

# Ornidazole: A new antiprotozoal compound for treatment of *Trichomonas vaginalis* infection

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**SUMMARY** A new anti-protozoal compound, ornidazole<sup>1</sup>, a derivative of nitroimidazole, was given in a single 2 g dose to 20 women with *Trichomonas vaginalis* infection. All the women were cured, but they suffered some side-effects. Plasma levels of ornidazole reached a peak five to eight times higher than minimum inhibitory concentrations and exceeded this level for at least 36 hours. It is therefore possible that a smaller dose might have had an adequate trichomonocidal effect and fewer side-effects. Further studies are in progress.

## Introduction

Since its introduction in 1959, metronidazole, a nitroimidazole derivative, has been the drug of choice for treatment of *Trichomonas vaginalis* infections. It has usually been given in multiple doses and failures have generally been due to incomplete treatment, either of the patients and/or the partners.

Ornidazole is a recently synthesised nitroimidazole derivative (Fig. 1) and the first clinical trials have shown excellent results—that is, a 100% cure rate with different dosages and even with a single 2 g dose (Warnnissorn, 1974).

- a laboratory examination of minimum inhibitory concentrations of ornidazole on *T. vaginalis* strains isolated from these patients
- a comparison of minimum inhibitory concentrations of ornidazole with those of metronidazole, nitrimidazine, and tinidazole on *T. vaginalis* strains isolated from clinical material
- a determination of plasma levels of unchanged ornidazole after oral administration of a 2 g dose.

## Material and methods

### EFFECT AND TOLERANCE STUDY

The clinical study was performed on 20 women out-patients aged between 15 and 36 years, with *T. vaginalis* infection. Subjective symptoms had been present for between two weeks and three years, except in eight who had no symptoms. The patients were selected because they were otherwise healthy, not pregnant, and were willing to return for further examination.

Ten of the patients had been treated with ampicillin for gonococcal infections at least three days before the study; seven women used contraceptive pills. No other medication was used. The patients were instructed to take 2 g of ornidazole just before going to bed (one of the side-effects noted in previous trials had been somnolence, Warnnissorn, 1974). This dose corresponded to 24 to 40 mg/kg body weight.

To prevent re-infection, partners were treated in

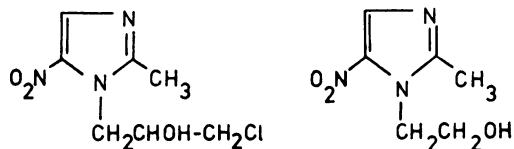


Fig. 1  
Ornidazole  
1-(3-chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole

Metronidazole  
1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole

To collect more data on ornidazole we made the following investigations:

- a study of the effect and tolerance of ornidazole when given as a single 2 g dose for *T. vaginalis* infection

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<sup>1</sup>Ro 7-0207, Tiberol, Kolpicid, F. Hoffmann-La Roche & Co Ltd, Basel

the same way as the patients, but were not included in the study.

The patients were examined just before treatment and then five days and one month after they had been treated. The following procedures were performed on each occasion:

- subjective symptoms—such as, itching, smarting pain and/or increased discharge—were recorded
- objective signs were noted. Of these, increased redness of the vaginal mucosa with or without increased discharge was considered to be the main criterion of vaginal infection
- specimens were collected for *T. vaginalis* culture (see laboratory diagnosis). This procedure would also reveal the presence of *Candida albicans*
- smears from the cervix were stained with methylene blue and examined microscopically for polymorphonuclear leucocytes (PMN) and intracellular diplococci. An average of 10 or more PMN seen in more than three high-power fields ( $\times 1000$ ) were recorded as 'leucocytic reaction' (Wallin *et al.*, 1974)
- Haemoglobin concentration, total and differential leucocyte count, thrombocytes, serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, and serum creatinine levels were determined using standard techniques.

#### LABORATORY DIAGNOSIS

Specimens were taken from the cervix with a sterile cotton swab which was immediately inserted into a modified Stuart's transport medium (Securline, MH 102, Cameco, Enebyberg, Sweden) and then sent to the bacteriological laboratory where specimens were inoculated into Diamond's medium and incubated at a temperature of 37°C. Wet preparations were examined daily by dark-field illumination. If no growth had appeared within one week, specimens were discarded as negative. According to Wallin *et al.* (1974), this is a better method than direct microscopical examination.

