Absorption and Presystemic Metabolism of Nefazodone Administered at Different Regions in the Gastrointestinal Tract of Humans

Punit H. Marathe,[1,5] Daniel E. Salazar,[2] Douglas S. Greene,[1] John Brennan,[3] Umesh A. Shukla,[4] and Rashmi H. Barbhaiya[1]

Received March 30, 1995; accepted June 22, 1995

Purpose. The absorption and disposition of nefazodone (NEF) and its metabolites hydroxynefazodone (HO-NEF), m-chlorophenylpiperazine (mCPP) and triazole dione (dione) were assessed in 10 healthy subjects following infusion of NEF solution into the proximal and distal regions of the intestine vs administration of NEF solution orally by mouth.

Methods. NEF HCl (400 mg) was infused over 5 hours into the proximal or distal intestine through a nasogastric tube, or orally ingested in 10 divided doses over 4.5 hours. The three treatments in the three-period crossover design were separated by one week.

Results. The bioavailability of NEF, based on AUC(INF), from proximal and distal regions relative to that from oral administration was 97% and 106%, respectively. NEF was absorbed equally well from all three treatments with median Tmax of 5.0 hours which coincided with the duration of infusion. Mean Cmax of NEF was not different between proximal and oral administrations, however, mean Cmax after distal instillation was 40% lower than that after oral administration. Exposure to HO-NEF, mCPP and dione, following proximal instillation was also comparable to that after oral administration. AUC(INF) of HO-NEF and dione was significantly lower after distal instillation compared to that after oral administration but AUC(INF) of mCPP was not. Cmax of all metabolites was significantly lower after distal administration in comparison to oral treatment. Terminal half-life for NEF, HO-NEF and mCPP after distal administration was longer than the other two treatments.

Conclusions. NEF is absorbed throughout the length of the gastrointestinal tract which supports the development of an extended-release formulation of NEF. The exposure to the metabolites (relative to NEF) was lower from the distal intestinal site compared to the proximal and oral site which may be explained by a reduced first pass of NEF by the cytochrome P450 3A4 in the distal intestine.

KEY WORDS: nefazodone; site of absorption; intubation; pharmacokinetics; P450 metabolism.

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) (molecular weight 506.5) (NEF, Serzone®) is a new antidepressant drug recently introduced to the US market (1). It is freely soluble in water to an extent of 10 mg/ml with a pKa of 6.6. Its partition coefficient (octanol/pH 7.4 buffer) is extremely high indicating a high degree of lipid solubility. It is chemically distinct from the tricyclics and monoamine oxidase inhibitors. NEF is an inhibitor of serotonin uptake with negligible effects on norepinephrine uptake and it is also known to antagonize 5-HT_2 receptors. Its preclinical pharmacology suggests that NEF may be more broadly effective than trazodone while having a lower incidence of sedation and hypotension (2).

NEF is extensively metabolized in vivo. Three pharmacologically active metabolites of NEF have been quantified in clinical studies viz. hydroxynefazodone (HO-NEF), m-chlorophenylpiperazine (mCPP) and triazole dione (dione) (3). NEF exhibits dose-dependent pharmacokinetics in animals (4) and humans (5,6). The pharmacokinetics of HO-NEF after administration of NEF is also dose-dependent while that of mCPP and dione appear to be dose-linear.

NEF as an antidepressant, is intended to be administered chronically. Current therapeutic regimen calls for bid dosing and therefore, an extended-release formulation is desirable to reduce the dosing frequency to a once-a-day regimen. One of the important biological parameters in assessing the feasibility of developing an extended-release dosage formulation is the drug-absorption throughout the length of the gastro-intestinal tract. One objective of this study was to determine whether there is region-specific absorption of NEF in the gastrointestinal tract.

NEF is metabolized by cytochrome P450 3A4 (R.I. Shader, personal communication). Mucosal cells of the small intestine are abundant in this P450 isozyme and thus it can be postulated that a substantial portion of the first-pass metabolism of NEF occurs in the gastro-intestinal tract (7). The activity of cytochrome P450 3A4 is generally higher in the duodenum and jejunum and it decreases in the lower part of the gastro-intestinal tract (8). Thus depending upon the site of absorption of NEF in the gastro-intestinal tract, the disposition of NEF and its metabolites may be different. The second objective of the current study was to explore the relative disposition of NEF and its three metabolites HO-NEF, mCPP and dione when NEF is administered at different sites in the gastro-intestinal tract.

