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Comparative Pharmacokinetics of Metronidazole and Tinidazole as Influenced by Administration Route

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Serum kinetics of metronidazole and tinidazole were compared in four separate randomized crossover studies. Single doses of each drug were given to healthy volunteers through intravenous infusion (500 mg over 20 min, six persons), by mouth (500 mg, nine persons), by rectum (1,000 mg, six persons), or intravaginally (500 mg, six persons). Concentrations of the unchanged drugs in serum, measured by high-pressure liquid chromatography, were similar after oral and intravenous administration, with mean peaks of 9.0 and 9.4 μg/ml for metronidazole and 7.5 and 10.1 μg/ml for tinidazole. Concentrations of tinidazole were significantly higher than those of metronidazole from 4 h onwards after intravenous infusion, and from 3 h onwards after administration by mouth. After rectal administrations, a significant difference was seen only at 48 h. After vaginal dosing, however, concentrations of metronidazole were significantly higher than those of tinidazole between 1.5 and 12 h. Bioavailability of either drug, calculated according to the formula (area under the curve for oral administration)/(area under the curve for infusion), was practically complete after oral administration and was poorer after rectal and especially vaginal administration. Whenever the parameters were calculable, the elimination half-life of tinidazole (range of means, 14.0 to 14.7 h) was significantly longer and total clearance (40.3 to 47.6 ml/min) was lower than the corresponding values of metronidazole (7.9 to 8.8 h and 71.8 to 80.1 ml/min, respectively).

Metronidazole and tinidazole have been used for some years as antiprotozoal drugs for prevention, and more recently for treatment, of infections with anaerobic bacteria (2, 3). The doses of these two drugs recommended for use against anaerobic infections are essentially the same and are much lower than those used for protozoal infections. There have been comprehensive comparisons of pharmacokinetics of metronidazole and tinidazole after oral ingestion (13, 14, 16), but there are not such studies related to intravenous, intrarectal, or intravaginal delivery, even though these compounds are also administered by these routes. The pharmacokinetics of metronidazole and tinidazole appeared to be different in isolated studies (4–6, 13a). The use of different assay procedures may have biased these results (10).

This report deals with a comparison of study design of serum kinetics of metronidazole and tinidazole administered via oral, intravenous, rectal, or vaginal routes to healthy volunteers at doses currently recommended for anaerobic infections. The concentrations of both drugs were analyzed by a high-pressure liquid chromatography method specific for unchanged metronidazole and tinidazole.

MATERIALS AND METHODS

Subjects and general design. The study consisted of four separate experiments in which metronidazole and tinidazole were compared after intravenous, oral, rectal, or intravaginal administration. In each experiment, the volunteers were randomly assigned to receive either metronidazole or tinidazole. The alternative drug was given 1 week later. The study was run crossover only regarding a comparison of metronidazole and tinidazole. Moreover, five subjects took part in both the infusion and oral experiments for calculations of the absolute oral bioavailability of the two drugs. Nine volunteers participated in the oral experiment, and the other experiments included six volunteers each (Table 1). All 22 volunteers proved healthy at physical examination and displayed normal laboratory parameters. None took any medication or alcohol before or during the study. The subjects were informed of the procedures and provided written consent.

An intravenous infusion of 500 mg of metronidazole (Flagyl, 5 mg/ml, Rhône-Poulenc) and tinidazole (Tricanix, 5 mg/ml, Neofarma) was given at a constant rate over 20 min, using an infusion pump (Extracorporeal

TABLE 1. Characteristics of the volunteers participating in different studies[a]

Drugs administered by:	n		Age (yr)	Weight (kg)	Height (cm)
	Female	Male			
Intravenous infusions		6	22 ± 2	77 ± 6	180 ± 3
Oral tablets[b]	1	8	22 ± 1	77 ± 11	178 ± 6
Rectal suppositories		6	23 ± 2	75 ± 9	180 ± 8
Vagitoria	6		23 ± 2	58 ± 5	165 ± 5

[a] Values for age, weight, and height are expressed as mean ± standard deviation.

