PHARMACOKINETICS OF TINIDAZOLE IN CHRONIC RENAL FAILURE AND IN PATIENTS ON HAEMODIALYSIS

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- 1 The pharmacokinetics of tinidazole after infusion (800 mg in 15 min) were studied in 12 patients with chronic renal failure (RI) and in five patients undergoing regular dialysis treatment (RD).
- 2 Tinidazole elimination plasma half-life was 15.09 ± 0.68 h (mean $\pm$ s.e. mean) (RI) and 12.9 ± 1.0 h after dialysis (RD), but there was a significant decrease in half-life during dialysis (4.25 ± 0.43 h) $P < 0.001$.
- 3 The apparent volume of distribution (0.64 ± 0.03 l/kg) was equal to extra and intracellular water volume and tinidazole was little bound to plasma protein (8%). There was a slight sex difference in apparent volume of distribution between male patients (0.70 ± 0.09 l/kg) and female patients (0.59 ± 0.10 l/kg) ($P = 0.07$), but as body clearance decreases in the same order, there was no modification of plasma half-life.
- 4 In renal failure, pharmacokinetics of tinidazole were not disturbed because no correlation between half-life, body clearance and creatinine clearance occurred; urine elimination was about 7% of administered dose.
- 5 Plasma clearance during dialysis was 49.9 ± 3.2 ml/min and about 43% of the available drug was eliminated during the 6 h dialysis procedure. These results suggest that an additional half-dose infusion should be given after the end of dialysis in patients undergoing regular dialysis treatment.

Introduction

Tinidazole has been used as an antiprotozoal agent for many years, but like metronidazole the drug also provides excellent inhibitory activity against anaerobic bacteria (Dornbusch & Nord, 1974; Hunt *et al.*, 1979) and has been used increasingly for the treatment of infections caused by these micro-organisms. Tinidazole was shown to have a longer half-life than metronidazole in healthy subjects (Nillsson-Ehle *et al.*, 1981; Taylor *et al.*, 1969) and the pharmacokinetics of metronidazole have been studied in chronic renal failure (Gabriel *et al.*, 1979). However, no such information has been published on the pharmacokinetic profile of tinidazole in this disease.

We report here a study of tinidazole pharmacokinetics after single infusion of the drug in patients with chronic renal failure and in patients undergoing regular dialysis treatment.

Methods

Our subjects were 12 patients with chronic renal

impairment (creatinine clearance between 4 to 50 ml/min) and five patients with terminal chronic renal failure treated by regular haemodialysis two or three times weekly (Table 1). All patients were fully informed of the nature of the study and gave formal consent to participate. No individual had been taking tinidazole prior to the study.

The patients fasted overnight before receiving the drug by constant rate infusion of 800 mg (two bottles of 400 mg in 200 ml) during 15 min.

In undialyzed patients, venous blood samples (3 to 5 ml) were withdrawn into heparinized tubes through an indwelling cannula in the contralateral arm at the start of infusion, 5, 10, 15 min after, then 5, 10, 20, 30, 45, 60, 90 min. and 2, 4, 6, 8, 12, 24, 36, 48, 72, 96 h after the end of infusion. Urine was collected for 0–12 h, 12–24 h, 24–48 h, 48–72 h, 72–96 h and 96–120 h.

In patients undergoing regular dialysis treatment, blood samples were taken, 1 h after the end of infusion, from the arterial side of the vascular access, once at the beginning and thereafter hourly during

