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Concentrations of Metronidazole and Tinidazole in Male Genital Tissues

J. VIITANEN,[1]†* H. HAATAJA,[2] AND P. T. MÄNNISTÖ[2]

Tampere University Central Hospital, Department of Surgery, Tampere,[1] and Orion Pharmaceutical Co., Research Center, Espoo,[2] Finland

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The steady-state concentrations of metronidazole and tinidazole in male genital tissues were analyzed in patients subjected to elective gonadal surgery. The nitroimidazoles were administered orally at 500 mg every 8 h, beginning 5 days before the operation. Eight hours after the last dose, the concentrations of tinidazole were 24.1 ± 2.5 μg (mean ± standard error of the mean)/g of prostatic tissue, 29.1 ± 2.9 μg/g of vas deferens, 22.1 ± 2.1 μg/g of epididymis, and 18.6 ± 2.3 μg/g of testis. The corresponding values of metronidazole were 14.3 ± 1.8 μg/g, 15.9 ± 1.2 μg/g, 14.0 ± 1.2 μg/g, and 12.5 ± 1.7 μg/g, respectively.

Nitroimidazoles have become a mainstay as effective therapeutic and prophylactic agents against anaerobic bacteria, notably *Bacteroides fragilis*. Metronidazole and tinidazole are known to penetrate well into various tissues after both enteral and parenteral administration (6, 8–11). The elimination half-life of tinidazole is 12 to 15 h, and that of metronidazole is 7 to 9 h (8). Owing to this difference, the steady-state concentrations of tinidazole in serum and tissues have been much higher than those given by the same dose of metronidazole (6, 8–11). The prostate and the testis are problematic organs in regard to the tissue penetration of most drugs. First, the pH of the prostate is exceptionally low (12). Second, the blood-testis barrier, resembling the blood-brain barrier (4), apparently prevents many drugs from diffusing into the testicular tissue.

The aim of the present comparative study was to determine how metronidazole and tinidazole penetrate into the male genital organs during a steady-state treatment with the same dosage of 500 mg every 8 h.

MATERIALS AND METHODS

Prostatectomy patients. Retropubic prostatectomies for treatment of prostate hypertrophy were performed on 20 men in Tampere University Central Hospital. Ten patients were given metronidazole orally as tablets (Elyzol, 500 mg; Dumex Ltd., Copenhagen, Denmark) every 8 h, beginning 5 days before the planned operation. Ten other patients were given the same dosage of tinidazole (Tricanix, 500-mg tablets; Neofarma, Finland). The last tablet was given about 8 h before the operation. The mean age (± standard deviation) of the patients in the metronidazole group was 65.6 ± 7.2 years, and that in the tinidazole group was 68.8 ± 4.8 years. The corresponding body weights were 74.0 ± 12.0 kg and 74.2 ± 7.8 kg, respectively.

Blood samples were taken 0, 2, and 4 h after the last tablet. Serum was separated after centrifugation and then stored at −20°C until analyzed. Tissue samples were taken at the end of the dose interval from the enucleated adenomas during the operations. The samples were immediately frozen in liquid nitrogen and kept frozen until analyzed.

Orchiectomy patients. Bilateral orchiectomy was performed in Tampere University Central Hospital on 20 patients with prostatic carcinoma. Eleven of the patients were given metronidazole and nine were given tinidazole as above, beginning 5 days before the planned operation. The last tablet was taken about 8 h before the operation. The mean age (± standard deviation) was 72.5 ± 8.5 years, and the weight was 74.6 ± 8.1 kg in the metronidazole groups; mean age was 73.1 ± 5.6 years, and weight was 75.8 ± 6.6 kg in the tinidazole group. Blood samples were taken as described above for prostatectomy patients. Tissue samples were taken at the end of the dose interval from the vas deferens, the epididymis, and testicular parenchyma during the operation. The tissue samples were handled as described above for prostatectomy patients.

