Comparative bioavailability of trazodone formulations using stable isotope methodology

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1 The bioavailability of trazodone, a new antidepressant, from 50 mg dividose (A) or film-sealed (B) tablets relative to an oral solution was determined in six healthy male subjects using 50 mg of D₄-trazodone as a stable isotope labelled standard. Concentrations of trazodone and D₄-trazodone were measured by GCMS.

2 The pharmacokinetics of trazodone and D₄-trazodone were identical indicating no isotope effect.

3 For formulation A, B and solution, the relative (trazodone/D₄-trazodone) C_{max} values were 0.84 ± 0.09, 0.90 ± 0.05 and 1.05 ± 0.04. The relative bioequivalence of the dosage formed with a power of 85% (power by conventional ANOVA was 54%).

4 Among subjects % relative standard deviations (RSD) for the D₄-trazodone AUC values, a measure of intra-subject variability, were 6 to 38% while the % RSDs by period, a measure of inter-subject variability, were 26 to 55%.

Keywords trazodone bioavailability stable isotope method

Introduction

Trazodone (Figure 1) is the first of a new generation of antidepressant drugs. The pharmacology and therapeutic use of trazodone have been recently reviewed (Brogden *et al.*, 1981). Despite its relatively widespread use, the clinical pharmacokinetics of trazodone have not been studied extensively. Following single doses, trazodone is rapidly and completely absorbed (Ankier *et al.*, 1981; Caccia *et al.*, 1982; Jauch *et*

al., 1976) with peak plasma concentrations achieved 0.5–2 h following administration. Following a 50 mg dose, peak concentrations of trazodone are 0.8 to 2.3 µg/ml (Ankier *et al.*, 1981). The mean elimination half-life of trazodone has been variously reported as 4 h (Ankier *et al.*, 1981) and 12 h (Jauch *et al.*, 1976). Trazodone is eliminated primarily by metabolism (Biocchi *et al.*, 1974).

Figure 1 Chemical structure of trazodone HCl and D₄-trazodone HCl.

Administration with food delays absorption (Jauch *et al.*, 1976). Patients with impaired renal function were noted to have somewhat higher plasma concentrations of trazodone; however, these differences were not statistically significant (Biocchi *et al.*, 1974). Steady state plasma concentrations of trazodone are reached within 4 days of multiple dosing (Biocchi *et al.*, 1974).

The objective of this study was to evaluate using stable isotope methodology the oral bioavailability of a new dosage form in comparison to the currently marketed trazodone tablet and a solution of trazodone. Using this approach, the plasma concentrations of trazodone from each dosage form are compared to those of a stable isotope labelled derivative of trazodone concomitantly administered in solution. This study design is similar to that used by Heck *et al.* (1979) to evaluate the bioavailability of imiprime formulations. A tetradeutero derivative of trazodone (D_4 -trazodone) (Figure 1) was used for this study.

Materials

Subjects

Six healthy male subjects aged 22 to 27 years (mean $\pm$ s.d. 24 ± 3.1 year) participated in the study after having given informed consent. Each subject was within 15% of his ideal weight (mean $\pm$ s.d. 70 ± 6 kg) based on his height (mean $\pm$ s.d. 173 ± 6.4 cm) and frame. The subjects were free of intercurrent disease and did not use alcohol, tobacco products or drugs chronically.

Study design

The study used an open, three period cross-over design. Each subject received 50 mg of trazodone HCl as a one-third fragment of a 150 mg dividose tablet (the new formulation), formulation A, one 50 mg film-sealed tablet (the commercial formulation), formulation B, or 5 ml of a 1% solution, in a random order determined from the rows of a 3×3 Latin square. In addition, each subject received 5 ml of a 1% solution of D_4 -trazodone concomitantly with each formulation. There was a 7 day interval between treatment sessions. All drug treatments were administered following an overnight fast.

Drug formulations

Formulation A, the one-third fragment of a 150 mg dividose tablet, was prepared by cutting the scored tablets into thirds. The trazodone HCl content of these fragments was 50.5 ± 0.5 mg.

