Original Article

Coadministration of Nefazodone and Desipramine: a pharmacokinetic interaction study

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Abstract

Objective: To determine the potential for pharmacokinetic interaction between nefazodone (NFZ), and desipramine (DMI).

Method: A single center, open-label, multiple-dose, parallel-group pharmacokinetic trial conducted in 28 healthy male and female subjects. Group A received DMI 50 mg/day for 2 days followed by DMI 75 mg/day for the next 17 days. On Days 10-14, subjects also received 100 mg NFZ twice daily, and during Days 15-19, the NFZ dose was increased to 150 mg twice daily. Group B received 100 mg NFZ twice daily for 5 days followed by 150 mg NFZ twice daily for the next 14 days. On Days 11-12, subjects also received 50 mg DMI and during Days 13-19, the DMI dose was increased to 75 mg daily. Serial blood samples were collected for Group A and Group B. Plasma concentrations of NFZ and its metabolites, mCPP, hydroxynefazodone (OH-NFZ), and triazoledione, DMI, and the DMI metabolite, 2-hydroxydesipramine (2-OH-DMI) were determined.

Results: Pharmacokinetic analysis demonstrated that the addition of NFZ to DMI did not result in any significant changes in the AUC_{0-12}, Cmax, or tmax of either DMI or 2-OH-DMI. Addition of DMI to NFZ resulted in statistically significant increases of 40% in the AUC_{0-12} and 42% in the Cmax of mCPP. A significant decrease in the AUC_{0-12} (19%) of OH-NFZ also was observed. The increase in mCPP may be attributable to inhibition of mCPP metabolism by DMI.

Conclusion: Overall, the combined administration of DMI and NFZ appeared to be safe and well tolerated in both treatment groups (JPMA 57:230;2007).

Introduction

The antidepressant, nefazodone (NFZ), is a potent antagonist of post-synaptic 5-HT2A receptors as well as an inhibitor of neuronal reuptake of both serotonin (5-HT) and norepinephrine (NE). It is chemically unrelated to and pharmacologically distinct from the tricyclic, tetracyclic, and the selective serotonin reuptake inhibitors (SSRIs).[1-3]

The metabolism of nefazodone is well characterized. In vitro[4] and in vivo[5,6] studies have demonstrated that NFZ is both a substrate and an inhibitor of the cytochrome P450-3A4 isoenzyme (CYP3A4). However, nefazodone was considerably weaker (approx. 100-fold) than ketoconazole as an inhibitor of triazolam metabolism in human liver microsomes in vitro.[6] Of the nefazodone metabolites, OH-NFZ is also an inhibitor, but neither mCPP nor triazoledione inhibit CYP3A4. Data from both in vitro and in vivo studies indicate that NFZ and its metabolites do not inhibit P450-1A2 (CYP1A2).[7] NFZ and OH-NFZ have also been shown in vitro to be extremely weak inhibitors of the P450-2D6 isoenzyme (CYP2D6) [at least 20-fold less potent than fluoxetine]. However, when NFZ's metabolism was evaluated in "poor" and "extensive" metabolizers of dextromethorphan (DM), the elimination of mCPP was slower in the "poor" metabolizers, indicating that CYP2D6 may be involved in the hydroxylation of mCPP.[8] Thus, mCPP's metabolism may be affected by other drugs which share the CYP2D6 pathway, or vice versa.

With TCAs having rather small therapeutic indices, it is important to know whether NFZ could inhibit TCA metabolism. The purpose of this study was, therefore, to evaluate in vivo whether NFZ would affect the metabolism of DMI as well as to evaluate whether DMI would affect the metabolism of NFZ.

Subjects and Methods

This was a single-center, open-label, multiple-dose, parallel-group study. The primary objective of the study was to determine whether co-administration of the two drugs would result in a significant change in the Cmax, Tmax, and AUC_{0-12} of either drug in comparison to the Cmax, Tmax, and AUC_{0-12} observed during steady-state treatment with either drug alone.

