Lack of an effect of nefazodone on the pharmacokinetics and pharmacodynamics of theophylline during concurrent administration in patients with chronic obstructive pulmonary disease

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The effect of nefazodone on the pharmacokinetics and pharmacodynamics of theophylline was evaluated in a multiple-dose, randomized placebo-controlled, double-blind two-period crossover study in 13 patients who were undergoing theophylline therapy for chronic obstructive pulmonary disease. Two treatments were administered, each for 7 days: theophylline + 200 mg nefazodone twice daily (every 12h) and theophylline + matching nefazodone placebo capsule twice daily (every 12h). Mean peak and trough plasma concentrations of theophylline ranged from 13.1 to 14.5 $\mu\text{g ml}^{-1}$ and 11.6 to 14.2 $\mu\text{g ml}^{-1}$, respectively, at steady-state when theophylline was administered with or without concurrent dosing of nefazodone. Similarly, the mean area under the curve for theophylline ranged from 93.5 to 103 $\mu\text{g ml}^{-1} \text{ h}$. When nefazodone and theophylline were co-administered, theophylline pharmacokinetic parameters did not significantly differ from those obtained when theophylline was administered with placebo. Forced expiratory volume in one second (FEV_1) measurements taken when nefazodone or placebo were administered with theophylline did not differ from those obtained at baseline. The plasma concentration-time profiles for nefazodone and its metabolites were similar to those in other studies where nefazodone was administered alone. Since nefazodone did not affect the pharmacokinetics or the pharmacodynamics of theophylline, no change in theophylline dose should be needed as a consequence of nefazodone co-administration.

Keywords nefazodone theophylline drug interaction

Introduction

Nefazodone (Serzone®), 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]-propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride, is a new antidepressant [1]. Concomitant administration of nefazodone has been shown to reduce the clearance of triazolam [2] and alprazolam [3] as a result of competitive inhibition of oxidative metabolism. Theophylline, also subject to oxidative metabolism, is a drug with a narrow therapeutic index and usually requires careful monitoring of serum concentrations for safe use in patients. Therefore, this study was designed

to investigate potential pharmacokinetic and pharmacodynamic interactions when theophylline and nefazodone are coadministered.

Methods

This was a multiple-dose, randomized placebo-controlled, double-blind two-period crossover study in which theophylline administration throughout the study continued according to the subject's regimen that was established for at least 2 weeks prior to study initiation.

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Nefazodone, 200 mg twice daily (every 12h) or placebo (every 12h) dosing, using blinded capsules, was administered on day 1 and continued through day 6 of each study period. On day 7 of each treatment, only the morning dose of nefazodone or placebo was administered. There was a 7–10 day washout for nefazodone between study periods after which treatments were crossed over.

After being advised of the nature and risks of the study and giving written consent, 13 subjects (eight men and five women) were enrolled. All subjects were being treated with theophylline for chronic obstructive pulmonary disease, but were otherwise in good health as determined by medical history, physical examination and clinical laboratory tests conducted prior to the study. Subjects received daily doses (600–1200 mg) of controlled-release theophylline (administered either once, twice or three times daily). Each dose was administered with about 200 ml water. Meals were timed so that subjects fasted for 10 h overnight prior to and for an additional 4 h after the dose administered the morning of days 1 and 7 of each study period. Subject ages ranged from 42 to 75 years (mean 57 years); weights from 61 to 128 kg (mean 80 kg); heights from 152–183 cm (mean 167 cm).

