 1991; **32**: 519–522.
- 20 Donovan MA, Heagerty AM, Patel L, Castleden M, Pohl JEF. Cimetidine and the bioavailability of propranolol. *Lancet* 1984; **i**: 164.
- 21 Wood M. Pharmacokinetic drug interactions in anesthetic practice. *Clin Pharmacokinet* 1991; **21**: 285–307.
- 22 Upton RA. Pharmacokinetic interactions between theophylline and other medication (Parts I & II). *Clin Pharmacokinet* 1991; **20**: 66–80 and 135–150.
- 23 Wilkinson CF, Hetnarski K, Yellin TO. Imidazole derivatives—a new class of microsomal enzyme inhibitors. *Biochem Pharmacol* 1972; **21**: 3187–3192.
- 24 Knodell RG, Browne DG, Gwozdz GP, Brian WP, Guengerich FP. Differential inhibition of individual human liver cytochromes P-450 by cimetidine. *Gastroenterology* 1991; **101**: 1680–1691.

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