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KINETICS OF ORAL TRIFLUOPERAZINE DISPOSITION IN MAN

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The disposition of trifluoperazine (TFP) was studied in five healthy volunteers following oral administration of a 5 mg tablet. Using a very sensitive GC-MS technique plasma TFP concentrations were measured up until 24 h following drug ingestion. Peak plasma concentrations varied widely (range: 0.53–3.09 ng ml^{-1}) and were reached 2.8 ± 0.5 h following ingestion of the TFP tablet. The apparent terminal elimination half-life of TFP was 12.5 ± 1.4 h. The area under the plasma concentration-time curve differed widely between subjects (range: 5.9–17.6 ng ml^{-1} h) suggesting large individual differences in the extent of presystemic TFP elimination.

Introduction

Although trifluoperazine (TFP) has been used in the treatment of psychiatric patients since 1958, its disposition in humans has not been studied following single oral administration. This is essentially due to the lack of a sensitive and specific analytical procedure.

Recently reported methods for the quantitation of TFP in plasma include GC-NPD (Gillespie & Sipes, 1981; Roscoe *et al.*, 1982), GC-MS (Midha *et al.*, 1982; Whelpton *et al.*, 1982), and RIA (Midha *et al.*, 1981a). Of these methods, the GC-MS procedure using selected ion monitoring is the most sensitive allowing the determination of TFP plasma concentrations in the 0.078–5.0 ng/ml range.

Methods

After an overnight fast, five healthy male volunteers (27–34 years, 73.4 ± 2.1 kg) ingested a 5 mg trifluoperazine hydrochloride tablet (Stelazine®, Smith Kline & French). Blood samples were withdrawn by venepuncture using evacuated tubes (Vacutainer®, Beckton & Dickenson) but carefully avoiding contact between blood and the rubber stopper to prevent redistribution of TFP between plasma and red blood cells (Midha *et al.*, 1981b). Blood sampling times were 0 (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4.5, 6, 8, 12 and 24 h following drug administration. TFP was determined in plasma samples by the recently described GC-MS method using selected ion monitoring (Midha *et al.*, 1982). Pharmacokinetic parameters were calculated using standard procedures (Gibaldi & Perrier, 1975).

Results

The individual semilogarithmic plasma concentration/time profiles following oral administration of TFP are shown in Figure 1. Peak concentrations in plasma (C_{max}) were reached 1.5 to 4.5 h (2.8 ± 0.5 h) following the ingestion of the TFP tablet. There was wide intersubject variability in TFP peak plasma concentrations, e.g. a six-fold difference was found between subjects one and four (Table 1). The mean area under the plasma concentration/time profile (AUC) was 11.7 ± 2.2 ng ml^{-1} h when calculated using the linear trapezoidal rule for prepeak and plateau plasma levels and the logarithmic trapezoidal method for postpeak plasma concentrations. Again, considerable intersubject variability in this parameter was noted (Table 1). The AUC extrapolation from 24 h to infinity increased the AUC_0^{24} by 25% but did not change the variability found between the different volunteers. After reaching a peak, TFP plasma concentrations did not decline monoexponentially. In all five volunteers, the apparent terminal elimination half-life ($t_{½,z}$) was unfortunately characterized by only two concentration points: 12 and 24 h. This apparent terminal half-life was on the average 12.5 ± 1.4 h. When the 24 h data point was ignored and the half-life calculated between 4.5 and 12 h a mean value of 5.1 ± 0.9 h was found (Table 1).