[b] Five subjects were the same ones in the infusion study.

model 2102). One tablet each of metronidazole (Elyzol, 500-mg tablet, Dumex) and tinidazole (Tricanix, 500-mg tablet, Neofarma) was ingested with 100 ml of water. The rectal doses were 1 g of metronidazole (Flagyl, 1-g suppository, Rhône-Poulenc) and 1 g of tinidazole (Tricanix, 500-mg suppository/vagitorium, Neofarma). The vaginal dose was 500 mg (Flagyl, vagitorium, or Tricanix, 500 mg suppository/vagitorium).

All treatments were given after an overnight fast. Eating was permitted 3 h after administration of the drugs. Blood samples were collected at 3, 8, and 13 min during infusion and at 0, 1, 2, 4, 6, 7, and 23 h after the completion of infusion. With other dosage forms, the samples were drawn at 0, 0.25, 0.5, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h after administration. Serum was separated by centrifugation and stored at −20°C until it was assayed.

Analytical methods. Tinidazole and metronidazole concentrations in serum were measured by a published high-pressure liquid chromatography method (8) modified as follows. A 1-ml aliquot of the sample was mixed with 2 ml of ethanol by vortexing for 20 s. After 15 min of standing at room temperature, the mixture was centrifuged at 2,000 × *g* for 10 min. The supernatant was transferred into vials, and 20 μl was injected into the high-pressure liquid chromatograph, which consisted of a constant flow pump (Waters Associates model 6000A), an automatic sampler (Wisp 710), and a variable-wavelength UV-Vis detector (Perkin-Elmer LC 75) set at 318 nm. The column was a Micro-Bondapak C18 (300 by 3.9 mm inside diameter, 10-μm particle size, Waters). The elution solvent was an acetonitrile-water mixture, 25:75 for tinidazole and 18:82 for metronidazole at a flow rate of 2 ml/min. The retention times for tinidazole and metronidazole were 2.9 and 2.7 min, respectively. Quantitation was performed by comparing peak heights with a calibration curve. The calibration curves, linear at the ranges of 0.15 to 15 and 0.2 to 15 μg/ml for tinidazole and metronidazole, respectively, were prepared by analyzing spiked serum samples at seven concentrations as described above. The lowest detectable concentration was 0.05 μg per ml of serum. Day-to-day precision (expressed as coefficient of variation) at the 10 μg/ml level was 1.6 (n = 12) and 1.5% (n = 12) for tinidazole and metronidazole, respectively.

Calculations. The data on metronidazole and tinidazole fitted a one-compartment open model. The elimination rate constant (K_E) was obtained by the least-squares regression analysis. The areas under the serum concentration-time curve (AUC) were determined by the trapezoidal rule, with extrapolation to infinity time, using the terminal slope. The peak concentration (C_{max}) and the time to reach it (t_{max}) were defined as the highest concentration recorded and the time required to reach this concentration, respectively. Total clearance (Cl_{tot}) and volume of distribution

