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Single Oral Dose Pharmacokinetics of Tiapride in Patients with Huntington's Disease

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Summary. The pharmacokinetic properties of a single oral dose of 100 mg of tiapride were studied in six patients with Huntington's disease.

The results for five patients were consistent with a two compartment open model. Peak plasma concentrations were observed within 2 h following drug administration with a mean value of 0.92 μg/ml being recorded.

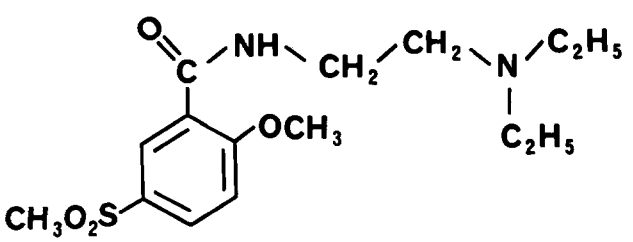
The drug was rapidly eliminated as unmetabolised tiapride in the urine, 51% of the dose was recovered in 24 h. The plasma elimination half-life was 5.3 h and the average apparent plasma clearance was 16.6 l/h.

Key words: tiapride, Huntington's disease; pharmacokinetics

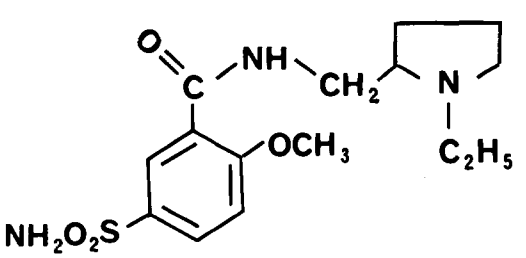
Tiapride (Tiapridal, Delagrange) is a substituted benzamide related structurally to sulpiride (see Fig. 1). Pharmacologically tiapride is a dopamine receptor antagonist, but without the ability to block dopamine stimulated adenylate cyclase (Elliott et al. 1977). It increases dopamine turnover in certain brain regions without binding potently to dopamine receptors (Elliott et al. 1977; Jenner et al. 1978).

Clinically tiapride has been used in a number of conditions but its major role maybe in the treatment of abnormal involuntary movements of diverse pathological origins. Tiapride has been reported as effective in the treatment of levodopa induced involuntary movements (Lees et al. 1979; Nielsen 1983), Parkinson's disease (Price et al. 1978), tardive dyskinesia (Greil et al. 1985) and in Huntington's disease (Lhermitte et al. 1977; Buruma et al. 1982; Roos et al. 1982).

There has been little data published on the pharmacokinetics of tiapride in either normal volunteers or in patients with movement disorders. Using radiolabelled tiapride Strolin-Benedetti et al. (1978) showed that the drug was excreted mainly by the kidneys in an unchanged form. Rey et al. (1982) examined the bioavailability of four forms of tiapride in normal volunteers. The results were compatible with a two-compartment open model with rapid absorption and distribution. The mean elimination half-life was around 3 h. Roos and coworkers (1986) reported the steady-state pharmacokinetics of tiapride in seven patients with movement disorders. Elimination half-life was about 4 h and greater than 50% of the dose was excreted in the urine as unchanged drug. The present study reports kinetic parameters in patients with Huntington's disease following a single oral dose of tiapride.



Tiapride



Sulpiride

Fig. 1. The structure of tiapride [N-(diethylamino-ethyl)-2-methoxy-methyl-5-sulphonyl benzamide]

Table 1. Patient characteristics

Patient number	Age	Sex	Weight (kg)	Comments
1	63	F	68	
2	32	F	47	5 mg diazepam 6 a.m.
3	49	F	49	
4	52	F	51	
5	67	M	73	
6	38	M	53	
7	55	M	48	withdrawn during study

Materials and Methods

Patients

Seven inpatients at the Arthur Preston Centre for Huntington's Disease were considered eligible for the study. Informed consent was obtained from the subjects and/or their next of kin. There were 3 males and 4 females aged from 32 to 67 years (mean = 50.9 ± 12.6 years). Other characteristics are given in Table 1. They had no history of renal, hepatic or gastrointestinal disease. One patient was withdrawn during the single dose study due to difficulties of obtaining samples. After a one week drug free period each subject received a single oral dose of 100 mg of tiapride 1 h after a standardised light breakfast consisting of tea and toast. Blood samples were collected before the dose and at noted regular intervals up to 12 h after the dose from an indwelling heparinised catheter inserted into an arm vein. An additional sample was taken 24 h after the dose by venepuncture. Samples of 10 ml were collected into lithium heparin tubes, centrifuged immediately and stored frozen until analysed. A 24-h urine sample was collected from each subject during the same 24 h period of drug administration. The total volume of the sample was measured and a 20 ml aliquot stored frozen at −20 °C until analysed for tiapride.