Eligible subjects were randomly assigned to one of two treatment groups A and B. Group A subjects received DMI 50 mg/day on Days 1-2 of the study. On Day 3, the DMI dose was increased to 75 mg/day and was maintained at this level for the rest of the study (Days 3-19). On Days 10-14, subjects were also treated with 100 mg NFZ twice daily, followed by dose escalation to 150 mg NFZ twice daily on Days 15-19 of the study. Pharmacokinetic profiles for Group A subjects were performed on Day 9,14 and 19. Trough plasma concentrations of DMI and NFZ were determined on Days 7-9, 12-

14 and 17-19 for the purpose of assessing whether steady-state conditions were met.

Group B subjects initially received 100 mg NFZ twice daily on Days 1-5 of the study. On Day 6, the dose of NFZ was increased to 150 mg twice daily and maintained at this level for the rest of the study (Days 6-19). On Days 11-12, subjects were also treated with DMI 50 mg/day, followed by a dose increase to 75 mg/day on Days 13-19. Pharmacokinetic profiles for Group B were performed on Days 10 and 19. Trough plasma concentrations of DMI and NFZ were determined on Days 8-10 and Days 17-19 for the purpose of assessing whether steady-state conditions were met.

Physical examinations, 12-lead EKGs, and laboratory evaluations were conducted at baseline (Day -1) and again on Day 20 prior to discharge from the study center. Follow-up testing was performed as required on Day 22. Additional laboratory evaluations were performed on Day 14 of treatment.

Twenty-eight healthy male (N = 19) and female (N = 9) volunteers between 18 and 40 years of age were enrolled after approval of the protocol by the clinical site's Institutional Review Board.

Subjects males or females between 18-45 years in good general health as determined by medical history, physical examination, 12-lead EKG, and clinical laboratory testing conducted within 2 weeks of the start of the study (screening period) were included.

Subjects were required to be within 15% of ideal body weight according to height (1983 Metropolitan Height and Weight Tables), must have abstained from smoking for at least 2 months prior to screening and women of childbearing potential were required to be practicing an effective method of contraception and to have a negative pregnancy test at screening and a second negative pregnancy test the day before receiving the study drugs.

Subjects with current medical condition, history of a medical condition like indications of cardiovascular (including heart block or arrhythmia), pulmonary, haematopoietic, renal, neurologic, or metabolic dysfunction were excluded

History of allergy, asthma, allergic rhinitis, or allergic rash, history of drug hypersensitivity or drug intolerance to NFZ or DMI, exposure to any investigational drug within 60 days of the start of the study and any condition requiring chronic treatment with drugs or had taken medication of any kind during the week before the start of the study were not considered.

Subjects with a history of drug or alcohol abuse within the previous year or with significant psychiatric disorders (both defined according to DSM III-R criteria), current gastrointestinal disease, surgery, or a history of malabsorption that could affect absorption of the study drug; a positive test result for hepatitis B surface antigens, evidence of glucose-6-phosphate dehydrogenase deficiency; and donation of blood within the month preceding the start of the study or during the study were also excluded.

All study subjects were required to be "extensive" metabolizers via CYP2D6. Thus, potential study candidates were evaluated for DMI-metabolism phenotype during the screening phase of the study and were excluded from participating in the study if they were found to be "poor" metabolizers of DMI. Urinary concentrations (0-8 hr) of DMI and its desmethyl metabolite, dextrophan, were determined by a high-performance liquid chromatography (HPLC) assay using fluorescence detection.[9]

NFZ was supplied as 100 mg nefazodone HCl tablets (Serzone ; Bristol-Myers Squibb Co.). DMI was supplied as 50 or 75 mg desipramine HCl tablets (Norpramin ; Marion Merrell Dow Company). All study medications were dispensed in an unblinded fashion by a staff pharmacist. DMI was administered once daily at 0800 hr. NFZ was administered twice daily at 0800 and 2000 hr. On days when blood samples were taken for pharmacokinetic analysis, study drugs were taken in the morning with 8 ounces of water after an overnight 10-hour fasting period. After receiving the study drugs, subjects were required to continue fasting for an additional 4 hours and to remain upright (sitting or standing) during this period.