Venous blood samples were collected pre-dose on day 3 and pre-dose and at 1, 2, 3, 4, 5, 6, 7, and 8 h after the morning theophylline dose on days 1 and 7 of each study period. Immediately after collection, each blood sample was centrifuged to separate the plasma. Plasma was stored frozen at or below -20°C until assayed for theophylline and nefazodone (NEF) and nefazodone metabolites hydroxynefazodone (HO-NEF), triazoledione (DIONE) and *m*-chlorophenylpiperazine (mCPP). Theophylline was assayed using a validated assay using a modification of a published h.p.l.c. method [4]. Sets of plasma standards containing theophylline (0.05 – $10\text{ }\mu\text{g ml}^{-1}$) were freshly prepared and assayed in every assay session. The low-standard concentration defined the lower limit of quantitation (LLQ) of the assay. The standard curves demonstrated good reproducibility as evidenced by consistency in slope (%CV = 5.3%) and high r^2 (≥ 0.995) for each curve. Predicted quality control (QC) concentrations were within 11% of nominal values and between and within day variability (%RSD) was $\leq 11\%$ confirming the accuracy and precision of the analytical runs and study sample stability. Nefazodone and its metabolites were assayed using a validated robotic h.p.l.c. method [5]. A set of spiked plasma standards containing NEF and DIONE (10 – 1000 ng ml^{-1}), and HO-NEF and mCPP (5 – 500 ng ml^{-1}) were freshly prepared and assayed in every assay session. The lower standard concentration defined the LLQ of the assay. The standard curves demonstrated good reproducibility as evidenced by consistency in slopes (%CV $\leq 8\%$) and high r^2 values (≥ 0.991). Predicted QC concentrations were within 10% of nominal values and between and within day variability (%RSD) was $\leq 11\%$ for all analytes confirming the accuracy and precision of the analytical runs and study sample stability. Forced expiratory volume in one second (FEV₁) measurements, expressed as per cent

of total expiratory volume, were performed prior to the start of each treatment and prior to dosing on day 7 of each treatment to determine the effect of nefazodone on theophylline pharmacodynamics.

Plasma concentration *vs* time data for theophylline were analysed by non-compartmental methods [6]. ANOVA was performed on log-transformed theophylline pharmacokinetic and untransformed pharmacodynamic parameters (i.e. C_{max} , AUC(0,8 h), C_{min} and FEV₁) to evaluate the effect of nefazodone on theophylline, with $P < 0.05$ regarded as significant. The 95% confidence intervals for the mean difference (theophylline/NEF–theophylline/placebo) were based on the ANOVA from the log-transformed data. Treatment differences become log differences which, in antilog, are equivalent to a ratio. Therefore, testing the hypothesis of no difference in log means is equivalent to testing the hypothesis that the ratio (antilog) is not significantly different from 1.

Results

There were no serious or unanticipated adverse events associated with the use of nefazodone or theophylline. The coadministration of theophylline and 200 mg twice daily doses of nefazodone was safe and well tolerated. Concomitant administration of nefazodone did not affect theophylline plasma level profiles (Figure 1). Mean peak and trough plasma concentrations of theophylline ranged from 13.1 to $14.5\text{ }\mu\text{g ml}^{-1}$ and 11.6 to $14.2\text{ }\mu\text{g ml}^{-1}$, respectively, at steady-state when theophylline was administered with or without concurrent dosing of nefazodone. Similarly, the mean area under the curve for theophylline ranged from 93.5 to $103\text{ }\mu\text{g ml}^{-1}\text{ h}$. Statistical analyses of the C_{min} data indicated theophylline steady-state plasma levels were maintained during the 7 day treatment period (Table 1). In addition, there were no significant differences in mean FEV₁ values or steady-state theophylline C_{max} , C_{min} and AUC(0,8 h) values between treatments.

Figure 1 Mean plasma concentration-time profiles for theophylline with (—○—) and without (—●—) co-administration of nefazodone.

Table 1 Mean (s.d.) pharmacokinetic and pharmacodynamic parameters for theophylline with and without co-administration of nefazodone.

Study day	Treatment ^a	C_{min} ($\mu\text{g ml}^{-1}$)	C_{max} ($\mu\text{g ml}^{-1}$)	AUC (0,8 h) ($\mu\text{g ml}^{-1} \text{ h}$)	FEV ₁ ^e (%)
1	Theophylline/NEF	12.7 (3.8)	13.5 (3.3)	93.5 (20)	—
	Theophylline/placebo	11.6 (2.4)	13.1 (2.2)	93.8 (16)	—
	95% confidence interval on difference ^b	0.92–1.26	0.90–1.16	0.88–1.11	
3	Theophylline/NEF	13.0 (3.6)	—	—	—
	Theophylline/placebo	11.7 (3.3)	—	—	—
	95% confidence interval on difference	0.94–1.31			
7	Theophylline/NEF	12.7 (3.3)	13.8 (3.1)	100 (23)	59 (25)
	Theophylline/placebo	14.2 (3.0)	14.5 (3.1)	103 (23)	59 (28)
	95% confidence interval on difference	0.76–1.04	0.84–1.08	0.88–1.10	0.92–1.08
	Treatment differences	NS ^{c,d}	NS ^d	NS ^d	NS ^d

^a Theophylline 600–1200 mg⁻¹ day; nefazodone 200 mg twice daily (every 12h); placebo twice daily (every 12h) as for NEF.