Formulation B, the 50 mg film-sealed tablet, was obtained from Mead Johnson Pharmaceutical Co. (USA). The 1% solution formulation used in this study was a buffered (citrate), isotonic solution for i.v. administration; the trazodone HCl content was found to be 10.2 g/l.

Trazodone plasma assays

A GCMS method for the independent measurement of trazodone and D_4 -trazodone (Gammans *et al.*, submitted for publication) was used. The linearity, precision and accuracy of the procedure have been assessed; the precision and accuracy of this method during the course of these analyses was evaluated by analysis of aliquots of quality control samples with each batch of subject plasma samples and were found to be within 10% and 5%, respectively. The lower limit of assay was 40 ng trazodone/ml.

Pharmacokinetic parameters and statistical analysis

Areas under the plasma concentration-time curves (AUC) were calculated by the trapezoidal rule; assay values reported as not quantifiable were assigned a value of zero. Elimination half-life values were computed from the first order elimination rates which were estimated by least squares linear regression of the terminal log linear phase of the log plasma concentration-time curves. The AUC, $C_{\max}$, $t_{\max}$, and half-life values were analyzed by the general linear model (IIA) of Wallenstein & Fischer (1977) extended to three periods but excluding all terms involving time.

Results

The D_4 -trazodone was administered to each subject three times during the course of this study. The individual pharmacokinetic parameters for D_4 -trazodone during the three study sessions and the overall mean are shown in Table 1. The differences between sessions were not statistically significant ($P > 0.05$).

D_4 -trazodone was administered in solution concomitantly with three different formulations of trazodone. The mean plasma concentration of trazodone from the solution and formulations A and B are shown in Figures 2, 3 and 4, respectively; the mean plasma concentration of D_4 -trazodone from the D_4 -trazodone solution administered with each formulation is also shown. The plasma concentrations of trazodone and D_4 -trazodone following the solution are virtually identical at each time point through 34 h

Table 1 Pharmacokinetic parameters for D₄ trazodone HCl administered in solution to the same subjects during three separate sessions.

Subject	AUC (ng ml ⁻¹)	C _{max} (ng/ml)	t _{max} (h)	Half-life (h)
<i>Experimental session I</i>				
1	5376	1030	0.5	21
2	7361	1170	0.7	16
3	3983	783	0.7	4
4	4071	643	1.0	12
5	5543	563	0.5	12
6	4523	552	0.5	18
Mean	5143	790	0.7	14
<i>Experimental session II</i>				
1	4823	757	0.5	12
2	8264	780	2.0	11
3	4674	842	0.5	6
4	3509	666	1.0	5
5	6392	1000	2.0	14
6	8407	1620	1.0	7
Mean	6012	944	1.2	9
<i>Experimental session III</i>				
1	3779	871	2.0	7
2	7846	988	0.7	11
3	6146	1080	0.7	8
4	4848	816	2.0	8
5	5651	681	2.0	21
6	4551	601	2.0	24
Mean	5470	840	1.3	13
Mean s.d.	5542 1148	858 79	1.1 0.5	12 5

Figure 2 Mean $\pm$ s.e. mean ($n=6$) plasma concentrations of trazodone (—) and D₄-trazodone (- - -) administered in solution.

Figure 3 Mean $\pm$ s.e. mean ($n=6$) plasma concentrations of trazodone from formulation A (—) and D₄-trazodone (- - -) from solution.

Figure 4 Mean $\pm$ s.e. mean ($n=6$) plasma concentration of trazodone (—) from formulation B and D₄-trazodone (- - -) from solution.

Table 2 Trazodone pharmacokinetic parameters by subject for each of the formulations.