MATERIALS AND METHODS

Study Design

This was a three way, open label, crossover study in 10 subjects. In period I, subjects were to be administered the drug as a solution through a nasogastric tube in the proximal (duodenum or jejunum) or distal (ileum or colon) intestinal region, depending upon how far the tube descended in the gastrointestinal tract. Since distal intubation is more difficult than proximal intubation, the former was attempted on all subjects in period I. In period II, drug was administered through a nasogastric tube to the location that was not intubated in period I. All subjects received NEF as an oral solution, administered by mouth, in period III.

[1] Department of Metabolism and Pharmacokinetics, Bristol-Myers Squibb Company, Princeton, New Jersey 08543.

[2] Department of Human Pharmacology, Bristol-Myers Squibb Company, Princeton, New Jersey 08543.

[3] Solvay Pharmaceuticals, Marietta, Georgia 30062.

[4] Hoechst Roussel Pharmaceuticals, Somerville, New Jersey 00876-1258.

[5] To whom correspondence should be addressed at P.O. Box 4000, Bristol-Myers Squibb Company, Princeton, New Jersey 08543-4000.

0724-8741/95/1100-1716$07.50/0

In periods I and II, each subject received a single 5-hour intestinal infusion of 400 mg NEF HCl as a solution through a nasogastric tube. In period III, 400 mg NEF HCl dose was given orally as 40 mg doses every 30 min over 4.5 hours with the objective of simulating the infusion rate in periods I and II. A 1-week interval separated each drug administration. Blood samples for pharmacokinetic analysis were obtained on the days when NEF was administered.

Subjects

A total of 10 male subjects completed this study after signing the informed consent. All subjects were male between 22 to 34 years of age. The body weight was within ±10% of the desirable weight for height as determined from actuarial tables (Metropolitan Life Insurance Co., 1983 Metropolitan Height and Weight Tables). The mean age of all subjects was 26.8 years (range of 22 to 34 years) with the mean body weight of 75.6 kg (range of 58.1 to 89.5 kg) and mean height of 181 cm (range of 169 to 192 cm). Good health was determined by medical history, clinical laboratory determinations, ECG and physical examinations conducted within 21 days prior to the start of the study. Medication or drug use of any kind within one week of the start of dosing, or within one month prior to study initiation with any agent which is known to induce or inhibit drug-metabolizing enzymes was prohibited. Due to the involvement of cytochrome P450 2D6 in the metabolism of mCPP (9), all subjects were phenotyped for the metabolism of dextromethorphan to dextrorphan. All subjects were extensive metabolizers of dextromethorphan, however, the phenotypic status was not used as a screening criterion. At the completion of the study, the subjects were given a post-study physical with ECG and laboratory examination. Following satisfactory completion of these tests, the subjects were discharged from the study.

Study Conduct

In period I, all subjects were confined to the study facility at least 37 hours prior to NEF administration. At that time, subjects were intubated by the introduction of a nasogastric tube through the nose into the intestine. The position of the tube in the gastrointestinal tract was verified by fluoroscopy after intubation. Lidocaine 5% spray (Xylocaine®, Astra Pharmaceutical Products, Inc.) was used as a local anesthetic during the intubation procedure and a radiopaque dye (Renografin®) was instilled into the nasogastric tube to assist in fluoroscopic visualization. On the dosing day, the position of the nasogastric tubing was verified again by fluoroscopy prior to drug administration. All subjects were successfully intubated in the distal intestinal region in period I. In period II, all subjects were confined to the study site at least, 13 hours prior to NEF dosing and were intubated in the proximal intestinal region by the same technique as that in period I. In period III all subjects were confined to the study site for at least 13 hours prior to NEF dosing by oral administration.

All subjects were fasted 10 hours prior to dosing. Dosing began at about 8 a.m. on each dosing day and was staggered by 5–10 minutes per subject. Each subject received a total of 400 mg NEF HCl by a 5 hour infusion in periods I and II and by ten 40 mg oral doses given every half hour in period III. For proximal and distal infusion, the contents of 2 vials (160 ml) of NEF HCl solution were administered to each subject through the nasogastric tube using an infusion pump at a rate of 0.53 ml/min. During the infusion period, the subjects were confined to bed in a sitting position and remained seated until approximately 1.5 hours after the end of infusion. For oral dosing, the subjects ingested 16 ml of NEF HCl solution at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 and 4.5 hours. The subjects remained seated throughout the dosing period and until approximately 2 hours after the last oral dose.