^b These are limits based on differences in log means which are equivalent to a ratio. The confidence interval containing the value 1 indicates no treatment difference.

^c No significant differences among study days for either treatment.

^d NS=no significant differences between treatments on a given study day.

^e FEV₁(%) is the percent of total forced expiratory volume that was expired in 1 s.

When administered with theophylline, the mean nefazodone C_{max} concentrations were 453 and 1523 ng ml⁻¹, for days 1 and 7, respectively. AUC(0,8 h) values were 1665 and 7674 ng ml⁻¹ h, respectively, and median t_{max} values were 1.5 and 2.0 h, respectively. The pharmacokinetics of nefazodone and its metabolites are shown in Table 2.

Discussion

Since this study was designed to assess the effects of nefazodone on the pharmacokinetics and pharmacodyn-

amics of theophylline, and patients required theophylline therapy, nefazodone was not administered to the subjects in the absence of theophylline. Therefore, the effect of theophylline on nefazodone pharmacokinetics cannot be directly evaluated. However, the pharmacokinetic parameters for nefazodone and its metabolites observed in the present study were similar to those seen when nefazodone was the sole drug administered [7].

Theophylline undergoes extensive metabolism in humans and forms three major metabolites by parallel pathways by both first-order and capacity-limited kinetic processes [8]. The major metabolite 1,3-dimethyluric acid is formed by hydroxylation in the C-8 position while 3-methylxanthine and the intermediate metabo-

Table 2 Mean (s.d.) pharmacokinetic parameters for nefazodone and its metabolites with co-administration of theophylline.

Study day	Treatment ^a	Parameter	Analyte			
			NEF	NO-NEF	mCPP	DIONE
1	Theophylline/NEF	C_{max} (ng ml ⁻¹)	453 (239)	174 (92)	34 (10)	950 (208)
		t_{max} ^b (h)	1.5 (1.0, 5.0)	1.5 (1.0, 5.0)	2.0 (1.0, 6.0)	5.0 (1.0, 7.0)
		AUC (0,8 h) (ng ml ⁻¹ h)	1665 (945)	758 (442)	159 (61)	5349 (1304)
		C_{max} (ng ml ⁻¹)	1523 (898)	456 (224)	37 (19)	1585 (588)
		t_{max} ^b (h)	2.0 (1.0, 5.0)	4.0 (1.0, 6.0)	4.0 (1.0, 6.0)	5.0 (0.0, 8.0)
7	Theophylline/NEF	AUC (0,8 h) (ng ml ⁻¹ h)	7674 (5381)	2780 (1701)	224 (121)	10098 (3551)

^a Theophylline 600–1200 mg⁻¹ day; nefazodone 200 mg twice daily (every 12h).

^b Median (Minimum, Maximum)

lite, 1-methylxanthine, result from *N*-demethylation. Xanthine oxidase converts 1-methylxanthine to 1-methyluric acid. A competitive inhibition of metabolism of theophylline could occur from common oxidative or *N*-demethylation metabolic pathways. C-8 hydroxylation and *N*-demethylation processes are mediated by CYP1A2 [9–12]. CYP1A2 and CYP2E1 are responsible for the 8-hydroxylation of theophylline while CYP2D6 plays only a minor role and CYP3A4 does not play a role in the *in vitro* metabolism of theophylline [11,12]. Interactions between theophylline and erythromycin [13,14], cimetidine and other drugs [8,16] have been noted to result in a decreased theophylline clearance due to processes not yet delineated.

Co-administration of nefazodone did not affect the pharmacokinetics or pharmacodynamics of theophylline. This lack of interaction is consistent with recent *in vitro* metabolic data which show that nefazodone inhibits CYP3A4 but does not inhibit CYP1A2 (R.I. Shader: personal communication, 1994), which is reported to be responsible for metabolism of theophylline [9–12,17]. Therefore, no change in theophylline dose should be needed as a consequence of nefazodone co-administration.

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