PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERISTICS OF TRAZODONE IN THE ELDERLY

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1 The pharmacokinetic and some pharmacodynamic characteristics of a single oral dose of 100 mg trazodone were compared in young and elderly volunteers.

2 The maximum plasma concentration of trazodone was similar in both age groups. The time to maximum concentration was apparently prolonged in four subjects who swallowed the capsule with a minimal volume of fluid. This may have been due to the capsule being retained in the oesophagus.

3 The terminal phase half-life of trazodone was significantly prolonged ($P < 0.05$) and area under the plasma concentration-time curve was significantly larger ($P < 0.01$) in the elderly. Apparent oral clearance was significantly reduced ($P < 0.01$) in the elderly.

4 Measurement of critical flicker fusion threshold and subjective assessment of alertness using a visual analogue scale, confirmed the sedative effect of trazodone in both age groups. The elderly subjects were less alert for a longer period following drug administration than the young.

5 The differing pharmacokinetic and pharmacodynamic characteristics of trazodone in the young and elderly may be due to an age-related reduction in hepatic drug-metabolising activity, a difference in regional distribution or a change in CNS sensitivity to the drug.

Keywords trazodone elderly subjects pharmacodynamics pharmacokinetics

Introduction

At least 5% of the elderly population have clinically significant depression (Gurland, 1976), and many will be prescribed antidepressant drugs. The prominent anticholinergic, neurological and cardiotoxic side-effects of the widely used tricyclic compounds are particularly troublesome in old age (Rodstein & Som Oei, 1979; Williamson, 1978) and consequently poor patient compliance becomes a common problem. The pharmacokinetics of both imipramine and amitriptyline alter significantly in the elderly, and there is great variability in the steady-state plasma concentrations achieved on standard dosage regimens (Nies *et al.*, 1977).

Trazodone (2-(3-(4-chlorophenyl)-1-piperazinyl)propyl)-1, 2, 4-triazolo (4,3-a) pyridin - 3 (2H) - one hydrochloride, 'Molipaxin') is a new antidepressant agent introduced into clinical practice in Britain in 1980. Its chemical structure is unrelated to existing psychotropic drugs, yet it possesses antidepressant activity equivalent to that of the tricyclics (Al-Yassiri *et al.*, 1981).

Pharmacokinetic studies in healthy volunteers have shown rapid and almost complete absorption after oral ingestion (Jauch *et al.*, 1976), and a mean half-life of elimination of the unchanged drug of 4.1 h (Ankier *et al.*, 1981). It is converted to inactive metabolites, mainly by oxidation and hydroxylation, and only a small fraction is excreted unchanged in the urine and faeces (Catanese & Lisciani, 1970).

Significant side-effects are uncommon and the lack of anticholinergic effects (Gershon & Newton, 1980) and absence of cardiotoxicity (Van de Merwe *et al.*, 1982) has made the use of trazodone particularly attractive for the elderly patient. (Gerner *et al.*, 1980; Branconnier & Cole, 1981).

The present study was undertaken in view of the well recognized changes in drug handling and response which may occur in old age (Crooks & Stevenson, 1979). It compares the pharmacokinetic and some pharmacodynamic characteristics of a single dose of trazodone in young and elderly healthy volunteers.

Methods

The study was approved by the local Ethical Committee. Twelve young and ten elderly volunteers took part, all of whom had given their informed written consent.

Details of age, weight and height are given in Table 1. All participants were in good health, having received a medical examination and a biochemical and haematological screen prior to acceptance into the

Table 1 Details of age, sex, weight and height of subjects studied

	Young (n = 12)	Elderly (n = 10)
Age (years) : Median	24	69.5
: Range	23–30	65–74
Sex : Male	4	1
: Female	8	9
Weight (kg) : mean $\pm$ s.d.	62.9 $\pm$ 9.2	62.7 $\pm$ 14.1
Height (cm) : mean $\pm$ s.d.	169.9 $\pm$ 5.7	164.5 $\pm$ 4.9

study. Three of the young volunteers were taking oral contraceptives but no other drugs were taken for 2 weeks before or during the study period. One subject in each age group smoked. Five of the young and seven of the elderly subjects were given the medication with 200 ml of milk. Otherwise all had fasted from 9 h prior to and for 3 h after the medication was taken, although water was allowed when desired. Bioavailability of trazodone is not adversely affected when the drug is taken with food.

Trazodone 100 mg was administered orally as a single capsule, and venous blood (5 ml) was collected from each volunteer into heparinised tubes just before and at 20, 40, 60, 80, 100, 120 min and 3, 4, 6, 8, 12, 24, 30, 36 and 48 h after dosage. The separated plasma was stored at 4°C within 30 min of venepuncture and plasma concentration of trazodone later determined using a high pressure liquid chromatographic assay (Ankier *et al.*, 1981). Trazodone 1 μ g/ml is equivalent to 2.45 μ mol/l.

