Eur J Clin Pharmacol (1986) 31: 191-194

European Journal of
Clinical Pharmacology

Pharmacokinetics of Tiapride in Patients with Tardive Dyskinesia and Huntington's Disease

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Summary. The pharmacokinetics of tiapride were determined at steady-state in 5 patients with tardive dyskinesia and 2 patients with Huntington's disease given tiapride 100 mg t.i.d. for 7 days. The maximum serum concentration of tiapride of 1.47 ± 0.35 μg/ml was reached after 1.4 ± 0.67 h. The half-life time of elimination was 229 ± 41 min. About 50% of the dose of tiapride was excreted unchanged by the kidney. Neither protein binding nor glucuronide, sulphate or acetyl conjugation was observed. Renal clearance in the patients appeared to be lower but the other pharmacokinetic parameters did not differ from previous findings in healthy young volunteers.

Key words: tiapride, Huntington's disease; pharmacokinetics, tardive dyskinesia

Tiapride, a substituted benzamide, has been used clinically for several years in cases of involuntary movement disorders, with variable therapeutic success. Beneficial effects have been reported in tardive dyskinesia (TD; Buruma et al. 1982; Chouza et al. 1982; Lipcsey and Nagy 1982; Miletto and Julou 1981; Rust 1983; Pollak et al. 1985), Huntington's disease (HD; Chouza et al. 1982; Lipcsey and Nagy 1982; Roos et al. 1982) and L-dopa induced dyskinesia (LID; Chouza et al. 1982; Lees et al. 1979; Lipcsey and Nagy 1982; Miletto and Julou 1981; Nielsen 1983). The pharmacokinetic parameters of tiapride have been little studied and then mainly in acute experiments in healthy young volunteers (Strolin-Benedetti et al. 1978; Ohkawa 1979; Rey et al. 1982). Those studies showed that tiapride was rapidly absorbed after oral and intramuscular administration, the peak serum concentration was usually reached within 2 h, and the half-life of elimination was about 3.5 h. Tiapride was mainly eliminated unmetabolized in urine. The aim of the present study was to assess the pharmacokinetics of tiapride in a clinical situation, i.e. in patients with tardive dyskinesia and Huntington's disease receiving chronic treatment with it.

Patients and Methods

Six chronic schizophrenic patients with tardive dyskinesia, 2 men and 4 women, of mean age 62 (46-73 years), and 2 males with Huntington's disease (61 and 55 years), took part in the study. The patients with tardive dyskinesia lived in a chronic care unit of a psychiatric hospital (Psychiatric Hospital Endegeest, Oegstgeest); the Huntington's disease patients were living at home. The patients had no other diseases of the central nervous system, nor any renal, hepatic or gastro-intestinal disorders. All patients gave their informed consent to the study, which was approved by the Medical Ethics Committee of the Leiden University Hospital. Previously prescribed medication was left unchanged during the trial (Table 1). It had not been changed in the 3 months prior to the start of the trial. The patients with HD had not previously taken any drugs. None of the patients had taken tiapride beforehand. Each patient received tiapride 100 mg t.i.d. for 7 days, at 8.00, 15.00 and 22.00 h. On the last day the patients were admitted from 8.00 a.m. till 3.00 p.m., and blood samples were collected from a butterfly cannula in a cubital vein for the 7 hours after the 8 a.m. dose of tiapride. Serum was collected after centrifugation and was stored at -20 °C until analyzed. Tiapride and creatinine were measured in the samples. Urine was sampled throughout the entire 7-hour period and was stored at -20 °C until analyzed.

Table 1. Pharmacokinetics of tiapride in 5 patients with tardive dyskinesia (TD) and 2 patients with Huntington's disease (HD)

Patient	Age (years)	Medication	t_{max} (h)	C_{max} (μg/ml)	$t_{½}$ (min)	AUC (0-7) (μg·h/ml)	CL (ml/min)	CL_R (ml/min)	(%)	V_z (l/kg)
1 TD	68	Perphenazine Amantadine	2.00	1.32	221	5.82	287	240	80	1.27
2 TD	59	Fluphenazine-chloride Orphenadrine	1.50	1.44	237	6.09	273	156	55	1.26
3 TD	68	Haloperidol Amantadine	2.00	1.02	176	3.39	491	180	40	2.60
4 TD	73	Perphenazine Haloperidol Orphenadrine	2.00	2.03	248	8.93	187	40	20	1.45
5 TD	59	Perphenazine Phenergan Haloperidol	0.75	1.21	192	4.79	348	227	62	1.09
6 HD	61	-	0.50	1.67	302	7.14	234	166	72	1.27
7 HD	55	-	0.75	1.60	225	5.08	328	*	*	1.57
Mean	63		1.40	1.47	229	5.89	307	162	54	1.50
±SD	± 6		±0.67	±0.33	± 41	±1.78	± 98	± 84	±22	±0.51