Determination of levels of nitroimidazoles in serum and tissue. Serum samples containing metronidazole and tinidazole were analyzed as described earlier (3, 4). Frozen tissue was cut into thin slices, and a sample (0.3 to 0.5 g) was weighed and homogenized with 3.0 ml of cold 0.9% sodium chloride. For determination of metronidazole levels, the homogenate was mixed with 250 μl of 70% perchloric acid to precipitate proteins. After the supernatant had stood for 15 min and had been centrifuged, 2.0 ml was transferred to a vial and neutralized with 150 μl of 10 M sodium hydroxide. A 15-μl portion was analyzed by high-pressure liquid chromatography (4). Tinidazole tissue homogenates were extracted with 5.0 ml of chloroform. After centrifugation, 4.0 ml of chloroform was evaporated to dryness. The residue was dissolved in 2.0 ml of the mobile phase (acetonitrile-water, 25:75) and centrifuged. A 15-μl portion was analyzed by high-pressure liquid chromatography (4).

Quantitation was performed by comparing peak heights of metronidazole and tinidazole with a calibration curve. Calibration curves were linear in the range studied. Standard samples were prepared by adding aqueous standard solutions to the tissue samples and allowing the mixture to equilibrate for 15 min.

The lower limit of quantitation for metronidazole and tinidazole was 0.5 μg/g of tissue. Day-to-day precision at the concentration of 10 μg/g of tissue was 3.0% (coefficient of variation, $n = 7$) and 4.5% (coefficient of variation $n = 6$) for metronidazole and tinidazole, respectively. Recovery was studied by adding standard solutions to tissue samples and comparing peak heights with those of standard solutions. Recovery was 102 ± 1% (standard deviation, $n = 4$) for

* Corresponding author.
† Present address: North Carelian Central Hospital, SF-80210 Joensuu, Finland.

metronidazole and 95 ± 3% (standard deviation, n = 4) for tinidazole at the level of 10 μg/g of tissue.

RESULTS

Concentrations of metronidazole and tinidazole in prostate tissue. The concentrations of tinidazole in prostate tissue (24.1 ± 2.5 μg/g, mean ± standard error of the mean) were much higher than those of metronidazole (14.3 ± 1.8 μg/g) about 8 h after the intake of the last dose. The steady-state tinidazole levels in serum were also quite high (Fig. 1) as compared with the metronidazole levels.

Concentrations of metronidazole and tinidazole in testis, epididymis, and vas deferens. The concentrations of tinidazole in the vas deferens were 29.1 ± 2.9 μg/g (mean ± standard error of the mean), those in the epididymis were 22.1 ± 2.1 μg/g, and those in the testis were 18.6 ± 2.3 μg/g. All these concentrations were higher than the metronidazole levels in the vas deferens (15.9 ± 1.2 μg/g), the epididymis (14.0 ± 1.2 μg/g), and the testis (12.5 ± 1.7 μg/g). As above, the tinidazole concentrations in serum also exceeded greatly the corresponding metronidazole concentrations (Fig. 2).

DISCUSSION

Nitroimidazoles penetrate well into different tissues because they are low-molecular-weight lipophilic compounds. The octanol-water partition coefficient of tinidazole is particularly high: 1.4 versus 0.16 with metronidazole (5). Comparative studies of the tissue penetration of nitroimidazoles are scanty. These studies have, however, demonstrated that after the same dosage, the steady-state concentrations of tinidazole both in serum and in several tissues were remarkably high as compared with those of metronidazole (6, 8–11). The same was the case in the present study concerning male genital tissues. This difference is naturally caused by the long elimination half-life of tinidazole. As we have recommended previously (6, 11), the dose interval of the tinidazole treatment could be prolonged to 12 h and the concentrations would still exceed those of metronidazole with equal dose.

