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COMMUNICATION

Comparative Bioavailability Study of a Generic Naltrexone Tablet Preparation

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ABSTRACT

The bioavailability of a generic preparation of naltrexone (Narpan) was compared with the innovator product, Trexan. Twelve healthy volunteers participated in the study, conducted according to a completely randomized, two-way crossover design. The preparations were compared using the parameters area under the plasma concentration–time curve $AUC_{0-\infty}$*, peak plasma concentration* C_{max}*, and time to reach peak plasma concentration* T_{max}*. No statistically significant difference was observed between the logarithmic transformed* $AUC_{0-\infty}$ *and the logarithmically transformed* C_{max} *values of the two preparations. Also, no statistically significant difference was observed between the untransformed* T_{max} *values. In addition, the 90% confidence interval for the ratio of the logarithmic transformed* $AUC_{0-\infty}$ *values of Narpan over those of Trexan was found to lie between 0.87 and 1.01, while that of the logarithmic transformed* C_{max} *values was between 0.94 and 1.23, both being within the bioequivalence limit of 0.80–1.25. The numerical values of the elimination half-life (*$t_{1/2}$*) obtained with the two preparations were also not significantly different and were comparable to those reported in the literature*.

INTRODUCTION

Naltrexone is a long-acting, potent, and nonaddictive narcotic antagonist (1–3) suggested for the treatment of narcotic addiction (1). When administered orally, only approximately 40% of the dose is bioavailable, attributable to its high first-pass metabolism (4). The expiration of its patent has prompted manufacturing of generic versions of the drug. However, it is essential that the generic preparations have similar bioavailability characteristics to the innovator preparation before they can be safely used as a substitute for it.

Therefore, the present study was conducted to compare the bioavailability of Narpan, a local generic prepa-

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ration of naltrexone, with that of the innovator preparation, Trexan. In addition, an attempt was also made to study the pharmacokinetics of naltrexone in the local population of Asian origin, which have not been investigated.

MATERIALS AND METHODS

Products Studied

Narpan (50 mg naltrexone HCl) tablets (batch no. 95253A, manufacturing date August 1995, expiration date August 1998) were manufactured by Duopharma, Malaysia. Trexan (50 mg naltrexone HCl) tablets (lot no. KA006A, manufacturing date July 1995, expiration date July 1998, registration no. PBKD/930054A) were manufactured by Du Pont (United States). Both naltrexone and naloxone HCl standards were obtained from Diosynth BV, The Netherlands.

Study Design

The study protocol was approved by an ethics committee. After providing written informed consent, 12 healthy adult male volunteers between 21 and 43 years old (mean = 34 years, SD = 7 years) and weighing from 54 to 76 kg (mean = 65 kg, SD = 7 kg) participated in the study. All were judged to be healthy and were not receiving any medication during the study period. The protocol used was a conventional, two-way, split groups, crossover study with 6 subjects in each of the two treatment groups and a washout period of 1 week. The volunteers were selected randomly to receive two tablets (100 mg) of Trexan or Narpan. Both preparations were administered with 150 ml of water in the morning at 10:00 A.M. after a 12-hr overnight fast. Food and drinks were withheld for at least 2 hr after dosing. Lunch and dinner of chicken with rice were served at 4 and 9 hr after dosing, respectively, and water was given ad libitum. Blood samples of 5 ml volume were collected in vacutainers (containing sodium heparin as an anticoagulant) at 0 (predose), 15 min, 30 min, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, and 24 hr after dosing. The blood samples were centrifuged for 15 min at 3500 rpm, and the plasma was transferred to separate glass containers to be kept frozen until analysis.

Analysis of Plasma Naltrexone Concentration

The plasma samples were analyzed using a reversed-phase high-performance liquid chromatographic (HPLC) method described by Peh, Billa, and Yuen (5).

Pharmacokinetic Analysis

The two preparations were compared using the parameters peak plasma concentration C_{max}, time to reach peak plasma concentration T_{max}, and area under the plasma concentration–time curve $AUC_{0-\infty}$, estimated from the plasma concentration–time profiles of the two preparations. Both C_{max} and T_{max} were obtained directly from the plasma data, while the $AUC_{0-\infty}$ was calculated by adding the area from time zero to the last sampling time t (AUC_{0-t}) and the area from time t to infinity ($AUC_{t-\infty}$). The former was calculated using the trapezoidal formula and the latter by dividing the last measurable plasma drug concentration by the elimination rate constant k_e. The k_e was estimated from the terminal slope of the plasma concentration–time curve after logarithmic transformation and application of linear regression (6), while the elimination half-life $t_{1/2}$ was calculated using $\ln 2/k_e$. For each of the parameters ($AUC_{0\text{-}4}$, C_{max}, and $t_{1/2}$), the values obtained for the two preparations were analyzed statistically using an analysis of variance (ANOVA) procedure appropriate for the study design (7). The $AUC_{0-\infty}$ and C_{max} values were logarithmically transformed prior to the statistical analysis. On the other hand, the T_{max} values were analyzed using the Wilcoxon signed-rank test for paired samples. A statistically significant difference was considered at $p < .05$.