The subjects received lunch approximately 1.5 hours after the end of the infusion (period I and II) or approximately 2 hours after the last oral dose (period III). The menus for each period were the same and the subjects were expected to finish the entire meal. Alcohol and xanthine containing beverages were not permitted 48 hours prior to, and for 72 hours after administration of NEF. The subjects were confined to the study site for 72 hours after each drug administration.

Serial blood samples (10 ml) were collected using Becton-Dickinson Vacutainers containing K_3EDTA as anticoagulant for the determination of NEF, HO-NEF, mCPP and dione concentrations. Blood samples were collected predose and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hr after the start of drug administration and plasma was stored frozen at or below −20°C until analysis.

Sample Assays

Plasma samples were analyzed simultaneously for NEF and its three metabolites, HO-NEF, mCPP and dione, by a validated HPLC-UV assay based on a previously published method (10). The standard curves were linear from 10–1000 ng/ml for NEF and dione and 5–500 ng/ml for HO-NEF and mCPP. Quality control (QC) samples containing the four analytes were prepared in human plasma prior to the study sample analysis and stored at −20°C along with the study samples. These QC samples were run in duplicate in each analytical run. For each analyte, the lower limit of quantitation (LLQ) was set as the lowest standard concentration and the upper limit of quantitation (ULQ) was set as the highest standard concentration. If the predicted concentration of an analyte in a study sample was greater than ULQ, the sample was reassayed with appropriate dilution in another analytical run.

Standard curve correlation coefficients were greater than 0.995 for all analytes. Standard curve reproducibilities, as measured by the percent relative standard deviation (%RSD) of the slopes, were within 17% of the means. The overall between- and within-day variabilities of the QCs were less than 12% RSD. QC deviations from nominal concentrations were within 10% for each analyte confirming the accuracy and precision of the analytical runs and study sample stability.

Pharmacokinetic Analysis

Each plasma concentration-time profile was analyzed by noncompartmental methods (11). Cmax and Tmax were determined as the highest observed concentration and the time to reach the maximum concentration, respectively. The

terminal log-linear phase of the plasma concentration-time curve was defined by the data points yielding the minimum mean square error in the regression analysis. The apparent elimination half-life ($t_{1/2}$) was calculated from the slope of the terminal log-linear phase. AUC(0-T) (where T is the last time point at which quantifiable plasma concentration is observed) was calculated using a combination of the trapezoidal and log-trapezoidal rules. The linear trapezoidal rule was used in the portion prior to the log-linear phase and the log trapezoidal rule was used in the log-linear phase. AUC(INF) was calculated from AUC(0-T) plus the extrapolated area determined by dividing the predicted concentration at the time of last >LLQ plasma concentration by the slope of the terminal log-linear phase. Ratios of AUC(INF) of metabolite to AUC(INF) of NEF adjusted for molecular weight (R(AUC)) were calculated to indicate exposure to the metabolites relative to NEF after each treatment.

Statistical Analysis

Statistical analysis was performed to compare Cmax, Tmax, AUC(INF), $t_{1/2}$ and R(AUC) from the three treatments. Analysis was performed separately for each compound. The analysis was based on a randomized block analysis of variance model. The general form of the model was: $y = \mu + \alpha + \beta + e$; where, μ is the grand mean, α is the subject effect, β is the treatment effect and e is the residual error term. If a statistically significant treatment effect was observed in the ANOVA, Tukey's method of multiple comparisons was used to compare the treatment means. Analysis of Tmax was based on ranked data. The relative bioavailability (AUC(INF)) from the proximal and distal administration was assessed with respect to the oral administration on the basis of the two one-sided tests procedure. The 90% confidence intervals were constructed for AUC(INF), utilizing the mean square error from the ANOVA. The statistical analysis was performed with the SAS package. All tests of significance were performed at the $p = 0.05$ level.

RESULTS

Safety and Tolerance Assessment

There were no serious adverse events (AEs) associated with the administration of NEF. The most common AE reported was headache with 7 reported events, 5 following oral administration and 2 following distal intestinal administration of NEF. There were 2 episodes each of vomiting and dizziness occurring several hours after the administration of nefazodone. There were singular episodes of abdominal pain, vertigo and dysuria. There did not appear to be any association of clinical AEs with any treatment administered. There were no clinically significant ECG or laboratory abnormalities.