Controls

Data for normal volunteers was taken from that previously published by Rey et al. (1982). They administered a single 200 mg oral dose of tiapride to 8 drug free, healthy subjects (4 M, 4 F; mean age 22.9 years; range 22–24 years). Plasma samples were collected on a similar time scale to that used in the present study and tiapride analysed by a HPLC method.

Pharmacokinetic Analysis

The areas under the plasma concentration time curves (AUC) were measured by the trapezoidal rule with extrapolation to infinite time using the last measured concentration divided by β. Terminal phase half-life ($t_{1/2}$) was calculated by linear regression using unweighted data.

The apparent volume of distribution (V_z) was calculated from the equation $V/f = D/AUC \cdot \beta$ where D is the dose. The apparent plasma clearance relative to the drug bioavailability (f) was calculated from $CL/f = D/AUC$. Mean renal clearance was estimated as amount in the urine/AUC (Wagner 1975). The estimated lag times and absorption rate constants (k_a) were obtained by using the AUTO-AN-NONLIN least-squares iterative computer programs for fitting the curves to a two-compartment open model with lag time and first-order absorption (Metzler 1969; Sedman and Wagner 1974). Apparent plasma clearance for the normal controls was calculated from the published V values. The value for β was calculated from $0.693/t_{1/2}\beta$ and CL was calculated as $V \cdot \beta \cdot Wt$ (l/h), (Rey et al. 1982).

Tiapride Analysis in Plasma and Urine

Both plasma and urinary concentrations of tiapride were determined using reversed phase high performance liquid chromatography. The details of the assay for plasma have been reported elsewhere (Norman et al. 1986). For urine specimens the method of analysis was based on that for plasma. Sulpiride, the internal standard (100 µl of 1 mg/ml ethanolic stock solution), was added to urine (100 µl) in a 10 ml glass stoppered tube and alkalinised with sodium hydroxide (1 ml of 0.1 M) and the contents thoroughly mixed. The solution was extracted twice with ethylacetate (5 ml) on a multitube vortexer for 2 min, centrifuged and the ethylacetate layer transfered to a clean set of tubes. The ethyl acetate layer containing tiapride and internal standard was then processed as described for plasma samples. The final extract was reconstituted in 10 µl of ethanol and injected into the high performance liquid chromatograph, under the conditions described previously. Standard curves were constructed in the range 0 to 4 µg/ml using drug free urine from normal volunteers. Using linear regression analysis the calculated equation was: peak height ratio = 1.09 concentration + 0.05 ($n = 6$; $r^2 < 0.995$). Precision and accuracy was assessed from two quality control samples 0.3 µg/ml (found = 0.29 CV% = 3.1) and 0.9 µg/ml (found = 0.90; CV% = 3.3).

Statistics

Comparisons between pharmacokinetic parameters for patients and volunteers were made using published data (Rey et al. 1982) and that determined in

Table 2. Pharmacokinetic parameters for tiapride

Patient number	k_a (h^{-1})	k_{21} (h^{-1})	k_{12} (h^{-1})	t_{lag} (h)	β (h^{-1})	$t_{½}$ (h)	CL/f ($l \cdot h^{-1}$)	(V_z/f) ($l \cdot kg^{-1}$)
1	3.12	0.592	0.263	0.482	0.142	4.87	10.14	1.05
2	1.31	0.217	0.129	0.426	0.127	5.46	15.98	2.68
3	1.05	0.254	0.108	0.000	0.154	4.49	24.44	3.24
4	1.66	0.115	0.088	0.307	0.088	7.87	16.13	3.59
5	1.02	0.241	0.070	0.563	0.107	6.47	16.13	2.06
Mean	1.63	0.284	0.132	0.356	0.124	5.83	16.56	2.52
±SEM	0.35	0.080	0.034	0.098	0.012	0.61	2.28	0.45
6[a]	0.615	-	-	0.94	0.409	1.70	36.36	1.68