Pharmacokinetic analyses were scheduled on Days 9 (DMI 75mg), 14 (DMI 75mg+NFZ 200mg), and 19 (DMI 75mg+NFZ300mg) for Group A, coinciding with the last day of treatment with 75 mg DMI alone, 75 mg DMI plus 100 mg NFZ bid, and 75 mg DMI plus 150 mg NFZ bid.. For group B, pharmacokinetic analyses were scheduled on Days 10 (NFZ 300mg) and 19 (NFZ 300mg+DMI 75mg), coinciding with the last day of treatment with 150 mg NFZ bid and 150 mg NFZ bid plus 75 mg DMI. Venous blood samples were taken before drug administration in the morning, as well as at 20 min, 40 min, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after drug administration for the determination of plasma concentrations of NFZ, its three metabolites (OH-NFZ, mCPP, and triazoledione), DMI, and the 2-hydroxydesipramine metabolite (2-OH-DMI). Additional venous blood samples were drawn before the morning drug administration on Days 7-9, 12-14, and 17-19 from Group A and on Days 8-10 and 17-19 from Group B for the purpose of determining trough plasma concentrations of DMI and NFZ as appropriate. The determination of trough plasma concentrations of DMI and NFZ was used to assess whether steady-state levels of each drug and drug metabolite had been obtained

Plasma samples were analyzed for NFZ, OH-NFZ, mCPP, and triazoledione by a validated HPLC method.[10] The assay demonstrated linearity for NFZ and its metabolites within the following ranges: 5 to 500 ng/mL for mCPP; 10 to 2000 ng/mL for NFZ; 5 to 1000 ng/mL for OH-NFZ; and 10 to 2000 ng/mL for triazoledione.

Plasma samples were analyzed for DMI and 2-OH-DMI using a validated method based on modification of the HPLC method for determining imipramine and metabolites in human plasma.[11] The HPLC assay method was observed to be linear for DMI and 2-OH-DMI within the following range: 5 to 1000 ng/ml.

Pharmacokinetic Analysis: Noncompartmental pharmacokinetic parameters were calculated by standard methods.[12] The highest observed plasma analyte concentration and the corresponding sampling time were defined as Cmax and tmax, respectively. The AUC from 0 to 12 hours (AUC0-12) was calculated according to the method of Riegelman and Collier.[13] A linear trapezoidal rule was used for the portion of the curve before the log-linear phase and a log trapezoidal rule was used for the portion of the curve in the log-linear phase. Trough plasma concentrations (Cmin) of analytes were determined from blood samples taken just before study medication was dispensed at 0800 hr.

Statistical Analysis: The sample size of 8 subjects per treatment group was chosen to provide at least an 87% chance of detecting a 25% change in the AUC of either NFZ or DMI (% = 0.05). Pharmacokinetic parameters including AUC0-12, Cmax, Tmax, and Cmin were calculated from the individual plasma concentration-time curves of subjects who completed the study without significant protocol violations (8 subjects in Group A and 9 subjects in Group B). Paired t-tests were used to compare the pharmacokinetic parameters for DMI on Days 14 and 19 (DMI 75mg+NFZ 200mg; DMI 75mg+NFZ 300mg, respectively) with those obtained on Day 9 (DMI 75mg) for Group A and to compare the pharmacokinetic parameters for NFZ on Day 19 (NFZ 300mg+DMI 75mg) with those obtained on Day 10 (NFZ 300mg) for Group B. Demographic data obtained at baseline and vital sign data obtained throughout the study were analyzed using the chi-square test or Fisher's exact test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. The evaluation of significant change in pharmacokinetic parameters and comparisons between the two treatment groups with respect to demographics and baseline characteristics were performed at a significance level of % = 0.05. All p-values were calculated based on two-tailed tests. All subjects who received at least one dose of either DMI or NFZ were included in the description of the safety data.