Pharmacokinetics of Nefazodone and Its Metabolites

NEF was absorbed equally well following administration in the proximal or distal region or orally by mouth. Peak concentrations were achieved at approximately 5 hr which was the duration of treatment for proximal and distal administration (4.5 hr for oral administration). Plasma concentration-time profiles after proximal administration were similar to that after oral administration (Figure 1). Cmax values after distal administration were significantly lower than the Cmax values after proximal and oral administration (Table I). Mean (sd) AUC(INF) values were comparable among the three treatments. The relative bioavailability (90% confidence interval) from the proximal region with respect to the oral treatment was 97% (84%, 113%) while from the distal region, it was 106% (92%, 123%). Mean $t_{1/2}$ after distal administration was significantly longer than that after the other two treatments.

Mean (sd) pharmacokinetic parameters for NEF metabolites HO-NEF, mCPP and dione and results of statistical comparisons are also presented in Table I. Peak concentrations of HO-NEF were attained within one hour after termination of drug administration for all three treatments. Plasma concentrations following proximal administration paralleled those after oral administration with similar Cmax, AUC and $t_{1/2}$ values (Figure 1). Like nefazodone, mean Cmax for HO-NEF after distal administration was lower compared to that after oral administration. However, unlike nefazodone, mean(sd) AUC(INF) of HO-NEF after distal administration was significantly lower than that after oral administration. The relative bioavailability (90% confidence interval) from the proximal region with respect to oral treatment was 94% (78%, 112%). From the distal region, the bioavailability relative to the oral treatment was 77% (64%, 91%). Terminal half-life for HO-NEF after distal administration was significantly longer than that after the other two treatments. R(AUC) for HO-NEF after distal administration was significantly smaller than the other two treatments.

Similar to NEF and HO-NEF, mean Cmax for mCPP after distal administration was significantly lower than Cmax after proximal and oral administration. Peak concentrations of mCPP were attained at approximately 5 to 5.5 hr after all three treatments. Mean (sd) AUC(INF) values were not significantly different among the three treatments. The relative bioavailability from the proximal and distal region with respect to the oral administration was 107% (93%, 124%) and 94% (81%, 109%), respectively. Terminal half-life after distal administration was significantly longer than that after oral administration. Two subjects (1 and 7) had inexplicably long half lives (144 and 77 hr respectively) after distal administration and the data from these subjects were not included in the statistical analysis of $t_{1/2}$, AUC(INF) and R(AUC). R(AUC) values for mCPP following the three treatments were not significantly different from each other.

Mean (sd) Cmax for dione after distal administration was significantly lower than mean Cmax after proximal and oral administration. Mean AUC(INF) values after distal administration were significantly lower than those after the other two treatments. The relative bioavailability from the proximal and distal region with respect to the oral treatment was 106% (92%, 122%) and 65% (56%, 74%), respectively. Terminal half-life for dione was not significantly different between treatments. R(AUC) after distal administration was significantly smaller than the other two treatments.