[a] one compartment model

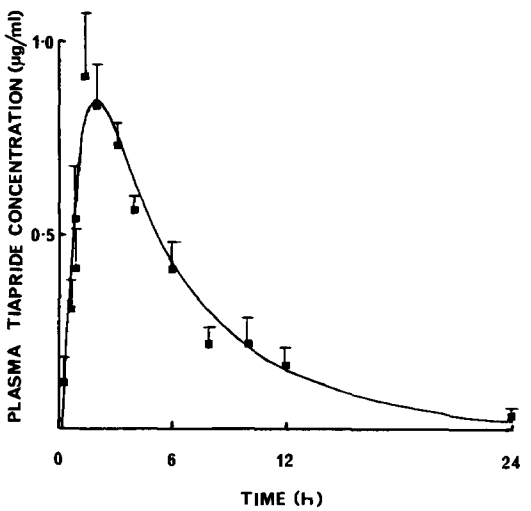


Fig. 2. Mean (±SEM) plasma concentration-time profile of 5 patients with Huntingtons disease who each received 100 mg of tiapride p.o. These 5 patients data could be fitted to a two compartment open model. Data for Patient 6 was fitted to a one compartment model

the present study. The Mann-Whitney U test was used to contrast patients and controls, males and females. All statistical procedures were performed with the SPSSX package (SPSS Inc., 1986).

Results

The plasma concentration-time data for 5 of the 6 subjects could be fitted to a two compartment open model with a lag time. The mean plasma concentration time profile is shown in Fig. 2. For each of these data sets a weighting factor of $1/Y^2$ gave the best fit (correlations between observed and predicted concentrations > 0.95). For the sixth patient the data set was best described by a one compartment model (again using a weighting factor of $1/Y^2$ (correlation $= 0.98$). The individual and mean pharmacokinetic parameters estimated from the models are given in Table 2. There were no differences in pharmacokinetic parameters between male and female patients. This result agrees with that of Rey et al. (1982) who also showed no sex differences in kinetic parameters in normal volunteers. Given the few male subjects in this study the absence of significant differences in kinetic parameters is not surprising.

Since sex was not an important determinant of pharmacokinetic parameters, the data for patients as a group (excluding Patient 6) were compared with the published data for normal controls (Rey et al. 1982). Patients had a smaller value for β (0.124 h^{-1} c.f 0.223 h^{-1}; $p < 0.005$), a larger volume of distribution (2.38 l/kg c.f 1.43 l/kg; $p < 0.05$). Both rate constants k_{12} (0.132 h^{-1} c.f. 4.58 h^{-1}; $p < 0.005$) and k_{21} (0.284 h^{-1} c.f 2.13 h^{-1}; $p < 0.005$) were smaller in the patients than in controls. For k_a, clearance, and t_{lag} no significant differences were observed between patients and normal controls. The mean maximum plasma concentration observed in the patients was 0.92 µg/ml reached between 1.5 and 2 h (mean 1.73 h) after the dose.

Discussion

The study reported here represents the first of the pharmacokinetics of tiapride in patients with Huntington's disease. While the parameters determined resemble those which have been reported in normal volunteers, using various dosage forms of unlabelled drug (Rey et al. 1982) and ^{14}C-labelled tiapride (Strolin-Benedetti et al. 1978), there are some important differences. The elimination rate constant (β) is smaller in the patient group than in normal subjects with a consequent increased elimination half-life. Clinically this difference is unlikely to be

important since the prolonged half-life does not alter prescribing habits. The prolonged plasma half-life of tiapride may be the result of the disease process or alternatively be an effect of age. Mean age of the patients was about twice that of the volunteers. Clearly further studies are needed to examine the relationship between age, disease state and drug pharmacokinetics.

Tiapride was eliminated in the urine mainly in the form of unmetabolised drug with recovery averaging 51%. This is smaller than the 75% recovered in some previous studies (Strolin-Benedetti et al. 1978; Rey et al. 1982), but comparable to that reported in other patients with movement disorders (Roos et al. 1986). Since urinary incontinence is a frequent occurence in Huntington's disease the wide variation in urinary recoveries may be related to incomplete collections. The measured urine volumes suggest that this might be the case in at least two subjects (Nos. 2 and 3). One of these patients (No. 2) had the lowest recovery recorded, 23%. Given this possible error the mean renal clearance was calculated for each patient assuming a complete 24 h urine collection and was 161 ml/min. This value is 58% of the apparent plasma clearance.

The mean volume of distribution is greater than the volume of body water suggesting accumulation of tiapride in the tissues. Patients again differ from published data in normal controls, where the volume of distribution was smaller. Since the mean patient apparent plasma clearance value is 16.6 l/h (227 ml/min) is not different from the reported value in normals (18 l/h or 300 ml/min), the changes in plasma half life can be ascribed to more extensive tissue distribution in the patients.

The pharmacokinetics of tiapride in Huntington's disease is described by a two compartment open model with peak plasma concentrations obtained within 2 h and an elimination half-life of 5.8 h.

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