RESULTS AND DISCUSSION

The mean plasma concentration–time curves of naltrexone obtained with Narpan and Trexan are shown in Fig. 1. Although the mean peak plasma concentration of

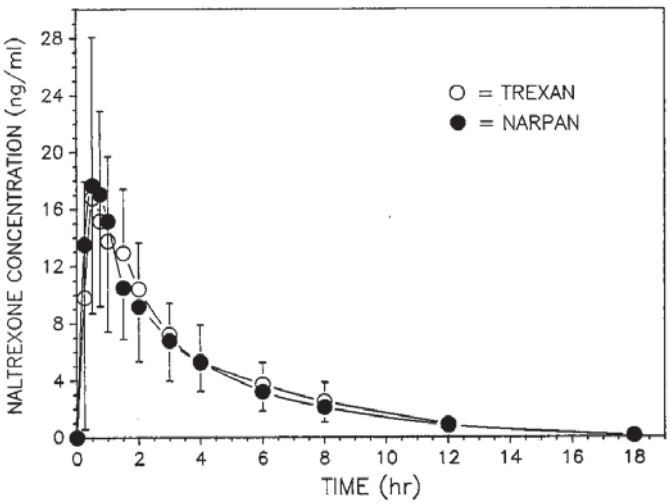

Figure 1. Mean plasma naltrexone concentration versus time curves of Narpan and Trexan (mean ± SD, $N = 12$).

Table 1

Numerical Values of T_{max}, C_{max}, $AUC_{0-\infty}$, *and* $t_{1/2}$

	Trexan				Narpan			
Subjects	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (hr · ng/ml)	$t_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (hr · ng/ml)	$t_{1/2}$ (hr)
MN	0.25	31.78	50.87	2.4	0.25	22.20	42.02	2.4
BN	0.25	10.11	58.09	2.9	0.75	8.60	58.80	3.2
SD	0.75	14.50	61.77	3.5	0.50	20.56	48.07	2.7
MD	0.50	26.24	69.72	3.7	0.50	26.98	65.02	3.7
CM	1.00	13.62	90.00	3.7	0.50	16.84	82.21	4.6
RV	0.50	34.07	124.68	3.4	0.25	48.60	127.52	4.6
MA	1.50	14.74	46.50	3.3	1.00	11.22	36.64	3.7
HM	0.75	10.53	54.17	4.3	0.50	13.14	55.50	3.9
SV	1.50	16.90	74.15	3.2	1.00	21.04	68.46	3.9
YS	0.50	19.68	51.75	2.8	0.50	22.84	47.14	3.0
AD	0.50	37.38	82.87	4.5	1.00	34.71	103.44	5.1
WT	0.75	12.66	46.77	3.5	0.75	15.81	44.10	3.2
Mean	0.73	20.18	67.61	3.4	0.63	21.88	64.91	3.7
SD	0.42	9.66	22.87	0.6	0.27	11.02	27.30	0.8

Narpan was observed to be slightly higher than that of Trexan, the two plots appeared to be almost superimposable. Both products achieved rapid absorption, producing peak plasma concentrations at approximately 1 hr after dosing, and no lag time in absorption was observed.

Table 1 gives the individual values of T_{max}, C_{max}, and $AUC_{0-\infty}$ obtained with Trexan and Narpan. No statistically significant difference ($p > .10$) was obtained between the T_{max} values of Trexan (0.73 ± 0.42 hr) and Narpan (0.63 ± 0.27 hr). Also, the values obtained are in good agreement with those reported by other workers (8,9). It can also be seen from Table 1 that the mean C_{max} and $AUC_{0-\infty}$ values of Narpan were comparable to those of Trexan. No statistically significant difference was observed between the logarithmically transformed C_{max} ($p = .3321$) and the logarithmically transformed $AUC_{0-\infty}$ ($p = .1204$) values of the two preparations. In addition, the 90% confidence interval for the ratio of the logarithmically transformed $AUC_{0-\infty}$ values of Narpan over those of Trexan was found to lie between 0.87 and 1.01, while that of the logarithmically transformed C_{max} values was between 0.94 and 1.23, both being within the acceptable bioequivalence limit of 0.80–1.25 (10,11).

Relatively wide intersubject variation was observed in the numerical values of the pharmacokinetic parameters *AUC* and C_{max}, which can be attributed to differences in body weight and drug disposition among the volunteers. However, the intrasubject variability of the parameter *AUC* was relatively small. When estimated using the mean square error obtained from the ANOVA analysis (12), the coefficient of variation was estimated to be 9.4%. Based on this value, 12 volunteers were found to be sufficient to provide a power $(1 - \beta)$ of greater than 80% for detecting a statistically significant difference in *AUC* between the two products at a type 1 error rate (α) of 0.05 if the true difference is equal to or greater than 20% (13). A power of approximately 80% was also obtainable with the parameter C_{max} under the same conditions. Sioufi et al. (14) have also reported that 12 volunteers were sufficient to provide an 80% power in detecting a difference in the *AUC* of greater than 16% in their study.

The numerical values of the pharmacokinetic parameter $t_{1/2}$ of the two preparations are given in Table 1. The mean values of the two preparations were closely similar and not significantly different statistically ($p = .2084$). Also, the values, which varied between 2.4 and 5.1 hr with a mean of 3.5 hr (Table 1), were comparable to those reported in the literature (9,15).

CONCLUSION

In conclusion, Narpan was found to be comparable to Trexan in both the rate and extent of bioavailability. Moreover, the numerical values of the parameter $t_{1/2}$ estimated from administration of the two products were not significantly different and were comparable to those reported in the literature.

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