Table 1 Data from the subjects

Subjects	Sex	Age (years)	Weight (kg)	C _{cr} (mg/l)	CL _{cr} (ml/min)	Drug treatment
<i>Patients not on dialysis</i>						
1	F	38	77.9	17	38	Canrenone, bumetamide
2	F	45	77.5	25	41.3	Canrenone, aldactone, timolol
3	F	59	103.9	24	22	Methyldopa, glibenclamide
4	M	51	82.6	32	29.8	Allopurinol, atenolol, canrenone, labetalol
5	M	63	58	34	20	Allopurinol, labetalol
6	F	64	75.1	42	19.3	Methyldopa, pindolol
7	F	64	51.6	44	22.6	Allopurinol, dihydralazine, labetalol
8	M	62	67.5	50	11.7	Allopurinol, methyldopa, atenolol, metformin
9	F	63	60.7	58	10	Allopurinol, acebutolol
10	M	68	85	80	9.1	Methyldopa, canrenone, bumetamide
11	M	50	69.5	79	5.5	Prazosin, calciferol
12	M	81	73.8	97	4	Allopurinol, digitoxin, isosorbide
<i>Patients undergoing regular dialysis treatment</i>						
13	F	49	37.6	84	0	Methyldopa, atenolol, captopril
14	F	56	48.5	96	0	Calciferol, clofibrate
15	M	70	76.4	118	0	Clonidine, methyldopa
16	M	52	64.4	155	0	Calciferol
17	M	62	66.9	157	1-2	Cimetidine, diclofenac
Mean		58.6	69.2			
s.d.		10.4	15.5			

dialysis (6 h). Venous samples were taken exactly 2 min after arterial samples at the second and third hour of dialysis, and 1, 2, 6, 12, 24, 36, 48 and 72 h after the end of dialysis. Blood was collected on dry heparin.

Dialysis was performed during the 6 h using a Travenol twin coil dialyser. The dialysate composition was: 140 mEq/l Na⁺, 100 mEq/l Cl⁻, 1 mEq/l K⁺, 3.5 mEq/l Ca⁺⁺, 34 mEq/l CH₃ COO⁻. Dialysate flow was 0.5 l/min. The average blood flow-rate was 300 ml/min. Ultrafiltration of fluid from blood during transit through the dialyzer was negligible (2 ml/min maximum) and did not influence venous tinidazole concentration.

Plasma and urine samples were stored at -20°C until analysis.

Plasma and urine tinidazole concentrations were determined by high performance liquid chromatography (h.p.l.c.) with UV spectrophotometer detector (at 315 nm). Urine (0.5 ml) added with 0.5 ml phosphate buffer (m/15, pH 7) or 0.5 ml to 1 ml plasma was mixed with 0.1 ml internal standard (plasma: metronidazole 20 µg/ml; urine: 825 Y (Pfizer) 50 µg/ml) and extracted by 5 ml ethylmethylcetone. Tubes were mechanically shaken (Vortex mixer) for 30 s, and centrifuged. The organic phase was evaporated to dryness at 55°C under a gentle stream of nitrogen. The residue was dissolved in 30 µl of methanol, mixed and 120 µl of phosphate buffer (0.025 M, pH 7). A 100 µl aliquot of reconstituted

extract was injected through an automated sampler (WISP Waters) on ODS C18 column (L = 300 mm, d = 4 mm), particle size 10 µm. The mobile phase used was potassium dihydrogen phosphate 0.025 M adjusted to pH 7 with Na OH 2.5 N-methanol (85-15 v/v) at a constant flow rate of 2 ml/min. In these conditions, retention times were: metronidazole: 290 s, tinidazole: 430 s, 825 Y: 710 s. The standard curve was linear in the range 0.05 to 50 µg/ml. The accuracy and precision (expressed as relative s.d.) of the method were determined by inter-day assay of several samples spiked with tinidazole: 5.2% for 0.5 µg/ml (n = 13), 4.5% for 5 µg/ml (n = 27).

Pharmacokinetic calculations

In patients without dialysis, pharmacokinetic analysis was performed on a computer using a mono or a bicompartamental post-infusion model (Caron, 1983). Apparent volume of distribution was also calculated by:

$$V_d \text{ area} = \frac{D}{\text{AUC} \times k_e} \quad (\text{equation 1})$$

equation in which *D* was administered dose, AUC area under plasma curve and *k_e* apparent elimination rate constant.

Renal tinidazole clearance was calculated by:

$$\text{CL}_r = \frac{U}{\text{AUC}} \quad (\text{equation 2})$$

in which U was amount excreted by urine and AUC area under plasma curve during the same time interval of urine collection.