t_{max} = time of maximal serum concentration after drug intake (h)
C_{max} = maximal concentration of tiapride after drug intake (μg/ml)
$t_{½}$ = half-life time of elimination (min)
AUC = Area under the serum concentration versus time curve, calculated by the trapezoidal method up to 7 h, AUC (0-7), (μg·h/ml)
CL = intrinsic clearance, assuming 100% absorption (Dose: AUC) (ml/min)
CL_R = renal clearance (urinary excretion per min divided by average serum concentration) (ml/min)
% = percentage of the oral dose, recovered in the urine during 7 h
V_z = apparent volume of distribution (CL × $t_{½}$: ln2 × body weight) (l/kg)
* = not determined

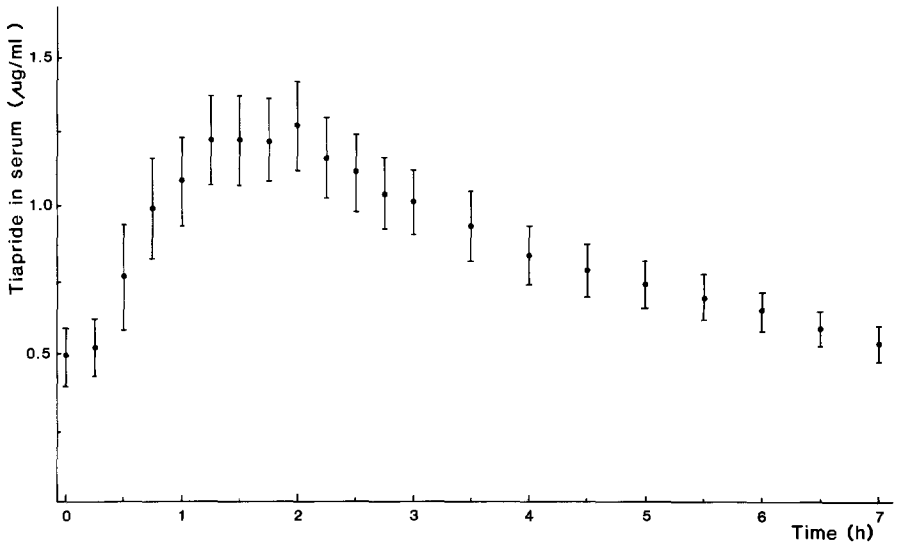

Fig. 1. Serum concentration-time curve of tiapride in 5 patients with tardive dyskinesia and 2 patients with Huntington's disease. *Vertical bars* represent SEM

Tiapride in serum and urine were measured by SP-HPLC. The assay method was: to 200 μl either of patient or a standard serum spiked with 0-4.0 μg/ml tiapride were added 50 μl NaOH 1.5 M, 200 μl internal standard (N-propionylprocainamide 10 μg/ml in dichloromethane) and 17 ml dichloromethane. After mixing for 10 min and centrifugation for 5 min, the upper layer was discarded and the organic layer was evaporated to dryness at 45 °C under N_2. The residue was dissolved in 50 μl eluent and 20 μl was injected into an HPLC equipped with an UV detector operating at 230 nm. The column was 100 × 3 mm Lichrosorb Si 60 5 μm; the eluent consisted of acetonitrile 250, methanol 55, ammonium hydroxide 13 (1 mol/l); the flow rate was 0.8-1.0 μl/min. Details of the method will be published elsewhere (de Wolff et al.).

Table 2. Mean (±SD) pharmacokinetic parameters of tiapride in 5 patients with tardive dyskinesia and 2 patients with Huntington's disease. Published results in healthy young volunteers are given for comparison. The urinary excretion is given as a percentage of the oral dose. For abbreviations see Table 1

Patients	Tiapride dose (mg)	t_{max} (h)	C_{max} (μg/ml)	$t_{½}$ (min)	CL (ml/min)	CL_R (%)	V_z (l/kg)
$n=7$	100	1.4	1.47	229	307	54	1.50
±SD		0.67	0.33	41	98	22	0.51
Controls							
$n=12$[1]	100[a]	1	1	±180	240	90	
$n=6$[2]	100[a]	2 ±0.04	0.73	±240		72	
$n=8$[3]	200[a]	1.06 ±0.69	1.55 ±0.28	194	310 ±38.3	76 ±12	1.43