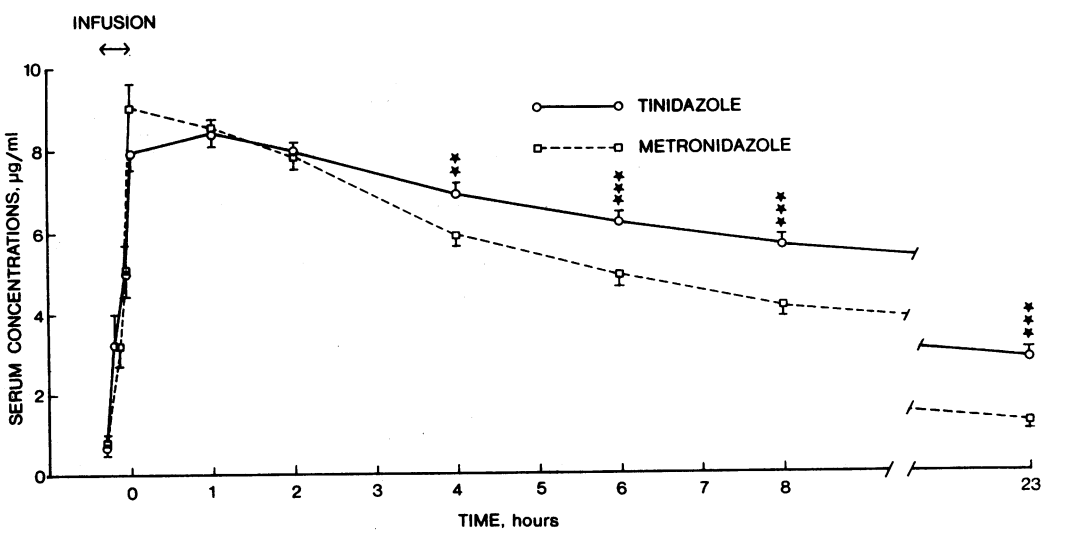

FIG. 1. Concentrations (mean ± SEM) of unchanged metronidazole and tinidazole in serum as a function of time when 500 mg of each drug was given as an intravenous infusion over 20 min (n = 6). Symbols: **, $P < 0.01$; ***, $P < 0.001$ versus metronidazole.

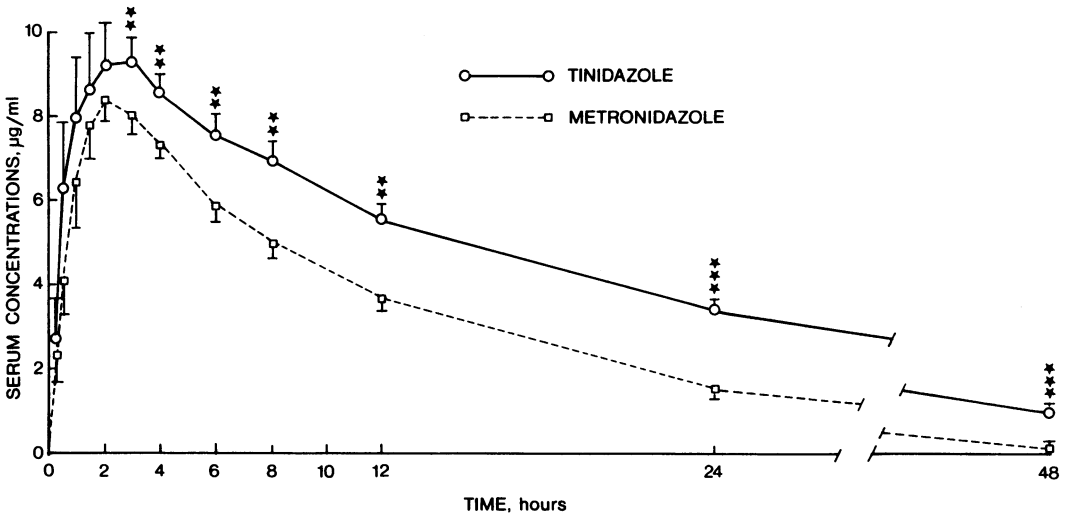

FIG. 2. Concentrations (mean ± SEM) of unchanged metronidazole and tinidazole in serum as a function of time after 500-mg tablets of each drug were taken after fasting (n = 9). Symbols: **, $P < 0.01$; ***, $P < 0.001$ versus metronidazole.

($V_{d\text{-area}}$)were calculated as follows: Cl_{tot} = dose/AUC, and $V_{d\text{-area}}$ = dose/AUC × K_E. Differences in t_{max} values were analyzed with Wilcoxon's rank test, and those in other parameters were analyzed with Student's t test.

RESULTS

The mean serum concentrations of metronidazole and tinidazole administered by different routes are recorded in Fig. 1, 2, and 3. The main pharmacokinetic parameters derived from these serum concentrations are shown in Table 2.

Drugs administered intravenously. The serum concentrations of tinidazole were significantly higher than those of metronidazole only at 4 h and onwards (Fig. 1). The calculated t½ (14.0 ± 0.7 h, mean ± standard error of the mean [SEM]), the apparent V_d (57.0 ± 1.7 liters), and $AUC^{0-\infty}$ (175.8 ± 12.7 µg · h/ml) of tinidazole exceeded significantly the corresponding parameters of metronidazole (7.9 ± 0.6 h, 53.2 ± 1.2 liters, and 106.9 ± 10.7 µg · h/ml, respectively), whereas the opposite was true for serum clearance (Table 2).