Subject	Trazodone AUC (ng ml ⁻¹ h)	Relative AUC	Trazodone C _{max} (ng/ml)	Relative C _{max}	Trazodone t _{max} (h)	Trazodone half-life (h)
<i>Formulation A</i>						
1	4098	1.08	629	0.72	2.00	8.6
2	8387	1.01	799	1.02	2.00	11.3
3	3696	0.93	430	0.55	2.00	4.3
4	4473	0.92	897	1.10	2.00	5.6
5	5250	0.95	519	0.92	4.00	11.5
6	5059	0.60	1140	0.70	2.00	5.7
Mean	5161	0.92	736	0.84	2.3	7.8*
s.d.	687	0.07	107	0.09	0.3	1.3
<i>Formulation B</i>						
1	5376	0.98	699	0.68	0.50	21.4
2	7846	0.98	964	0.98	0.75	10.6
3	4674	0.96	795	0.94	1.00	5.9
4	4071	0.96	631	0.98	1.00	11.9
5	6391	0.96	860	0.86	2.00	13.9
6	4550	0.99	581	0.97	2.00	23.8
Mean	5336	0.97	755	0.90	1.4	14.6
s.d.	575	0.01	59	0.05	0.3	2.8
<i>Solution</i>						
1	4881	1.01	829	1.10	0.50	11.2
2	7156	0.97	1260	1.08	0.75	16.0
3	6086	0.99	1090	1.01	0.75	7.8
4	3403	0.97	588	0.88	1.00	4.9
5	5624	1.00	721	1.06	2.00	21.5
6	4556	1.01	661	1.20	0.50	18.6
Mean	5284	0.99	858	1.05	0.9	13.3
s.d.	532	0.01	108	0.04	0.2	2.6

* Significantly different ($P < 0.05$)^a Ratio of trazodone AUC/D₄-trazodone AUC^b Ratio of trazodone C_{max}/D₄-trazodone C_{max}

after dosing (Figure 2). The C_{max} for trazodone occurs somewhat later for the tablet formulations A and B (Figures 3 and 4), a fact reflected in the somewhat longer t_{max} values (Table 2).

The ratio of trazodone AUC to D₄-trazodone AUC, the relative AUC value, was near 1.0 for all three formulations (Table 2). The relative C_{max} value was also nearly 1.0 although the mean t_{max} for formulations A and B were 0.5 and 1.4 h later than that of the solution. The half-life values ranged from 7.8 to 14.6 with a mean of 12.1 h. Analysis of variance of these pharmacokinetic parameters (Table 2) indicated no statistically significant differences except for the half-life means which showed the formulation A trazodone half-life mean to be lower than the others. The D₄-trazodone half-life mean associated with administration for formulation A was also significantly less; however, the trazodone

and D₄-trazodone half-lives were not significantly different for any of the three pairs of data (Table 3). The Westlake (1976) symmetric confidence intervals for relative AUC and trazodone AUC were approximately (80%, 20%) for each pairwise comparison and the 95% confidence intervals encompassed zero for each contrast (Table 4). The power of the test to detect a difference equal to 20% of the solution relative AUC value was 85% while the power of the test to detect a difference equal to 20% of the trazodone AUC value was 54%.

Discussion

Since D₄-trazodone was administered to each subject during three successive sessions, these data provide an estimate of the intrasubject and

Table 3 Trazodone pharmacokinetic parameters for each of the formulations tested^a.

Pharmacokinetic parameter	Trazodone formulation		
	A	B	Solution
Trazodone AUC (ng ml ⁻¹ h)	5161 (687)	5336 (575)	5284 (532)
D ₄ -trazodone AUC (ng ml ⁻¹ h)	5804 (841)	5485 (575)	5336 (551)
Relative AUC ^b	0.92 (0.07)	0.97 (0.01)	0.99 (0.01)
Trazodone C _{max} (ng/ml)	736 (107)	755 (59)	858 (108)
D ₄ -trazodone C _{max} (ng/ml)	906 (149)	851 (77)	818 (102)
Relative C _{max}	0.84 (0.09)	0.90 (0.05)	1.05 (0.04)
Trazodone t _{max} (h)	2.3 (0.3)	1.4 (0.3)	0.9 (0.2)
D ₄ -trazodone t _{max} (h)	1.10 (0.3)	1.1 (0.3)	0.9 (0.2)
Trazodone half-life (h)	7.8 (1.3)*	14.6 (2.8)	13.3 (2.6)
D ₄ -trazodone half-life (h)	8.3 (1.2)*	14.6 (2.7)	13.4 (2.6)