[1] = Strolin-Benedetti et al. 1978
[2] = Ohkawa and Yamada 1979 (internal report De la Grange)
[3] = Rey et al. 1982
[a] = acute experiments

All measurements of serum tiapride concentrations were performed on the same day. The within-day reproducibility at 0.1 μg/ml and 2 μg/ml were 2.2% and 1.9%, respectively. The day-to-day reproducibility at 0.1 μg/ml and 2 μg/ml were 17% and 4.5%, respectively. The standard curve was linear in the range 1–25 μg/ml ($r=0.999$). Recovery at 0.1 μg/ml and 2 μg/ml was 96.1% and 96.9%, respectively. The detection threshold was 60 ng/ml.

Urine samples were incubated for 17 hours at pH 5 and 37 °C with β-glucuronidase and aryl sulphatase (Boehringer Mannheim) for the detection of glucuronide and sulphate conjugates. Urine was boiled for 10 min at pH 1 for assessment of acetylation.

Protein binding was studied by equilibrium dialysis using a Diachema dialyser with cellulose hydrate membranes (cut-off 5000 Daltons). Serum/ml was dialysed for 90 min at 37 °C, at a rotation frequency of 12 RPM, against an isotonic buffer containing (mmol/l): trishydroxymethylaminomethane 20 at pH 7.4, Na^+ 133, K^+ 4, Ca^{2+} 1, Mg^{2+} 1, Cl^- 108, HCO_3^- 30, PO_4^{3-} 1, glucose 5, urea 5, creatinine 0.1. Tiapride in both compartments was determined after the dialysis.

Results

Data from one patient with tardive dyskinesia had to be omitted because he had already taken 100 mg tiapride before the first blood sample was collected at 8.00 a.m.

The mean serum concentration-time curve for the remaining seven patients is shown in Fig. 1. For each patient the time of maximal concentration, t_{max}, the maximal concentration, C_{max}, the area under the concentration-time curve calculated by the trapezoidal method between t_0 and t_7, AUC (0–7), the half-life time of elimination, $t_{½}$, the total clearance, CL assuming 100% absorption, the renal clearance, CL_R and the relative volume of distribution (V_z) are given in Table 2. The mean results are given in Table 3, and are compared with reported data for healthy young volunteers.

About half of the dose was excreted unchanged by the kidney. There was no correlation between the renal clearances of tiapride and creatinine ($r=0.56$). The results in the two HD patients did not differ from those in the dyskinesia patients. No protein binding could be detected using an in vitro dialysis technique. The drug was not excreted in urine as a glucuronide, sulphate or acetyl conjugates. A metabolite peak, probably due to N-monodesethyl-tiapride, was seen in the chromatograms of the urine extracts, but its identity has not yet been confirmed.

Discussion

The pharmacokinetics of tiapride have been studied in 5 elderly patients, who had developed tardive dyskinesia after long term treatment with neuroleptic drugs, and 2 patients with Huntington's disease. The study was performed in patients in steady-state, so it can be assumed that the total amount of tiapride excreted in the period investigated (one dosage interval) was equal to the dose of tiapride taken if the absorption of the drug is assumed to be 100%. It appears that the maximal concentration of tiapride (C_{max}), the time at which it is reached (t_{max}), the half-life of elimination ($t_{½}$), the total clearance (CL) and the apparent volume of distribution (V_z) did not differ from published results obtained in healthy young

volunteers after a single oral dosage of 100 mg tiapride (Table 2). The percentage renal clearance, however, tended to be somewhat lower in the patient group. This observation is probably due to the fact that the renal clearance of tiapride is related to creatinine clearance, which gradually decreases with age. This shows that pharmacokinetic parameters of a drug, determined in young healthy volunteers, cannot simply be extrapolated to patients. The presence of Huntington's disease and tardive dyskinesia did not appear to influence the main pharmacokinetic parameters of tiapride.

From the results it can be concluded that, to obtain a constant plasma level during the day, tiapride should be given in at least three and probably four equal daily doses at regular intervals.

Acknowledgements. We thank Dr. J. G. Goekoop, Psychiatric Hospital Endegeest, Oegstgeest, for his help in selecting the patients, and Dr. J. v. d. Nes and Mrs. E. Solognier for their assistance on the day of admission. DelaGrange supplied the tiapride. Mrs. A. Koetsier and Mrs. K. N. Wagensveld-Hansen typed the manuscript.

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Received: December 16, 1985
accepted in revised form: April 18, 1986

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