Results

Of the 28 subjects (19 males and 9 females) enrolled in the study, a total of 9 subjects prematurely discontinued from the study (3 from Group A and 6 from Group B): 2 discontinued for adverse events (tachycardia during DMI treatment alone and toothache from an infected tooth during treatment with NFZ alone) and 7 discontinued for "personal preferences" (3 prior to receiving any medication). Of the remaining subjects, two subjects in Group B were dosed with DMI in error on Day 8 and were excluded. Thus, the 8 subjects in Group A and 9 subjects in Group B completed the study. The mean age of these subjects was 27.0 $\pm$ 1.5 years, the mean weight was 161.1 $\pm$ 5.4 pounds, and the mean height was 69.1 $\pm$ 0.9 inches. There were no significant differences between the Group A and Group B subjects in terms of age, weight and height.

Effect of Nefazodone on Desipramine Pharmacokinetics (Group A)

There were no statistically significant differences among the Cmin values for DMI and 2-OH-DMI obtained on Days 7-9, indicating that steady-state conditions had been obtained with DMI. Analysis of Cmin values for DMI and 2-OH-DMI on Days 17-19 revealed a significant difference (p 0.05) in concentrations of DMI among the three days, suggesting that steady-state levels of DMI may not have been fully reached by Day 19 of the study. However, no significant increases in the Cmin values of DMI or 2-OH-DMI were observed on Day 19 (DMI 75mg+NFZ 300mg) when compared with Cmin values obtained on Day 9 (DMI 75mg). Mean Cmin values for DMI and 2-OH-DMI (Group A) obtained on study Days 9 and 19 are presented in Table 1. Analysis of Cmin values for NFZ and its metabolites on Days 17-19 indicated that steady-state conditions with NFZ had been attained during combination treatment.

The AUC0-12, Cmax, and Tmax values for DMI and 2-OH-DMI obtained on Day 9 (DMI 75mg), Day 14 (DMI 75mg+NFZ 200mg), and D19 (DMI 75mg+NFZ 300mg) are presented in Table 1. Comparisons of the values obtained on Day 9 with those obtained on Day 14 and Day 19 revealed no significant changes in any of the pharmacokinetic parameters of DMI and 2-OH-DMI during coadministration with NFZ at either dosage.

Effect of Desipramine on Nefazodone Pharmacokinetics (Group B)

There were statistically significant ($p = 0.04$) differences among the Cmin values for mCPP obtained on Days 17-19, but no differences were observed for either NFZ, OH-NFZ, or triazoledione on Days 7-9 and Days 17-19. The Cmin values of NFZ or its metabolites on Day 19 (N300 & D75) were not different than Cmin values obtained on Day 10 (NFZ 300mg). Mean Cmin values for NFZ and its metabolites on Day 10 and Day 19 are presented in Table 2. Overall, these data indicate that steady-state plasma concentrations of NFZ were reached in the presence and absence of DMI.

When DMI at 75 mg was co-administered with NFZ, significant changes in the pharmacokinetic parameters of mCPP and OH-NFZ were observed. The mean AUC0-12 and mean Cmax values of mCPP during the combined treatment phase were significantly increased (44% and 48%, respectively) from values obtained during treatment with NFZ alone ($p<0.01$) table 2. In addition, a statistically significant decrease of 19% ($p=0.05$) in the mean AUC0-12 of OH-NFZ was observed during the combined treatment

Table 1. Effects of Nefazodone (NFZ) on Desipramine (DMI) and 2-Hydroxydesipramine (2-OH-DMI).