DISCUSSION

Antidepressant therapy with NEF is expected to con-

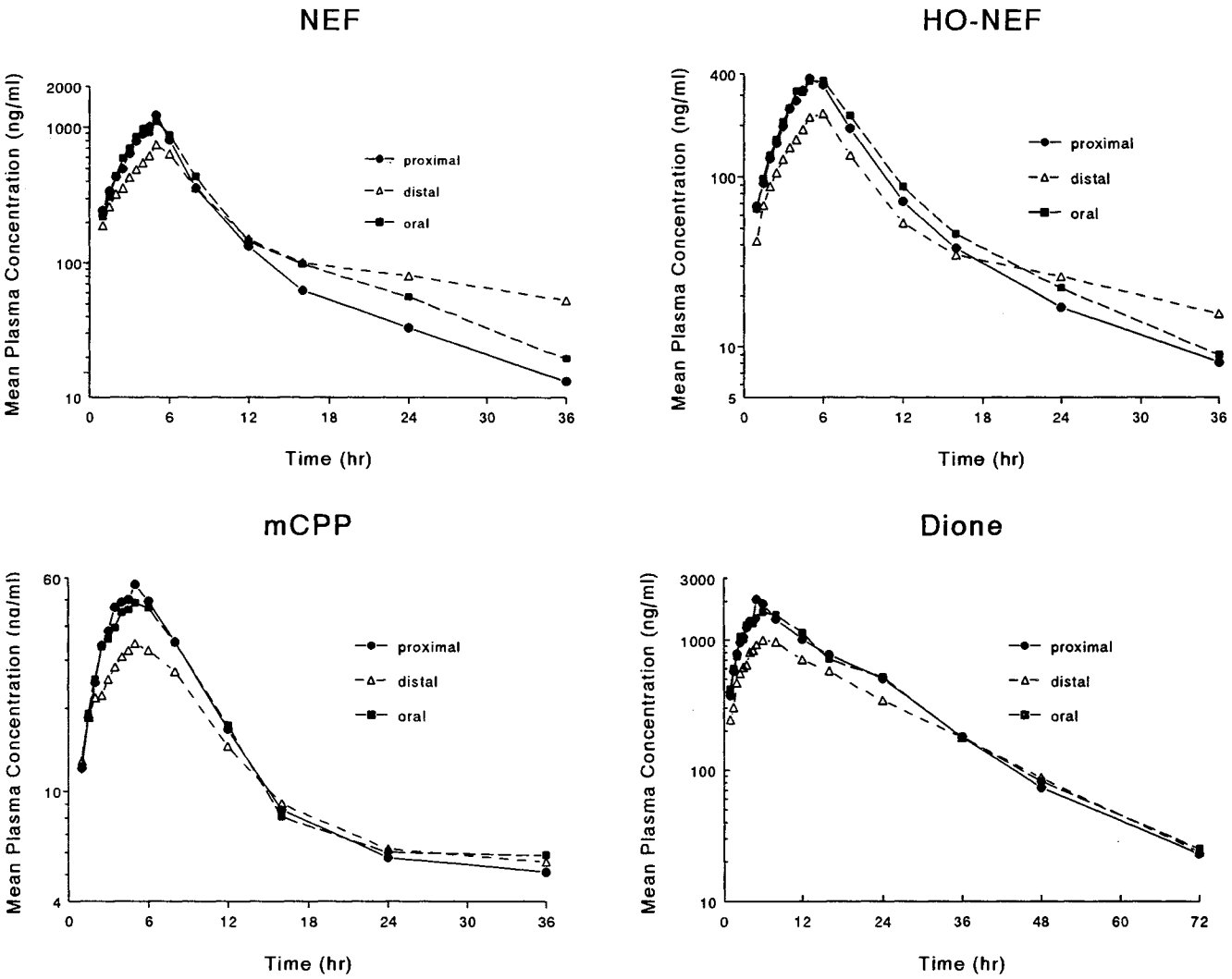

Fig. 1. Mean plasma concentration-time profiles for NEF, HO-NEF, mCPP and dione after proximal, distal and oral administration.

tinue for at least 2–3 months. The recommended therapeutic regimen is twice a day dosing. Reducing the dosing frequency from twice a day to once a day would be both desirable and advantageous. Patient compliance would be expected to improve and the frequency of adverse events may decrease. An extended-release formulation could be developed to accomplish these goals. This study was designed to determine if absorption of NEF occurs throughout the gastrointestinal tract which would support the development of an extended-release formulation.

NEF is completely absorbed when given as an oral solution (12). In this study, the oral solution was used as the reference in estimating the relative bioavailability from the proximal and distal intestine. The results indicate that NEF was absorbed equally well following proximal, distal and oral administration with Tmax nearly equal to the duration of infusion. The exposure to NEF, as measured by AUC(INF), following proximal and distal instillation was comparable to that after oral administration by mouth. Exposure to HO-NEF, mCPP and dione following proximal instillation was also comparable to that after oral administration.

Following distal administration exposure to the metabolites was significantly lower compared to oral administration. The decrease in mean AUC(INF) after distal administration for HO-NEF and dione was 21% and 33%, respectively. For mCPP, mean AUC(INF) after distal administration was comparable to that after oral administration. Maximum plasma concentration for all analytes after proximal administration was comparable to that after oral administration, whereas they were 36 to 43% lower after distal administration. Terminal half-life values of NEF and its metabolites except for dione after distal administration were longer than the other two treatments. The diminished Cmax and increased $t_{1/2}$ following distal intestinal infusion most likely reflect a slower rate of absorption. A similar phenomenon has been observed with ranitidine (13). Plasma levels after cecal administration of ranitidine were significantly lower compared to those after gastric and jejunal administration and were attributed to a slower rate of absorption from the cecal region. Absorption may be slower in this region due to several factors including differences in regional pH causing a decrease in the solubility of a weakly basic drug, decreased surface area for absorption and decreased blood flow in the colon relative to the small intestine. The