Urinary apparent elimination half-life

$$t_{1/2}u = \frac{0.693}{ke_u}$$

was determined by exponential regression analysis of $\Delta U/\Delta t$ vs time.

In dialysed patients, elimination plasma half-life ($t_{1/2} = 0.693/ke$) was calculated by exponential regression analysis of arterial concentrations during dialysis and venous concentrations observed starting from the twelfth hour after dialysis.

Dialysis clearance was:

$$CL_D = \frac{C_a - C_v}{C_a} \times Q \times (1 - Ht) \quad (\text{equation 3})$$

where C_a and C_v were arterial and venous plasma levels respectively, Ht was the haematocrit and Q the blood flow rate through the dialyzer.

The fraction of dose which is removed from the body during dialysis (Gwilt & Perrier, 1978) was:

$$f = \frac{(t_{1/2})_i - (t_{1/2})_d}{(t_{1/2})_i} \left(1 - \frac{0.693}{e^{(t_{1/2})_d}} \times T\right) \quad (\text{equation 4})$$

in which $(t_{1/2})_i$ and $(t_{1/2})_d$ are plasma half-lives inter and during dialysis respectively and T time of dialysis.

Tinidazole plasma protein binding (PB %) was determined at 37°C by equilibrium dialysis using dia-norm system with a cuprophane membrane against an equal volume of phosphate buffer solution (pH 7.4, 0.1 M) for 3 h. Plasma was collected 2 h after infusion in undialyzed patients or at the beginning of the dialysis in other patients.

Results

In patients without dialysis, plasma tinidazole levels were fitted by mono-compartmental analysis in three subjects (subjects 8, 10, 12), the others were fitted by a two-compartment model. Mean plasma concentrations are shown in Figure 1.

Tinidazole plasma concentrations, at the end of infusion, was 22.6 ± 1.6 mg/l (mean $\pm$ s.e. mean) (Table 2). Apparent volume of distribution of central and peripheral compartments was 27.0 ± 3.2 l and 18.6 ± 3.7 l respectively. The area apparent volume of distribution for all subjects was 46.8 ± 2.5 l (0.64 ± 0.03 l/kg). Plasma half-life was 15.1 ± 0.7 h and was comparable with urine half-life in 10 subjects, $t_{1/2}u = 13.6 \pm 0.6$ h. Fraction of dose eliminated by urine was

Figure 1 Plasma tinidazole levels (mean $\pm$ s.e. mean) observed after infusion of 800 mg during 15 min to 12 patients with renal insufficiency.

Table 2 Plasma pharmacokinetic constants calculated after infusion of 800 mg tinidazole to 12 patients with renal insufficiency

Subjects	Co (mg/l)	V _{dc} (l)	V _{dt} (l)	V _{darea} (l/kg)	AUC [(mg/l) h]	CLc (ml/min/kg)	t _{1/2} (h)	PB (%)
1	23.52	31.9	9.4	0.53	368.3	0.464	13.28	6
2	22.68	28.3	13.6	0.54	535.5	0.321	18.48	4
3	20.14	26.2	34.3	0.59	304.6	0.422	16.07	10
4	16.16	48.2	7.6	0.68	270.4	0.597	13.17	4
5	33.01	13.6	35.3	0.86	340.9	0.674	14.64	14
6	26.62	24.4	12.7	0.50	414.8	0.428	13.39	8
7	28.30	19.7	20.9	0.79	398.8	0.648	14.13	14
8	19.63			0.60	361.5	0.546	12.67	5
9	25.46	28.4	7.5	0.59	434.3	0.506	13.52	7
10	13.19			0.71	362.7	0.432	18.97	7
11	25.64	22.2	26.3	0.70	337.9	0.568	14.31	14
12	16.82			0.64	425.7	0.424	17.45	5
Mean	22.60	27.0	18.6	0.64	379.6	0.503	15.09	8
s.e. mean	1.64	3.2	3.7	0.03	19.9	0.031	0.68	1.1

Co tinidazole plasma concentration at the end of infusion.