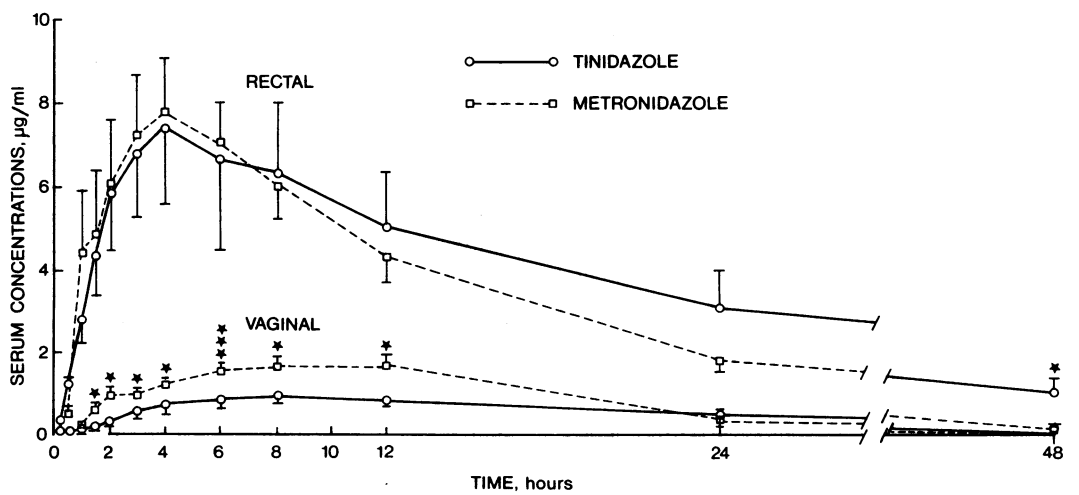

FIG. 3. Concentrations (mean ± SEM) of unchanged metronidazole and tinidazole in serum as a function of time after 1,000 mg of each drug was given rectally (n = 6) or 500 mg vaginally (n = 6). Symbols: *, $P < 0.05$; ***, $P < 0.001$ between the two drugs.

TABLE 2. Pharmacokinetic parameters of tinidazole and metronidazole

Dose (amt) and drug	Parameter (mean ± SEM)[a]					
	C_{max} (μg/ml)	t_{max} (h)	$AUC^{0-\infty}$ (μg · h/ml)	$t_{1/2}$ (h)	V_d (liters)	Cl_{tot} (ml/min)
Infusion dose (500 mg/20 min)						
Tinidazole	7.5 ± 1.2	–	175.8 ± 12.7	14.0 ± 0.7	57.0 ± 1.7	47.6 ± 2.6
Metronidazole	9.4 ± 0.5	–	106.9 ± 10.7***	7.9 ± 0.6***	53.2 ± 1.2*	80.1 ± 5.2***
Oral dose (500 mg)[b]						
Tinidazole	10.1 ± 0.6	1.6 ± 0.2	216.8 ± 15.0	14.7 ± 0.7		
Metronidazole	9.0 ± 0.5**	1.9 ± 0.2	122.2 ± 10.3***	8.9 ± 0.6***		
Rectal dose (1,000 mg)						
Tinidazole	7.9 ± 1.8	3.4 ± 0.9	169.2 ± 42.6	14.2 ± 1.1		
Metronidazole	8.8 ± 1.1	2.8 ± 0.5	129.8 ± 18.6	8.8 ± 0.4**		
Vaginal dose (500 mg)						
Tinidazole	1.0 ± 0.2	8.7 ± 1.2	22.6 ± 3.3			
Metronidazole	1.9 ± 0.2**	7.7 ± 1.6	31.0 ± 5.0			

[a] *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ versus tinidazole.

[b] Five subjects received both the injection and the tablet. Systemic availability was 125 and 111% for doses of tinidazole and metronidazole, respectively.