Analyte DMI (N=8)	Mean Trough Plasm Conc. ng/mL(mean + SE)	p-value	AUC0-12 ng/mL mean + SE	p-values[b]	Cmax ng/mL mean + SE	p-values[b]	tmax mean + SE	p-values[b]
Day 9 (D 75)	23.1 + 5.4	--	468.7 (90.1)	--	48.3 (9.0)	--	6.0 (0.5)	--
Day 14 (D 75+N 200)		--	478.4 (89.3)	0.642	48.9 (8.7)	0.789	6.0 (0.7)	1.000
Day 19 (D 75+N 300)	27.7 + 7.3	0.084	508.7 (98.9)	0.218	53.2 (9.2)	0.092	5.4 (0.6)	0.250
Analyte 2-OH-DMI=8								
Day 9 (D 75)	14.9 + 2.5	--	302.3 (24.7)	--	32.8 (2.0)	--	4.6 (1.2)	--
Day 14 (D 75+N 200)		--	300.0 (21.2)	0.835	31.0 (1.8)	0.402	3.9 (0.7)	0.629
Day 19 (D 75+N 300)	14.9 + 2.2	0.185	302.7 (22.9)	0.969	32.7 (2.0)	0.973	2.9 (0.2)	0.128

-- p-values not shown due to short sampling time
b: p-values are based on comparison with D 75 treatment period values
D 75 = desipramine 75 mg/day, N 200 = nefazodone 200mg/day, N 300 = nefazodone 150 mg every 12 hrs.

Table 2. Effects of Desipramine (DMI) on Nefazodone (NFZ) and its metabolite Hydroxynefazodone (OH-NFZ), Triazoledione and m-Chlorophenylpiperazine (mCPP).

Analyte by Rx Period	Mean Trough Plasma Conc. ng/mL mean + SE	p-value	AUC0-12 ng/mL mean + SE	p-values[b]	Cmax ng/mL mean + SE	p-values[b]	tmax mean + SE	p-values[b]
NFZ (N=9)								
Day 10 (N 300)	148.7 + 80.4	--	5243 (1511)	--	1332 (200)	--	1.1 (0.1)	--
Day 19 (N 300+D 75)	97.7 + 47.0	0.176	4089 (870)	0.162	1116 (125)	0.243	1.2 (0.2)	0.750
OH-NFZ (N=9)								
Day 10 (N 300)	66.9 + 27.8	--	1866 (363)	--	362 (45)	--	1.7 (0.4)	--
Day 19 (N 300=D 75)	48.1 + 18.9	0.090	1507 (271)	0.047	304 (40)	0.067	1.9 (0.4)	0.648
Triazoledione N=9								
Day 10 (N 300)	656.4 + 130.6	--	11143 (2152)	--	1359 (219)	--	2.6 (0.4)	--
Day 19 (N 300+D 75)	794.9 + 200.6	0.252	13356 (3080)	0.270	1524 (311)	0.363	2.4 (0.3)	0.766
mCPP (N=9)								
Day 10 (N 300)	5.8 + 0.7	--	139 (15)	--	21.2 (2.5)	--	1.8 (0.2)	--
Day 19 (N 300+D 75)	6.6 + 0.8	0.103	194 (18)	0.002	30.0 (3.1)	0.003	2.2 (0.4)	0.198

-- p-values not shown due to short sampling time
b: p-values are based on comparison with D 75 treatment period values
D 75 = desipramine 75 mg/day, N 200 = nefazodone 200mg/day, N 300 = nefazodone 150 mg every 12 hrs.

phase as well as a non-significant decrease of 15% (p=0.07) in mean Cmax with no change in mean Tmax.

Overall, the addition of 150 mg NFZ twice daily to treatment with 75 mg DMI daily (Group A) or the addition of 75 mg DMI daily to 150 mg NFZ twice daily (Group B) did not result in any discernable changes in vital signs (i.e., blood pressure, pulse rate, respiratory rate, 12-lead ECG, and body temperature).