V_{dc} apparent volume of distribution of central compartment.V_{dt} apparent volume of distribution of peripheral compartment.

AUC area under plasma concentration time curve.

CLc total body clearance.

t_{1/2} plasma half-life.

PB percentage of plasma protein binding.

7.7 ± 0.7% and renal clearance was very low and represented about 8% of total body clearance (0.039 ± 0.004 vs 0.504 ± 0.031 ml min⁻¹ kg⁻¹) (Table 3).

There was no linear correlation between total body clearance or apparent volume of distribution (V_{darea}) of tinidazole and creatinine clearance ($r = 0.189$, and

$r = 0.282$, NS). It seems that the degree of renal insufficiency does not disturb plasma elimination of tinidazole.

In patients undergoing regular dialysis treatment, the effect of haemodialysis on plasma tinidazole levels is shown in Figure 2. During dialysis plasma drug levels decreased and the mean apparent plasma half-life was calculated to be 4.2 ± 0.4 h (Table 4). After haemodialysis, the plasma tinidazole plot was a rising slope for a few hours (2 h) (Figure 2), and decreased slowly with an apparent half-life of 12.9 ± 1.0 h, value comparable with that observed in impaired renal patients.

Tinidazole dialysis clearance was 49.9 ± 3.2 ml/min and dialysis extraction ratio (f) represented about 43% of tinidazole amount which was in the body at the beginning of haemodialysis.

Plasma protein binding of tinidazole was very low, about 8% in the two groups of patients.

Discussion

Tinidazole plasma half-life was not modified in renal failure, according to our results. In renal insufficient patients with creatinine clearance above 4 ml/min (15.1 h) and in dialyzed patients (12.9 h), plasma half-lives were comparable with values observed in healthy subjects after intravenous administration (12–14 h) (Charuel *et al.*, 1981; Nillsson-Ehle *et al.*, 1981) or oral administration (9–13 h) (Jokipii &

Table 3 Urinary pharmacokinetic parameters calculated after infusion of 800 mg tinidazole to 12 patients with renal insufficiency

Subjects	U (% dose)	t _{1/2} (h)	CLr (ml min ⁻¹ kg ⁻¹)
1			0.051
2	11.3	15.38	0.034
3	8.5	14.14	0.035
4	5.2	12.30	0.030
5	10.7	13.95	0.072
6	9.9	12.07	0.040
7	7.8	14.46	0.048
8	5.8	10.27	0.032
9			0.040
10	4.9	17.50	0.020
11	8.3	13.31	0.048
12	4.9	12.42	0.020
Mean	7.7	13.58	0.039
s.e. mean	0.7	0.63	0.004

U % dose percentage of dose excreted in urine.

t_{1/2} urine half-life.

CLr renal clearance.

Figure 2 Mean plasma tinidazole levels (mean $\pm$ s.e. mean) observed after infusion of 800 mg during 15 min, administered 1 h before the beginning of haemodialysis (HD).

Jokipii, 1979; Taylor *et al.*, 1970; Welling & Monro, 1972; Wood & Monro, 1975). After haemodialysis, in patients undergoing regular dialysis treatment, the plasma half-life was slightly shorter than in patients with terminal renal failure but that have not yet been dialyzed (CL_{cr} between 4 and 10 ml/min). We have also observed this phenomenon with atenolol, a drug

in which the plasma half-life after dialysis (51.2 ± 17.3 h) is shorter than that in patients before the first haemodialysis treatment (73.4 ± 28.8 h) (Flouvat *et al.*, 1980). In our patients, the apparent tinidazole volume of distribution (0.64 ± 0.03 l/kg) was equivalent to extra and intracellular water volume (0.55–0.65 l/kg) (Rowland & Tozer, 1980).

Table 4 Pharmacokinetic constants calculated after infusion of 800 mg tinidazole to five dialysis patients during and after haemodialysis.