Immediately after taking each blood sample, psychometric and subjective tests were completed. Critical flicker fusion threshold, an assessment of the level of CNS arousal, was determined three times each with increasing and decreasing frequency, and the means of the results recorded. Subjects were also asked to assess how alert they felt, using a 100 mm visual analogue scale (0 = very alert; 100 = very drowsy).

The maximum plasma concentration ($C_{\max}$) and the time taken to reach it ($t_{\max}$) were obtained from each subject's plasma concentration-time curve. Terminal phase half-life values ($t_{1/2}$) were estimated

by considering the linear regression of the terminal phase of the log-concentration against time. The area under the plasma concentration-time curve from 0 to 48 h (AUC_{0-48}) was calculated using the trapezoidal rule. The total area under the curve ($AUC_{0-\infty}$) was calculated from the equation:

$$AUC_{0-\infty} = AUC_{0-48} \div \frac{48 \cdot t_{1/2}}{0.693}$$

where C_{48} was the plasma concentration of trazodone at 48 h. The apparent oral total drug clearance (CL_0) of trazodone was estimated from the ratio of the administered dose to $AUC_{0-\infty}$ (Wilkinson & Shand, 1975).

Analysis of variance was used to compare the pharmacokinetic and pharmacodynamic test results considering age and the 'milk factor'. In all tests, the critical P value for statistical significance was less than 0.05.

Results

The mean plasma concentrations of trazodone for each subject group are shown in Table 2. Mean values for the young and the elderly are plotted in Figure 1, showing significantly higher plasma concentrations in the elderly at 8, 24, 30, 36 and 48 h. Pharmacokinetic data is given in Table 3, based on results from 19 of the volunteers. One young and two elderly volunteers had a missing plasma concentration value in the early stages of the trial and, as it was not possible to estimate the values with any certainty, they were excluded from the pharmacokinetic calculations (but included in the pharmacodynamic calculations).

There were no significant differences between the maximum plasma concentrations observed in any group, although values ranged from 0.9 μ g/ml to 2.3 μ g/ml, with a mean of 1.6 μ g/ml. The majority of subjects reached maximum concentration between 20 and 120 min, but four of those who took the medication without milk (three young and one elderly) did not reach maximum concentration until 3 h. Mean terminal phase half-life was significantly prolonged in the elderly ($P < 0.05$) with values ranging from 4.6 to 8.3 h in the young and from 6.0 to 16.2 h in the old. $AUC_{0-\infty}$ was significantly larger in the elderly than the young ($P < 0.01$) and apparent oral clearance was significantly reduced ($P < 0.01$).

The visual analogue sedation scale demonstrated the sedative effect of trazodone (Figure 2). Thirteen of the subjects had a maximum visual analogue score, i.e. were feeling most drowsy, between 0 and 40 min after the maximum plasma concentration. At 12 h, the elderly subjects were significantly more drowsy than the young ($P < 0.05$). Similarly, critical flicker fusion threshold was reduced following trazodone (Figure 3) and took longer to return to baseline in the

Table 2 Mean $\pm$ s.e. mean plasma concentration of trazodone ($\mu\text{g/ml}$) after a single oral 100 mg dose

Time	Young volunteers		Elderly volunteers	
	Fasted (n = 7)	With milk (n = 5)	Fasted (n = 3)	With milk (n = 7)
20 min	0.2 ± 0.1	0.2 ± 0.1	0.9 ± 0.4	0.1 ± 0.1
40 min	0.7 ± 0.2	0.7 ± 0.3	1.3 ± 0.3	1.1 ± 0.4
60 min	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	1.2 ± 0.2
80 min	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.2	1.3 ± 0.2
100 min	1.1 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	1.0 ± 0.1
120 min	1.1 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
3 h	1.3 ± 0.1	0.9 ± 0.1	1.3 ± 0.3	0.8 ± 0.1
4 h	0.9 ± 0.1	0.7 ± 0.1	1.3 ± 0.2	0.8 ± 0.1
6 h	0.6 ± 0.1	0.5 ± 0.1	0.8 ± 0.1	0.6 ± 0.1
8 h	0.4 ± 0.1	0.3 ± 0.0	0.7 ± 0.1	0.5 ± 0.0
12 h	0.3 ± 0.0	0.2 ± 0.0	0.4 ± 0.0	0.3 ± 0.1
24 h	0.1 ± 0.0	0.1 ± 0.0	0.4 ± 0.2	0.2 ± 0.0
30 h	0	0	0.1 ± 0.1	0.1 ± 0.0
36 h	0	0	0.2 ± 0.0	0.1 ± 0.0
48 h	0	0	0.1 ± 0.1	0

elderly (8 to 12 h) than in the young (4 to 6 h). The difference was significant at 80 min, 2, 3, 4 and 6 h.

