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The disposition of [^{14}C]metronidazole in rats following vaginal and oral administration

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The absorption, tissue distribution and excretion of [^{14}C]metronidazole (^{14}C-MTZ) were compared during the first 4 h after administration of 10 mg kg^{-1} of ^{14}C-MTZ either orally or intravaginally (i.v.g.) to rats. Peak ^{14}C blood concentrations were reached at 1 h in both groups. Blood samples collected at 0·5, 3 and 4 h had a higher ^{14}C concentration in orally dosed rats ($P < 0·05$) than in i.v.g.-treated animals. About 3% of the i.v.g. applied dose remained in the vagina at 4 h. After 4 h, the plasma, liver, kidney, brain, lung and uterus concentrations of ^{14}C were similar in both groups, whereas the blood, skeletal muscle and fat ^{14}C values were significantly greater in the orally dosed rats. The total recoveries of ^{14}C in the urine and faeces did not differ (ca 38% over 4 h) between the two groups. These results suggest that the kinetics of metronidazole are similar after the administration of equal amounts of this drug by either route.

The rate and extent of absorption of the trichomonacidal drug metronidazole through the vaginal mucosa has received little attention. We have compared its absorption, distribution and elimination following intravaginal and oral administration to female rats which were used because no catheterization is required and drug losses by urination are prevented once the vaginal lips are closed.

MATERIALS AND METHODS

Chemicals

[2-^{14}C]Metronidazole (^{14}C-MTZ) (kindly supplied by May and Baker Ltd. U.K.) had a specific activity of 26·9 μCi mg^{-1} (radio-purity 98%). Unlabelled metronidazole was a gift from Poulenc Ltd. Montreal, Quebec. Soluene-100 (Packard) and Aquasol (New England Nuclear) were purchased.

Animals and treatment

Virgin female Wistar rats (200–240 g) from Canadian Breeding Farms, Montreal, Quebec, were acclimatized at least 1 week before an experiment when they had free access to food and tap water. Rats treated orally had water but no food overnight before the experiment. The stage of the oestrus cycle was not assessed.

The unlabelled drug dissolved in a 7% ethanol solution was mixed with ^{14}C-MTZ to give a specific activity of about 2 μCi mg^{-1} and a dose of 10 mg kg^{-1} (0·2 ml/100 g) was administered by gavage. To ensure optimal absorption of the drug, food but not water was withheld during the experiment. The time of dosing was designated as zero time.

In the intravaginal (i.v.g.) experiment, rats were anaesthetized with ether and the drug in 80 μl/100 g weight (10 mg kg^{-1}) was placed in the vagina the lips of which were closed with clips to preclude leakage.

Blood concentration profiles, tissues, urine and faeces collection

Immediately after treatment, rats were placed in individual metabolism cages that allowed the separate collection of urine and faeces. Duplicate tail blood samples (10 μl) were collected at preselected times up to 4 h and digested overnight in scintillation vials containing 1 ml of Soluene and the radioactivity determined (Buttar et al 1973).

At 4 h, the animals were anaesthetized with ether and killed by withdrawing blood from the abdominal aorta in a heparinized syringe. Plasma was separated by centrifugation and duplicate samples (10 μl) were taken for ^{14}C estimation. The tissues were immediately dissected and frozen until analysed for total radioactivity. Duplicate samples (50–100 mg) from all isolated tissues were digested overnight in 1 ml of Soluene.

Also at 4 h, urine was removed from the bladder by syringe, pooled with that collected previously and the volume measured to the nearest 0·01 ml. Duplicate samples (100 μl) were transferred to scintillation vials and radioactivity was determined after the addition of 15 ml Aquasol.

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The intestine was removed after being ligated at the pylorus and the rectum, and washed in cold tap water to remove the extraneous blood. The intestinal contents (herein referred to as faeces) were scraped and combined with faeces collected previously, weighed, homogenized with distilled water (1:9), the total volume recorded, and duplicate 100 μl samples added to 1 ml of Soluene and analysed as for blood.

To determine the amount of ^{14}C-MTZ remaining in the vaginas of similarly killed animals, the uterine branches were ligated with silk thread, the vagina excised, freed from connective tissue, digested in 5 ml of Soluene and duplicate 100 μl samples taken for ^{14}C estimation.

Radioactivity determination and statistics

Radioactivity was determined by liquid scintillation spectrophotometry. Quenching was corrected by the external standard ratios method. Metronidazole concentrations were estimated by computer processing and the values were expressed as unchanged metronidazole. The significance of the difference between means was taken as $P < 0.05$ using Student's two-tailed t-test.

RESULTS AND DISCUSSION

Blood concentration profiles

The profiles of radioactivity in Fig. 1 are expressed as MTZ μg ml^{-1} blood. Radioactivity was detected in the 5 min blood sample, reached a peak in 1 h with both routes, and then followed a progressive and parallel decline. The peak blood values corresponded to the time of maximum serum concentration of drug observed after single, oral doses to patients (Kane et al 1961) and healthy volunteers (Welling & Monro 1972). At 1 h the mean concentration of ^{14}C was 9·6 and 8·7 μg ml^{-1} of blood in the orally and i.v.g.-treated rats, respectively. The blood ^{14}C concentration was significantly higher in the orally-treated than in the i.v.g.-treated animals, only at 0·5, 3 and 4 h ($P < 0.05$).