Table I. Mean (sd) Pharmacokinetic Parameters of NEF, HO-NEF, mCPP and Dione after Proximal, Distal and Oral Administration (N = 10)

Analyte	Parameter	Treatment						Statistics[a]
		Proximal		Distal		Oral		
	C_{max}[b]	1281	(628)	776	(576)	1303	(5.30)	d p* o*
	T_{max}[b,c]	5.0		5.0		5.0		o* p*# d#
NEF	AUC (INF)[b]	6958	(4127)	7364	(3727)	7276	(5175)	NS
	$t_{1/2}$[b]	3.27	(1.30)	13.8	(14.5)	2.77	(1.17)	o* p* d
	C_{max}	393	(224)	234	(203)	405	(167)	d p* o*
	T_{max}	5.0		6.0		5.5		p o* d*
HO-NEF	AUC(INF)	2710	(1681)	2307	(1444)	2910	(1989)	d* p*# o#
	$t_{1/2}$	3.56	(1.93)	12.2	(7.71)	3.69	(2.21)	p* o* d
	R(AUC)[e]	0.367	(0.06)	0.294	(0.10)	0.383	(0.07)	d p* o*
	C_{max}	56.4	(26.5)	34.1	(21.3)	53.0	(16.6)	d o* p*
	T_{max}	5.0		5.5		5.0		NS[d]
mCPP	AUC(INF)	536	(206)	476	(188)[f]	486	(150)	NS
	$t_{1/2}$	8.90	(8.42)	11.4	(10.3)[f]	6.64	(7.26)	o* p*# d#
	R(AUC)	0.239	(0.13)	0.200	(0.11)[f]	0.220	(0.11)	NS
	C_{max}	2110	(824)	1030	(737)	1809	(552)	d o* p*
	T_{max}	5.0		6.0		6.0		p* o*# d#
Dione	AUC(INF)	29166	(8680)	18613	(9380)	28363	(11105)	d o* p*
	$t_{1/2}$	12.8	(8.25)	13.9	(6.37)	12.3	(5.05)	NS
	R(AUC)	5.85	(3.56)	3.75	(4.06)	5.65	(4.16)	d o* p*

[a] Treatments with a common superscript are not significantly different.
[b] Units: C_{max} – ng/ml, T_{max} – hr, AUC(INF) – ng.hr/ml, $t_{1/2}$ – hr.
[c] Medians.
[d] NS—not statistically significant.
[e] Ratio of metabolite AUC(INF) to NEF AUC(INF) adjusted for molecular weight.
[f] N = 8.

longer $t_{1/2}$ values following distal administration may therefore indicate prolonged absorption thereby making computation of AUC(INF) less reliable. However, the results obtained from the statistical comparison of AUC(0-T) values for NEF from the three treatments were comparable to those obtained from AUC(INF) comparisons.

The AUC ratios of metabolite to parent after distal administration were significantly lower for HO-NEF and dione compared to those after oral and proximal intestinal administration. The alterations in the metabolic profile observed following distal intestinal infusion are most likely due to reduced first pass metabolism of NEF by the gut. The involvement of intestinal cytochrome P450 3A4 is well established in the literature (7) and NEF is a substrate for cytochrome P450 3A4. As the activity of the intestinal P450 decreases in going from the proximal to the distal intestinal region (8), the conversion of NEF to its metabolites decreases giving rise to a lower exposure to the metabolites relative to NEF. Another explanation for the differential disposition from the distal intestinal region may be a reduced first-pass through the liver. Intestinal venous blood almost entirely passes through the liver via the portal vein where the drug is subject to first pass metabolism prior to entry into the systemic circulation. In contrast, a substantial portion of the colonic venous blood enters the systemic circulation directly without passing through the liver and the dissolved drug avoids first-pass metabolism (14). Since the relative bioavailability of NEF from the distal intestinal region is comparable to that from the oral and proximal intestinal administration in spite of a lower metabolite to parent AUC ratio, it is suspected that the absorption of NEF from the distal intestinal region is also reduced in comparison to the proximal region. Alternatively regional differences in the absorption of metabolites formed within the gastrointestinal tract may be responsible for lower metabolite to parent AUC ratio from the distal intestine. Such a phenomenon was recently documented for sumatriptan where the metabolite to parent AUC ratio was two-fold lower after cecal administration compared to that after oral administration (15).