Subjects	$t_{1/2}$ (h) during dialysis	$t_{1/2}$ (h) after dialysis	CL_D (ml/min)	f	PB (%)
13	2.78	11.26	41.0	0.58	6
14	3.88	11.76	57.8	0.44	3
15	4.47	15.12	56.3	0.43	11
16	5.14	15.54	49.4	0.37	13
17	4.96	10.84	44.8	0.31	8
Mean	4.25	12.90	49.9	0.43	8
s.e. mean	0.43	1.0	3.2	0.05	1.1

Tinidazole was found not to bind to tissues and its distribution was not disturbed by renal failure. In healthy subjects, after an 800 mg infusion, Wood *et al.* (1982) found an apparent volume of distribution of 0.67 l/kg in four male volunteers and 0.64 l/kg in four female volunteers. In our study, we found a more marked difference in the apparent volume of distribution of tinidazole between female patients (0.59 ± 0.10 l/kg) and male patients (0.70 ± 0.09 l/kg) ($P = 0.065$). This sex difference was not thought to be the result of the disease, because there was no correlation between apparent volume of distribution and creatinine clearance. Although Wood *et al.* (1982) did not observe differences between the sexes, Welling & Monro (1972) suggested that the higher serum levels of tinidazole compared to those observed by Taylor *et al.* (1970), were a partial reflection of greater body weight and a greater proportion of total body water in the human male. Thus there was a slight sex difference in the distribution of tinidazole.

In our female patients, with reduced V_d , there was also a decrease in the body clearance of tinidazole ($0.46 \text{ ml min}^{-1} \text{ kg}^{-1}$, vs $0.54 \text{ ml min}^{-1} \text{ kg}^{-1}$ in male), and this explains why the half-lives were not modified between the two populations. Indeed half-life is equal to the ratio between clearance and volume ($0.693/t_{1/2} = \text{CL}/V_d$) and if all the terms of equation were to decrease by the same order, the ratio would not be affected (Rowland & Tozer, 1980).

In renal failure, plasma tinidazole pharmacokinetics were not changed and there was no correlation between V_d , CLc or $t_{1/2}$ with creatinine clearance. The tinidazole binding to human plasma protein in these patients was low, about 8%, a value which is comparable to the 12% observed in healthy subjects (Taylor *et al.*, 1970).

In our patients, the urinary excretion of tinidazole (7.7%) was much lower than in normal subjects in whom about 15 to 25% of the dose was excreted in the urine unchanged (Nilsson-Ehle *et al.*, 1981; Taylor *et al.*, 1970). Renal clearance was about 8% of total body clearance, whereas in healthy subjects renal clearance was approximately 25% of body clearance,

but this decrease in renal clearance in renal failure was not sufficient to modify plasma tinidazole elimination. It was thought possible that most of the drug (either unchanged or metabolized) was eliminated through the liver and the bile (Hunt *et al.*, 1982) into the gastrointestinal tract, especially in renal failure, during which there would be an increase in hepatic blood flow (1.1 l/min in normal to 1.7 l/min in terminal renal failure).

During haemodialysis, the mean apparent plasma half-life of tinidazole (4.25 h) was significantly shorter ($P < 0.001$) than the average value after dialysis (12.9 h). The rapid removal of tinidazole from plasma by haemodialysis is shown by a clearly accelerated decrease of the plasma concentration of the drug (Figure 2). This was consistent with a satisfactory dialysis of tinidazole through the membrane; we found a clearance of tinidazole during dialysis of 49.9 ± 3.2 ml/min for a mean blood flow-rate of 330 ml/min; this was the value for plasma clearance during dialysis, calculated from plasma concentrations (arterial and venous) and plasma flow-rate. The very low plasma protein binding of tinidazole in our patients (8%) would account for the good clearance of this drug during dialysis. Tinidazole dialysis clearance was comparable with metronidazole dialysis clearance which in an earlier study (Moirot *et al.*, personal observations) we found in acute renal failure to be 57.9 ± 6.3 ml/min for a mean blood flow-rate of 222 ± 16 ml/min, ($n = 9$).