Combined treatment of NFZ and DMI was well tolerated. Only two subjects experienced adverse events that were rated as severe. One subject (Group A) experienced severe tachycardia while receiving DMI only and was withdrawn from the study. Another subject (Group B) experienced severe insomnia approximately 3.5 hours after receiving 150 mg dose of NFZ on the evening of Day 11 (first day of combined NFZ and DMI treatment). The subject continued the study without any further evidence of insomnia.

Discussion

The results presented here demonstrate that the pharmacokinetics of DMI and the 2-OH-DMI metabolite are not significantly changed by coadministration of NFZ. The AUC0-12 and Cmax of DMI and 2-OH-DMI were not significantly increased by the presence of steady-state levels of NFZ (100 mg bid and 150 mg bid). When DMI was added to NFZ, a statistically significant decrease in the AUC0-12 of OH-NFZ and a statistically significant increase in the AUC0-12 and Cmax of mCPP were observed. No statistically significant changes were observed for NFZ and triazoledione.

The lack of effect of NFZ on DMI metabolism is consistent with both in vivo and in vitro data showing that NFZ is metabolized by CYP3A4 and that both NFZ and OH-NFZ are inhibitors of CYP3A4 albeit considerably less potent than ketoconazole. The metabolites mCPP and triazoledione, in contrast, do not inhibit CYP3A4. In addition, these results further support the view that NFZ does not substantially inhibit CYP2D6, consistent with in vitro data.[14]

These results of the lack of effect of NFZ on DMI metabolism have to be viewed carefully since the trough level data suggest that DMI and OH-DMI may not have been at steady-state on Day 19. This means that NFZ may have been having some effect on DMI clearance although the effect is apparently modest. While the analysis of trough levels (Days 17-19) suggested that

steady state had not been reached, comparison of the trough levels on Day 19 with Day 9 showed no difference.

The effects that DMI had on the metabolism of mCPP (increased AUC_{0-12} by 44%) supports previous results suggesting that hydroxylation of mCPP is CYP2D6 mediated. "Poor" metabolizers of DMI have been shown to eliminate mCPP more slowly than "extensive" metabolizers of DMI.[8] In addition, fluoxetine and paroxetine have been shown to substantially inhibit CYP2D6 mediated drug metabolism[15-17], producing 4- to 6-fold increases in plasma levels of co-administered drugs, such as DMI[18,19] which are principally CYP2D6 substrates. Thus, it is most likely that mCPP is a substrate for CYP2D6, and the increased levels observed during co-administration of NFZ and DMI were due to competition with DMI for CYP2D6. However, the modest observed increase in mCPP levels is unlikely to be clinical relevant. There did not appear to be any increase in adverse events associated with increased mCPP levels. Also, in this study, the AUC_{0-12} of mCPP represented only 5% of the AUC_{0-12} for NFZ during combined NFZ and DMI treatment compared to 3% during NFZ treatment alone. According to the manufacturer's product information, the AUC_{0-4} for mCPP is about 7% the AUC_{0-4} for the parent in healthy volunteers receiving NFZ alone.

Overall, the combined administration of DMI and NFZ appeared to be safe and well tolerated. Dizziness, lightheadedness, and insomnia were more frequently experienced when the two drugs were combined than when either drug was administered alone. However, these symptoms were generally mild and transient. The apparent increased incidence of tachycardia with the combination of the two drugs warrants some discussion. However, since tachycardia was reported in 2 of 10 patients receiving DMI alone and none of the subjects receiving NFZ alone, the incidence of tachycardia is more likely to be related to the class-specific safety profile of DMI rather than changes in the pharmacokinetic profile of NFZ (and its metabolites) observed when DMI was co-administered.