In summary, all three treatments were safe and no differences in the safety profiles between the three treatments were apparent. The results of the present study show that there is no window of absorption for NEF in the gastrointestinal tract which supports feasibility of developing an extended-release formulation. Administration of NEF in the distal intestinal region showed some alterations in the exposure to the metabolites which suggests the role of intestinal cytochrome P450 3A4 in the first pass metabolism of NEF.

ACKNOWLEDGMENTS

The authors thank John E. Franc for plasma sample analysis and James S. Lee for statistical evaluation of the data.

REFERENCES

1. J. P. Feigher, R. Pambakian, R. C. Fowler, W. F. Boyer, and F. M. D'Amico. A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. *Psychopharmacol. Bull.* 25:219–211 (1989).

2. A. S. Eison, M. S. Eison, J. R. Torrente, R. N. Wright, and F. D. Yocca. Nefazodone: preclinical pharmacology of a new antidepressant. *Psychopharmacol. Bull.* **26**:311–315 (1989).
3. R. F. Mayol, C. A. Cole, G. M. Luke, K. L. Colson, and E. H. Kerns. Characterization of the metabolites of antidepressant drug nefazodone in human urine and plasma. *Drug Metab. Disp.* **22**:304–11 (1994).
4. U. A. Shukla, S. Kaul, P. H. Marathe, K. A. Pittman, and R. H. Barbhaiya. Pharmacokinetics of Nefazodone Following Multiple Escalating Oral Doses in the Dog. *Eur. J. Drug Metab. Phamacokinet.* 17:309–318 (1992).
5. R. H. Barbhaiya, U. A. Shukla, P. Chaikin, D. S. Greene, and P. H. Marathe. Time to steady state after escalation/de-escalation of nefazodone bid doses. (Submitted for publication to Eur. J. Clin. Pharmacol).
6. S. Kaul, U. A. Shukla, and R. H. Barbhaiya. Nonlinear pharmacokinetics of nefazodone after escalating single and multiple doses. J. Clin. Pharmacol. 35:830–839 (1995).
7. J. C. Kolars, P. Schmieden-Ren, J. D. Schuetz, and P. B. Watkins. Identification of rifampin-inducible p450IIIa4 (cyp3a4) in human small bowel enterocytes. *J. Clin. Invest.* **90**:1871–1878 (1992).
8. K. F. Ilet, L. B. G. Tee, P. T. Reeves, and R. F. Minchin. Metabolism of drugs and other xenobiotics in the gut lumen and wall. *Pharmac. Ther.* **46**:67–93 (1990).
9. A. B. Buch, U. A. Shukla, K. A. Pittman, and R. H. Barbhaiya. Pharmacokinetics of nefazodone in extensive (EM) and poor (PM) metabolizers of dextromethorphan. *Pharm. Res.* **10**:S134 (1993).
10. J. E. Franc, G. F. Duncan, R. H. Farmen, and K. A. Pittman. High-performance liquid chromatographic method for the determination of nefazodone and its metabolites in human plasma using laboratory robotics. *J. Chromatog.* **570**:129–138 (1991).
11. M. Gibaldi, and D. Perrier. Pharmacokinetics, 2nd Edition, Marcel Dekker, New York, 1982.
12. R. H. Barbhaiya, K. A. Dandekar, and D. S. Greene. Pharmacokinetics, absolute bioavailability and disposition of [^{14}C]nefazodone in humans. Submitted for publication to Drug Metab. Disp.
13. M. F. Williams, G. E. Dukes, W. Heizer, Y. Han, D. J. Hermann, T. Lampkin, and L. J. Hak., Influence of gastrointestinal site of drug delivery on the absorption characteristics of ranitidine. *Pharmaceutical Research* 9:1190–1194 (1992).
14. A. B. de Boer, L. G. J. Leede, and D. D. Breimer. Rectal drug administration: partial avoidance of hepatic first pass elimination. *Pharm. Int.* 3:267–269 (1982).
15. P. E. Warner, K. L. R. Brouwer, E. K. Hussey, G. E. Dukes, W. D. Heizer, K. H. Donn, I. M. Davis, and J. R. Powell. Sumatriptan absorption from different regions of the human gastrointestinal tract. *Pharm. Res.* **12**:138–143 (1995).