Whereas 25% of total metronidazole was removed in a 6 h haemodialysis session, 43% of total tinidazole which was present in the body at the beginning of the dialysis, was removed during the same period. In patients undergoing regular dialysis treatment, who require treatment for anaerobic infections it would seem advantageous to administer a half infusion dose of tinidazole after the end of haemodialysis, if the tinidazole treatment starts a dialysis day.

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References

- CARON, A. (1983). Recognition of dynamical exchanges by linear compartmental modes. Infusion models in pharmacokinetics. *Mathematical Biosciences*, (in press).
- CHARUEL, C., NACHBAUR, J., MONRO, A.M. & DE PALOL, J. (1981). The pharmacokinetics of intravenous tinidazole in man. *J. Antimicrob. Chemother.*, **8**, 343-346.
- DORNBUSCH, K. & NORD, C.E. (1974). *In vitro* effect of metronidazole and tinidazole on anaerobic bacteria. *Med. Microb. Immunol.*, **160**, 265-267.
- FLOUVAT, B., DECOURT, S., AUBERT, P., POTAU, L., DOMART, M., GOUPIL, A. & BAGLIN, A. (1980). Pharmacokinetics of atenolol in patients with terminal renal failure and influence of haemodialysis. *Br. J. clin. Pharmacol.*, **9**, 379-385.
- GABRIEL, R., PAGE, C.M., WELLER, I.V.D., COLLIER, J., HOUGHTON, G.W., TEMPLETON, R. & THORNE, P.S. (1979). The pharmacokinetics of metronidazole in patients with chronic renal failure. In *Proceedings of the 2nd international symposium anaerobic infections*, Geneva 25-27 April 1979. The Royal Society of Medicine, pp. 49-54. London: Academic Press.
- GWILT, P.R. & PERRIER, D. (1978). Plasma protein binding and distribution characteristics of drugs as indices of

- their hemodialyzability. *Clin. Pharmac. Ther.*, **24**, 154-161.
- HUNT, P.S., FRANCIS, J.K., PECK, G., FARRELL, K. & SALI, A. (1979). Tinidazole in the prevention of wound infection after elective colorectal surgery. *Med. J. Aust.*, **40**, 107-109.
- HUNT, P.S., DAVIDSON, A.J.L., ALDEN, J. & CHENG, S. (1982). Bile and serum levels of tinidazole after a single oral dose. *Br. J. clin. Pharmac.*, **13**, 233-234.
- JOKIPII, L. & JOKIPII, A.M.M. (1979). Single dose metronidazole and tinidazole as therapy for giardiasis: success rates side effects, and drug absorption and elimination. *J. infect. Dis.*, **140**, 984-988.
- NILLSSON-EHLE, I., URSING, B. & NILLSSON-EHLE, P. (1981). Liquid chromatographic assay for metronidazole and tinidazole: pharmacokinetic and metabolic studies in human subjects. *Antimicrob. Agents Chemother.*, **19**, 754-760.
- ROWLAND, M. & TOZER, T.N. (1980). In *Clinical pharmacokinetics. Concepts and applications*, pp. 36-41. Philadelphia: Lea and Febiger.
- TAYLOR, J.A., JOSEPH, J.R., MIGLIARDI, R. & SCHACH VON WITTENAU, M. (1969). Tinidazole and metronidazole pharmacokinetics in man and mouse. *Antimicrob. Agents Chemother.*, 267-270.
- WELLING, P.G. & MONRO, A.M. (1972). The pharmacokinetics of metronidazole and tinidazole in man. *Arzneim. Forsch.*, **22**, 2128-2132.
- WOOD, B.A. & MONRO, A.M. (1975). Pharmacokinetics of tinidazole and metronidazole in women after single large oral doses. *Br. J. vener. Dis.*, **51**, 51-53.
- WOOD, B.A., FAULKNER, J.K. & MONRO, A.M. (1982). The pharmacokinetics, metabolism and tissues distribution of tinidazole. *J. Antimicrob. Chemother.*, **10**, suppl. A, 43-58.

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