Discussion

The main findings of this study are the approximate two-fold increase in terminal phase half-life and the significantly higher plasma concentrations of trazodone in elderly, compared to young, healthy volunteers. Apparent oral clearance was significantly reduced. There was a concomitant increase in intensity and duration of drug effect as measured by critical flicker fusion threshold and visual analogue sedation scale.

Trazodone is almost exclusively eliminated by oxidative metabolism in the liver. The apparent oral clearance of a drug that is fully absorbed and completely metabolized by the liver provides an estimate of the intrinsic hepatic clearance of the drug (Wilkinson & Shand, 1975).

Despite three of the young volunteers taking oral contraceptives which are known to inhibit drug metabolism, the apparent oral clearance of trazodone was slower in the elderly, suggesting an age-related reduction in hepatic drug-metabolising activity. Such a reduction has been clearly demonstrated in animals (Kato & Tanaka, 1968) and studies in man have confirmed a reduction in liver size and the number of functioning liver cells with increasing age (Sato *et al.*,

Figure 1 Mean plasma trazodone concentration following oral administration of 100 mg to 12 young (Δ) and 10 elderly ($\bullet$) volunteers.

(* Denotes significant difference between groups, $0.01 < P < 0.05$, ** denotes $P < 0.01$).

Table 3 Pharmacokinetic parameters of trazodone

	Fasting (n = 7)	With milk (n = 4)	Fasting (n = 3)	With milk (n = 5)	
$C_{\max}$ mean $\pm$ s.e. mean ($\mu\text{g/ml}$)	1.6 ± 0.1	1.5 ± 0.1 1.3 ± 0.2	1.7 ± 0.1	1.7 ± 0.1	NS
$t_{\max}$ median and range (min)	100 (40–180)	120 (40–180)	60 (20–180)	90 (40–100)	—
$t_{1/2}$ mean $\pm$ s.e. mean (h)	6.4 ± 1.2 6.0 ± 0.5	11.6 ± 1.1 7.0 ± 0.6	13.6 ± 1.5	10.3 ± 1.4	$P < 0.05$
$AUC_{0-\infty}$ mean $\pm$ s.e. mean ($\mu\text{g ml}^{-1}\text{ h}$)	10.1 ± 1.0 10.9 ± 1.3	18.0 ± 2.8 8.8 ± 1.3	23.1 ± 6.4	14.9 ± 1.7	$P < 0.01$
CL_0 mean $\pm$ s.e. mean (l/h)	10.8 ± 1.3	10.8 ± 1.0 12.1 ± 1.6	6.3 ± 0.8 5.1 ± 1.4	7.1 ± 0.9	$P < 0.01$

1970). In the elderly, the decreased plasma clearance of antipyrine (O'Malley *et al.*, 1979) and propranolol (Castleden & George, 1979), have been attributed to a lower rate of metabolism. They all share, with trazodone, a common route of elimination; hydroxylation. The slower elimination of trazodone in the elderly might also be responsible for the altered pharmacodynamic responses, although these might also be explained by an age-related difference in regional distribution or a change in central nervous system sensitivity to the drug.

In view of the increased proportion of fat to lean body mass with increasing age (Forbes & Reina,

1970), and the strongly lipophilic properties of trazodone, an increase in apparent volume of distribution might be expected in the elderly. However, the peak plasma concentrations obtained in this study are not consistent with such an interpretation.

Absorption from the gut and presystemic hepatic elimination of trazodone, as reflected by the peak plasma concentrations and the time taken to reach them were not significantly different between the two age groups. The apparent delay in reaching peak plasma concentration in some of the subjects who had taken the capsule without milk, but with just sufficient water (about 15 ml) to assist swallowing, may

Figure 2 Visual analogue sedation scale: mean values following 100 mg trazodone in 12 young (○) and 10 elderly (●) volunteers.

(* Denotes significant difference between groups $\bar{P} < 0.05$).

Figure 3 Critical flicker fusion threshold: mean changes from pre-test baseline following 100 mg trazodone in 12 young (O) and 10 elderly (●) volunteers.
(* Denotes significant difference between groups $0.01 < P < 0.05$, ** denotes $P < 0.01$).

have been due to the capsule being retained in the oesophagus. Evans & Roberts (1981) have demonstrated that this is not uncommon when capsules are swallowed with insufficient water to wash them down and the importance to pharmacokinetic studies after oral dosing, as well as to everyday clinical practice, is clear.

In the absence of data following intravenous administration, no definite conclusions can be made concerning relative plasma clearance and volumes of distribution in the young and old. Single dose studies in healthy volunteers are, of course, of limited value in planning chronic dose regimens which must be tailored to the needs of the individual.

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