Drugs administered orally. The C_{max} and subsequent serum concentrations were statistically significantly higher after tinidazole administration than after metronidazole (Fig. 2). The t½ of tinidazole (14.7 ± 0.7 h) was significantly longer than that of metronidazole (8.9 ± 0.6 h). The V_d of tinidazole (50.7 ± 2.2 liters) exceeded significantly that of metronidazole (38.9 ± 3.6 liters). The V_d of metronidazole was significantly smaller after oral (38.9 ± 3.6 liters) than after intravenous administration (53.2 ± 1.2 liters). The apparent bioavailabilities of the tablets according to $AUC_{oral}/AUC_{infusion} \times 100$ in five subjects who took part in both studies were 125 and 111% for tinidazole and metronidazole, respectively.

Drugs administered rectally. There was a significant difference between the serum concentrations of metronidazole and tinidazole only at 48 h (Fig. 3). The t½ of tinidazole was significantly longer than that of metronidazole (Table 2). The average absorptions of tinidazole and metronidazole from rectum were about 39 and 53%, respectively, corrected for dose and calculated by comparing the AUC values after rectal and oral administrations to the separate groups of volunteers.

Drugs administered vaginally. C_{max} and AUC values of both drugs were only a fraction of the corresponding values after other routes of administration (Table 2). Compared with oral dosing, only about 10 and 25% of the intravaginal tinidazole and metronidazole, respectively, was absorbed on the average. Serum levels of metronidazole were significantly higher than those of tinidazole from 1.5 h onwards (Fig. 3).

DISCUSSION

Because the microbiological properties of metronidazole and tinidazole are rather similar (2, 3), a direct comparison of their concentrations is feasible. There was no significant difference between the C_{max} values of metronidazole and tinidazole after intravenous and oral administrations. Considering the dose, the peak levels were similar to or somewhat lower than those previously reported (1, 4–6, 13, 14, 16). Calculations on the basis of corresponding AUC values indicated complete absorption of both drugs after oral administration. Several factors may contribute to apparent bioavailability values exceeding 100%. Nitroimidazoles were given not as a bolus injection but as a 20-min infusion. Even during the short infusion, these drugs were rapidly distributed in tissues (13a); metabolism also can occur. Another possibility is intestinal reabsorption of nitroimidazoles. This may exaggerate the concentrations of nitroimidazoles in serum after oral administration. No approximations were done to correct the influence of these shifts. With these reservations, our results are keeping with the reports on the 90 to 108% bioavailabilities of metronidazole and tinidazole (3, 9).

Considering the different dose, the absorption upon rectal administration was about one-half or even less of that upon oral administration. A similar rectal absorption of metronidazole was reported by others (10, 11). Conversely, Bergan and Arnold (1) and Ioannides et al. (7) reported a good bioavailability of metronidazole after a

rectal dose. Our results are in accordance with those of Bergan and Arnold (1) in the sense that the variation in serum levels between volunteers was much greater after rectal than after oral administration.

After vaginal administration, the serum levels of tinidazole were significantly lower than metronidazole levels, possibly owing to the fact that tinidazole was given as a rectal suppository and not as a specifically aimed vagitorium, as was metronidazole. However, the serum concentrations of both nitroimidazoles remained clearly inferior to those yielded by other dosage forms. Hence, the vaginal nitroimidazoles exerted mainly a local action.

Our results confirmed earlier findings about the significantly slower rate of elimination of tinidazole compared with that of metronidazole (4, 6, 9, 13, 14, 16). The elimination half-life of tinidazole was significantly longer, and plasma clearance was lower, than the corresponding parameters of metronidazole. Serum tinidazole levels remained above 3 μg/ml (90% minimal inhibitory concentration value for most anaerobes [3]) for at least 24 h after oral and rectal administrations. After intravenous infusion, the mean concentration was marginally below 3 μg/ml as late as 23 h. Conversely, the metronidazole concentrations remained above 3 μg/ml for no longer than 12 h after enteral administration and only 8 h after the infusion. Accordingly, in the studies of Wood and Monro (16), the average tinidazole concentrations were three and five times higher than those of metronidazole at 24 and 48 h, respectively.