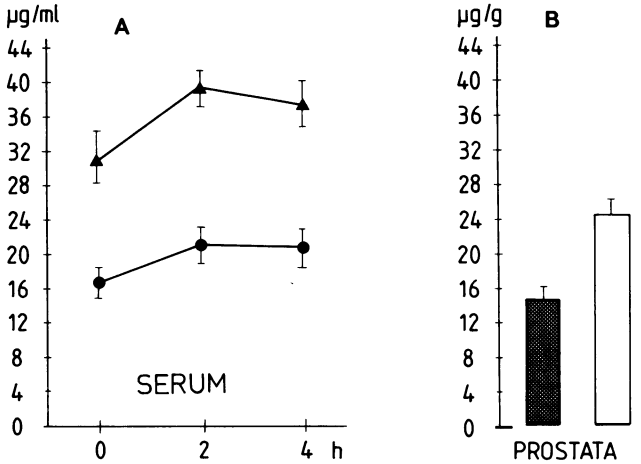

FIG. 1. The concentrations of metronidazole and tinidazole in serum (A) and prostata (B). The dosage of each drug was 500 mg orally every 8 h for 5 days. The serum samples were taken just before (0 h) and 2 and 4 h after the last dose. Tissue samples were obtained at about 8 h after the last dose. n = 10. Mean values for metronidazole (● and ■) and tinidazole (▲ and □) are shown; standard error of the mean is shown by vertical bars.

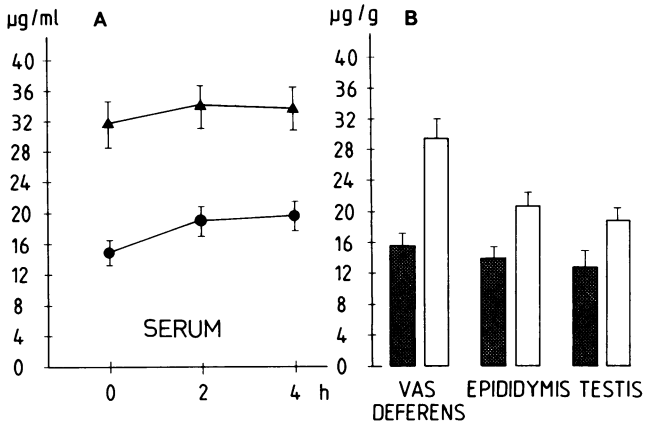

FIG. 2. The concentrations of metronidazole and tinidazole in serum (A) and vas deferens, epididymis, and testicular tissue (B). The dosage of each drug was 500 mg orally every 8 h for 5 days. The serum samples were taken just before (0 h) and 2 and 4 h after the last dose. Tissue samples were obtained at about 8 h after the last dose. n = 11 (metronidazole) and n = 9 (tinidazole). Mean values for metronidazole (● and ■) and tinidazole (▲ and □) are shown; standard error of the mean is shown by vertical bars.

However, so far there are no clinical data supporting this proposal.

At steady state (6, 11) and even after a single dose (6, 10, 11), the concentrations of nitroimidazoles in tissues have been at about the same level as in the corresponding serum samples. The same was the case in the present study in regard to most male genital tissues. There have been, however, a few exceptional tissues in which concentrations are lower than in serum: subcutaneous fat (10, 11), aqueous humor (9), and ovarian tissue (6). Testis may now be added to this tissue list, at least in regard to tinidazole penetration at steady state. In fat, the reason is the low tissue perfusion. In the aqueous humor, the apparent blood-chamber barrier, resembling the blood-brain barrier (9), prevents drug penetration. However, we do not have enough data to discuss the hypothetical blood-gonadal barrier (4).

The prostate gland is one of the tissues in which most drugs penetrate poorly. The pH of the normal prostate is acid, and hence only basic drugs, like erythromycin and trimethoprim, penetrate well (12). In the present study, nitroimidazoles also penetrated well into the prostate when concentrations were well above the 100% MIC of most anaerobic bacteria (3 μg/ml [1, 2]) and, excluding amebiasis, also above the antiprotozoal concentrations (3). Therefore, these nitroimidazoles may be considered potentially effective antimicrobial agents in anaerobic and protozoal prostatic infections.

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