* Significantly different ($P < 0.05$) from formulation B or solution^a Values mean (s.e. mean); $n=6$ ^b Ratio of trazodone AUC/D₄-trazodone AUC^c Ratio of trazodone C_{max}/D₄-trazodone C_{max}

intersubject variability inherent in human bioavailability or bioequivalence studies. Since the D₄-trazodone was administered in solution, which is generally considered the most bioavailable oral dosage form, the data in Table 1 should represent only variation in the pharmacokinetic parameters with relatively little contribution from the dosage form. The % relative standard deviation (% RSD) in the AUC values among the six subjects, a measure of intrasubject variability, ranged from 6% to 38% while the % RSD for AUC by period, a measure of the intersubject variability, ranged from 26% to 55%. The dramatic increase in power of the test in stable isotope dilution bioavailability studies noted by Heck *et al.* (1979) and in this study is apparently due to the reduction of both the intrasubject and intersubject variability when relative AUC and relative C_{max} are used as the measurements of dosage form bioavailability.

Use of stable isotope dilution methodology for bioavailability testing rests, in part, on the assumption that introduction of the stable isotopic label does not alter the drug kinetics. Differences in the pharmacokinetics of deuterated captopril and nadolol (Devlin *et al.*, 1982) have been observed. When trazodone and D₄-trazodone were administered in solution, the plasma concentrations of the two compounds were found to be virtually identical at each sample time point (Figure 2). The relative AUC and C_{max} values were not significantly different ($P < 0.05$) from 1. These data support the conclusion that trazodone pharmacokinetics were not altered by deuterium labelling in the triazolopyridine ring (Figure 1).

Of the model independent pharmacokinetic parameters evaluated in this study, only the trazodone and D₄-trazodone half-life values following formulation A were significantly dif-

Table 4 Confidence intervals and power of the test for contrasts of the three trazodone formulations tested.

Contrast	Confidence intervals	Relative AUC	Trazodone AUC	Relative C _{max}	Trazodone C _{max}
A vs Solution	Westlake 95% ^a	(81.5,118.5) (-0.21,0.06)	(79.9,120.1) (-1160,912)	— (-0.4,0.0)	— (-466,221)
B vs Solution	Westlake 95%	(86.1,113.9) (-0.15,0.11)	(80.3,119.7) (-984,1088)	— (-5.4,0.1)	— (-446,240)
A vs B	Westlake 95%	(83.4,116.6) (-0.19,0.08)	(79.5,120.5) (-1212,860)	— (-0.3,0.2)	— (-363,324)
Power ^b		85%	54%	—	—

^a 95% confidence interval around difference between mean values.^b Power of the test to detect a 20% difference using the solution as standard.

ferent (Table 3) from those observed following formulation B or solution. However, the trazodone and D₄-trazodone, which was always administered as a solution, half-life values were not significantly different from each other for any of the three trazodone formulations tested. The latter indicates that the shorter half-life observed with formulation A is not a property of the formulation. However, we can offer no plausible explanation for the shorter half-life observed following formulation A.

No marked differences were observed between the trazodone dosage forms used in this study. The ability to demonstrate dosage form equivalence is greatly enhanced when the data are normalized using the data from the concomitantly administered D₄-trazodone. This is demonstrated by the relatively smaller Westlake and 95% confidence intervals and increased power for the smaller Westlake and 95% confidence intervals and increased power for the relative AUC data compared to the trazodone AUC data as shown in Table 4. While the power of 85% for the relative AUC data is quite adequate, it is somewhat lower than that reported by Heck

et al. (1979) in their description of stable isotope dilution bioavailability studies. In this study one of the six subjects has an anomalously low relative AUC value of 0.60 for formulation A while all the other relative AUC values ranged from 0.92 to 1.08. Re-analysis of the data without that subject markedly decreased the residual mean square error and increased the power from 85% to 99%; the mean relative AUC values for these five subjects were 0.98, 0.97 and 0.99 for formulations A, B and solution, respectively.

In conclusion, these data indicate that the two formulations of trazodone HCl tested are bioequivalent to each other and to an oral solution. The study results further demonstrate the value of stable isotope dilution bioavailability testing as a means of increasing the power of the test thus decreasing the number of subjects required to demonstrate bioavailability. This increase in power appears to be due to a reduction of the impact of both intrasubject and intersubject variability on the results when the data are normalized using the data from the stable isotope labelled standard.

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