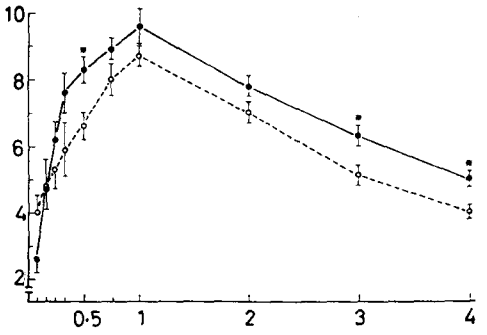

FIG. 1. Concentration of ^{14}C-radioactivity (expressed as unmetabolized metronidazole, MTZ) (ordinate: μg ml^{-1} blood) in blood samples taken during the 4 h (abscissa: time (h)) following oral (●——●), and intravaginal (○- - - -○) administration of ^{14}C-MTZ. Each point represents the mean value from 6–8 rats. Vertical lines represent s.e. * $P < 0.05$.

Thus ^{14}C-MTZ is well absorbed through the vagina, and nearly equivalent blood concentrations of ^{14}C are attained after the administration of equal amounts of this drug by either route. If these results are confirmed in women, the intravaginal route may represent alternative mode of administration for the drug, avoiding the possibility of its undesirable gastrointestinal side effects, e.g. nausea, vomiting and abdominal distress (Taylor 1964) and loss of appetite (Lehman & Ban 1967).

Tissue distribution

The tissue concentrations and distribution of ^{14}C 4 h after ^{14}C-MTZ administration are shown in Table 1. While the plasma, liver, kidney, lung, brain and uterus concentrations of ^{14}C were similar in both groups, the blood, skeletal muscle and fat ^{14}C values were significantly greater in the orally dosed rats compared with the i.v.g-treated animals. The highest ^{14}C concentrations in both groups were in the kidneys > liver > plasma. Lowest values in fat. The pattern of ^{14}C distribution corresponded with the whole body autoradiographic results obtained with ^{14}C-MTZ in rats (Ings et al 1975) and in mice (Placidi et al 1970).

Table 1. Tissue distribution of radioactivity, expressed as unchanged metronidazole (^{14}C-MTZ), 4 h after oral and intravaginal administration of ^{14}C-MTZ (10 mg kg^{-1}).

Tissue	Oral (6)	Intravaginal (8)
Blood	5·0 ± 0·2[a]	4·2 ± 0·3*
Plasma	5·5 ± 0·6	4·6 ± 0·4
Liver	7·2 ± 0·6	6·0 ± 0·3
Kidney	8·2 ± 0·6	7·3 ± 0·4
Lung	4·8 ± 0·2	4·2 ± 0·3
Skeletal muscle	4·6 ± 0·3	3·8 ± 0·2*
Brain	4·2 ± 0·2	3·8 ± 0·2
Fat	1·2 ± 0·1	0·9 ± 0·05*
Uterus	4·8 ± 0·2	4·3 ± 0·3

[a] Values expressed as μg g^{-1} wet weight tissue or per ml fluid, represent the mean ± s.e. Number of animals are shown in parentheses. * $P < 0.05$ when compared with orally dosed rats.

The amounts of ^{14}C-MTZ recovered after 4 h from the vaginas ranged from 2·2 to 3·9% (average

recovery = 3·01% of the dose) suggesting that metronidazole is rapidly absorbed through the vaginal mucosa of the rat.

Excretion of ^{14}C into urine and faeces

The amounts of radioactivity excreted into urine and faeces in the 4 h after administration of ^{14}C-MTZ (Table 2) were not statistically different, either in the urinary or faecal or total excretions of ^{14}C between either treatment group. Ings et al (1975) noted that after intravenous injection of ^{14}C-MTZ (10 mg kg^{-1}) in the rat, up to 6·5% of the dose appeared in bile, and about 13% entered the gastrointestinal tract directly during 4 h. Our results also demonstrate that nearly 20% of the intravaginally administered dose is excreted into the faeces; suggesting that the disposition of metronidazole following intravaginal application is similar to that of intravenous administration.

Table 2. Excretion of ^{14}C into urine and faeces of rats during 4 h following the oral and vaginal administration of ^{14}C-MTZ (10 mg kg^{-1}).

	Radioactivity recovered (% of dose)		
Route	Urine	Faeces	Total
Oral (6)	16·2 ± 1·9[a]	20·8 ± 0·6	37·1 ± 2·0
Vaginal (8)	20·2 ± 1·8	19·4 ± 2·0	39·6 ± 2·3

[a] Values represent the mean ± s.e. Number of animals are shown in parentheses.

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