Discussion

The disposition of most phenothiazines in humans is characterized by the existence of multi-exponential decay curves. The same phenomenon is apparent from the present oral disposition study. At least 2 and

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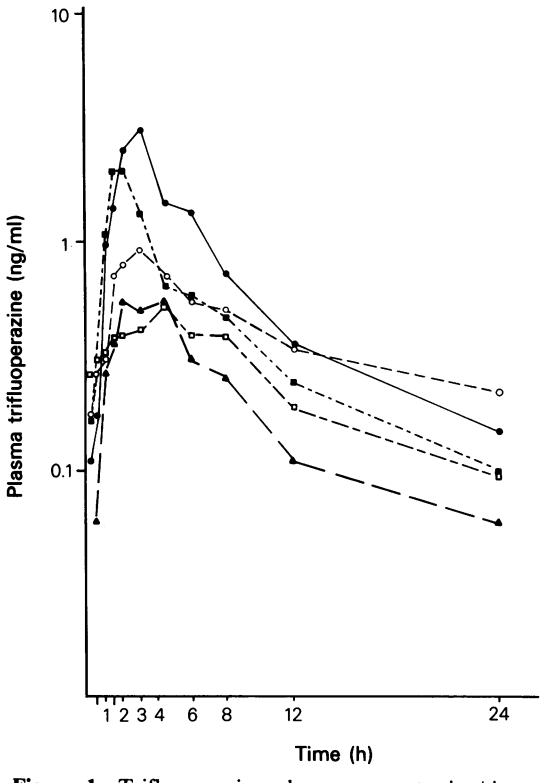

Figure 1 Trifluoperazine plasma concentration/time profiles in five healthy volunteers following ingestion of a single 5 mg tablet. (●——● subject 1; O– – –O subject 2; ■—·—■ subject 3; □– –□ subject 4; ▲– –▲ subject 5).

possibly 3 distinct phases can be found in the individual plasma concentration/time profiles after the peak concentration is reached. The $t_{\frac{1}{2},z}$ measured in this study was 12.5 h. However, this value must be considered an estimate since it is based on only 2 data points. Nevertheless, from the plasma concentration/time curves (Figure 1), it is clear that the 12–24 h portion is a distinct phase in the elimination of TFP. Multicompartmental disposition of a drug can suggest the existence of deep drug pools which may result in the slow disappearance of the drug from the body after cessation of a chronic dosage regimen. TFP is extensively metabolized in laboratory animals and man (Breyer *et al.*, 1974; Breyer & Schmalzing, 1977). Like other tricyclic psychoactive drugs, phenothiazines are subject to a high hepatic extraction in laboratory animals (Breyer & Schmalzing, 1977; Schmalzing, 1977). A similar extensive biotransformation of TFP during its first pass through the liver in humans would be a reasonable explanation for the wide intersubject variability in C_{max} and AUC found in the present study. Large interindividual differences in the extent of presystemic elimination is a well-known phenomenon (Routledge & Shand, 1979). With highly extracted drugs, the AUC after oral administration depends more, if not entirely, on the activity of the hepatic drug metabolizing enzymes and not on liver blood flow (Wilkinson & Shand, 1975).

The present study clearly shows that plasma TFP levels can be reliably measured even following a single oral 5 mg dose. This should permit investigation of the possible relationship between TFP plasma levels and clinical effects. In addition, large interindividual variations in TFP plasma concentrations were observed in the five subjects studied. These large variations underscore the fact that monitoring individual patient TFP levels may improve the efficacy of this neuroleptic in antipsychotic therapy.

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Table 1 Trifluoperazine kinetics in five volunteers following ingestion of a single 5 mg tablet (Stelazine ®)

Subject	*Age (years)*	*Weight (kg)*	t_{max} *(h)*	C_{max} *(ng/ml)*	$t_{½}$ *(4.5–12 h) (h)*	$t_{½,z}$ *(h)*	AUC_0^{24} *(ng ml^{-1} h)*	*AUC (ng ml^{-1} h)*
1	28	75	3.0	3.09	3.5	9.5	15.5	17.6
2	34	74	3.0	0.93	8.1	16.9	10.0	15.3
3	32	70	1.5	2.08	5.2	9.5	10.6	12.0
4	27	68	4.5	0.53	5.3	13.0	5.8	7.7
5	27	80	2.0	0.56	3.4	13.7	4.7	5.9
Mean	30.6	73.4	2.8	1.44	5.1	12.5	9.3	11.7
± s.e. mean	± 1.3	± 2.1	±0.5	±0.50	±0.9	± 1.4	± 1.9	± 2.2

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