Metronidazole and tinidazole are currently recommended and used at doses of 400 to 500 mg orally or intravenously and 1 g rectally, two or three times daily. It appears that the three times daily dose schedule is appropriate for metronidazole. In the case of tinidazole, either smaller doses or less frequent administrations seem justified. This view is supported by the efficient tissue penetration of tinidazole, which has been substantiated in earlier studies in which actual tissue concentrations have been measured. In several key tissues and serum, the tinidazole levels were nearly identical after a single intravenous dose (12, 13a, 15). In the present study, the superior tissue distribution of tinidazole over metronidazole was seen as a larger apparent volume of distribution.

LITERATURE CITED

1. **Bergan, T., and E. Arnold.** 1980. Pharmacokinetics of metronidazole in healthy adult volunteers after tablets and suppositories. Chemotherapy **26**:231–241.
2. **Brogden, R. N., R. C. Heel, T. M. Speight, and G. S. Avery.** 1978. Metronidazole in anaerobic infections: a review of its activity, pharmacokinetics and therapeutic use. Drugs **16**:387–417.
3. **Carmine, A. A., R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery.** 1982. Tinidazole in anaerobic infections. A review of its antibacterial activity, pharmacological properties and therapeutic efficacy. Drugs **24**:85–117.
4. **Charuel, C., J. Nachbaur, A. M. Monro, and J. de Palol.** 1981. The pharmacokinetics of intravenous tinidazole in man. J. Antimicrob. Chemother. **8**:343–346.
5. **Gjerløff, C., and E. Arnold.** 1982. Pharmacokinetics of intravenous metronidazole in man. Acta Pharmacol. Toxicol. **51**:132–135.
6. **Houghton, G. W., P. S. Thorne, J. Smith, R. Templeton, and J. Collier.** 1979. Comparison of the pharmacokinetics of metronidazole in healthy female volunteers following either a single oral or intravenous dose. Br. J. Clin. Pharmacol. **8**:337–341.
7. **Ioannides, L., A. Somogyi, J. Spicer, B. Heinzow, N. Tong, C. Franklin, and A. McLean.** 1981. Rectal administration of metronidazole provides therapeutic plasma levels in postoperative patients. N. Engl. J. Med. **305**:1569–1570.
8. **Marques, R. A., B. Stafford, N. Flynn, and W. Sadée.** 1978. Determination of metronidazole and misonidazole and their metabolites in plasma and urine by high-performance liquid chromatography. J. Chromatogr. **146**:163–166.
9. **Mattie, H., B. A. C. Dijkmans, and C. van Gulben.** 1982. The pharmacokinetics of metronidazole and tinidazole in patients with mixed aerobic-anaerobic infections. J. Antimicrob. Chemother. **10**:59–64.
10. **McLean, A.** 1982. Rectal administration of metronidazole. N. Engl. J. Med. **307**:121–122.
11. **Nitsche, V., and H. Mascher.** 1981. Pharmacokinetics of metronidazole after application on different routes, p. 169–181. Proceedings of the First European Congress on Biopharmacy and Pharmacokinetics, Technique et Documentation. Clermomt Ferrand, part I.
12. **Ripa, T., L. Weström, P.-A. Mårdh, and K.-E. Andersson.** 1977. Concentrations of tinidazole in body fluids and tissues in gynaecological patients. Chemotherapy **23**:227–235.
13. **Taylor, J. A., J. R. Migliardi, and S. von Wittenau.** 1970. Tinidazole and metronidazole pharmacokinetics in man and mouse, p. 267–270. Antimicrob. Agents Chemother. 1969.

13a. **Viitanen, J., O. Auvinen, and T. Tunturi.** 1983. Serum and tissue tinidazole concentrations after intravenous infusion. Chemotherapy **29**:13–17.

14. **Welling, P. G., and A. M. Monro.** 1972. The pharmacokinetics of metronidazole and tinidazole in man. Arzneim. Forsch. **22**:2128–2132.
15. **Wood, B. A., J. K. Faulkner, and A. M. Monro.** 1982. The pharmacokinetics, metabolism and tissue distribution of tinidazole. J. Antimicrob. Chemother. **10**:43–57.
16. **Wood, B. A., and A. M. Monro.** 1975. Pharmacokinetics of tinidazole and metronidazole in women after single large oral doses. Br. J. Vener. Dis. **51**:51–53.