It is therefore anticipated that the addition of NFZ in daily dosages up to 300 mg per day to existing DMI therapeutic regimens and other TCA-based therapeutic regimens would not result in clinically significant increases in the incidence of adverse events or necessitate a reduction in TCA dosage. Likewise, the addition of TCA-based therapy to existing treatment regimens with NFZ would be considered equally safe within the dosing parameters of this study, based on pharmacokinetic analysis alone.

References

1. Eison A, Eison M, Torrente J, Wight RH, Yocca FD, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull 1990;26:311-5.
2. Owens MJ, Ieni JR, Knight DL, Winders K, Nemeroff CB. The serotonergic antidepressant nefazodone inhibits the serotonin transporter: in vivo and ex vivo studies. Life Science 1995;57:373-80.
3. Taylor DP, Carter RB, Eison AS, Mullins UL, Smith HL, Torrente JR, et al. Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. J Clin Psychiatry 1995;56:3-11.
4. von Moltke LL, Greenblatt DJ, Harmatz JS, Duan SX, Harrel LM, Cotreau-Bibbo MM, et al. Triazolam biotransformation by human liver microsomes in vitro: effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. J Pharmacol Exp Ther 1996;276:370-9.
5. Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH. Coadministration of nefazodone and benzodiazepines: III. A pharmacokinetic interaction study with alprazolam. J Clin Psychopharmacol 1995;15:399-408.
6. Barbhaiya RH, Shukla UA, Kroboth PD, Greene DS. Coadministration of nefazodone and benzodiazepines: II. A pharmacokinetic interaction study with triazolam. J Clin Psychopharmacol 1995;15:320-6.
7. Dockens RC, Rapoport D, Roberts D, Greene DS, Barbhaiya RH. Lack of an effect of nefazodone on the pharmacokinetics and pharmacodynamics of theophylline during concurrent administration in patients with chronic obstructive pulmonary disease. Br J Clin Pharmacol 1995;40:598-601.
8. Barbhaiya RH, Buch AB, Greene DS. Single and multiple dose pharmacokinetics of nefazodone in subjects classified as extensive and poor metabolizers of dextromethorphan. Br J Clin Pharmacol 1996;42:573-81.
9. Franc JE. A robotic HPLC procedure for metabolizer phenotyping using dextromethorphan in human urine. 1989;Bristol-Meyers Squibb Co., PRI, Report No. FRAN-JE-21140:
10. Franc JE, Duncan GF, Farmen RH, Pittman KA. High-performance liquid chromatographic method for the determination of nefazodone and its metabolites in human plasma using laboratory robotics. J Chromatogr Biomed Appl 1991;570:129-38.
11. Nielson KK, Brosen K. High-performance liquid chromatography of imipramine and six metabolites in human plasma and urine. J Chromatography 1993;612:87-94.
12. Gibaldi M, Perrier D. Pharmacokinetics. New York, NY: Marcel Dekker, Inc., 1982; pp. 409-17.
13. Riegelman S, Collier P. An application of statistical moment theory to the evaluation of in vivo dissolution time and absorption. J Pharmacokinet Biopharm 1980;8:509-34.
14. Schmider J, Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Inhibition of cytochrome P450 by nefazodone in vitro: studies of dextromethorphan O- and N-demethylation. Br J Clin Pharmacol 1996;41:339-43.
15. Brosen K, Skjelbo E. Fluoxetine and norfluoxetine are potent inhibitors of P450IID6 - the source of the sparteine/debrisoquine oxidation polymorphism. Br J Clin Pharmacol 1991;32:136-7.
16. Crewe HK, Lennard MS, Tucker GT, Woods FR, Haddock RE. The effect of paroxetine and other specific 5-HT re-uptake inhibitors on cytochrome P450 2D6 activity in human liver microsomes. Br J Clin Pharmacol 1991;32:5.
17. Shader RI, von Moltke LL, Schmider J, Harmatz JS, Greenblatt DJ. The clinician and drug interactions - an update (editorial). J Clin Psychopharmacol 1996;16:197-201.