#### DETERMINATION OF MINIMUM INHIBITORY CONCENTRATION

Positive cultures were re-inoculated into fresh, prewarmed Diamond's medium which was incubated overnight. The cultures were then diluted 1 in 10 in Diamond's medium and 0.10 ml volumes of this suspension were inoculated into a series of 5 ml volumes of Diamond's medium containing concentrations of ornidazole decreasing in two-step

dilutions from 20 µg/ml to 0.08 µg/ml. Altogether 18 of the trichomonas strains isolated, and an additional 13 strains from other patients not in the study, were treated in this way. Minimum inhibitory concentration values for nimorazole (Naxogin®), metronidazole (Flagyl®, Elyzol®) and tinidazole (Fasigyn®) were also estimated using the 13 strains.

The influence of these drugs on the normal serum bactericidal effect was determined according to Forsgren and Gnarpe (1973). Serum specimens were obtained from five healthy women. The respective drugs were added to the serum specimens in two different concentrations, 40 and 10 µg/ml. The same strain (*Escherichia coli* Tr 1) as in earlier studies was again used.

#### PHARMACO-KINETIC STUDY

Five healthy female volunteers, aged between 24 and 45 years, were given 2 g ornidazole (corresponding to 28–39 mg/kg body weight) after a light breakfast without fat. Serial samples of 10 ml of blood were taken before and 2–72 hours after administration. Plasma was separated within one hour, immediately frozen and sent to Basel<sup>1</sup> for analysis of unchanged ornidazole in plasma by thin-layer chromatography (Hezel, 1973).

#### Results

The results of the clinical study are shown in Table 1. All 20 women attended the first follow-up, and 19 of these returned a month later. All cultures were negative after treatment although one of the patients still had a discharge. Of the eight symptomless patients at the beginning of the study, two noticed reduction of their usual discharge after treatment.

Table 1 *Results before and after treatment of T. vaginalis infection with ornidazole in a single dose of 2 g. Figures represent number of patients*

	Before treatment (n = 20)	After treatment	
		5–8 days (n = 20*)	One month (n = 19†)
Positive <i>T. vaginalis</i> culture	20	0	0
Objective signs	10	7	2
Subjective symptoms	12	2	1

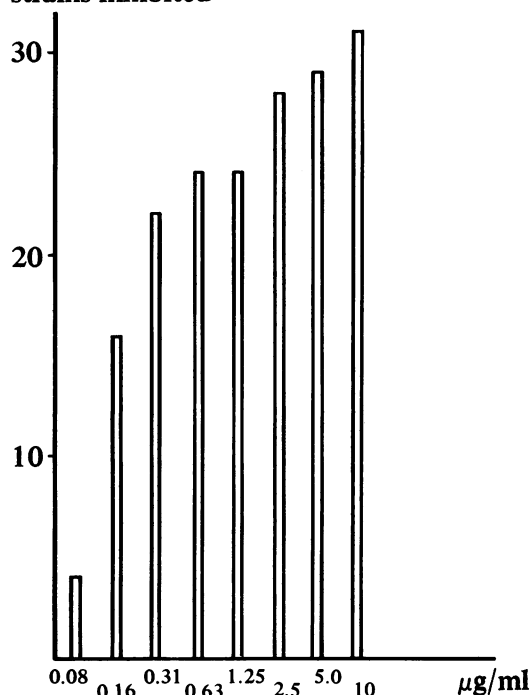
\*No clinical evaluation of one patient because of menstruation

†One patient did not attend the last follow-up

Eight patients complained of side-effects at the first follow-up visit, Table 2. These were not related to dose/kg body weight. Sixteen patients had leucocytic reaction before treatment and this was still present in 14 of them at the last visit. (This particular examination was inadvertently omitted on the other two patients.)

<sup>1</sup>These determinations were performed by Dr D. E. Schwartz, Department of Experimental Medicine, F. Hoffmann-La Roche & Co Ltd, Basel

### Number of strains inhibited



□ Ro 7-0207

Fig. 2 Minimum inhibitory concentrations of ornidazole for 31 strains of *T. vaginalis*.

Table 2 Side-effects after drug administration

Side-effects	Hours				Σ
	1/2	1	2	8*	
Fatigue and dizziness	1	—	1	—	2
Fatigue	—	1	—	1	2
Muscle pain	—	—	—	1	1
Nausea	1	1	—	—	2
Euphoria	1	—	—	—	1
Total	3	2	1	2	8

\*After one night's sleep

No intracellular diplococci could be demonstrated and *C. albicans* was not isolated from any culture. Haematological and biochemical parameters before and after treatment showed no change that could be related to the treatment. The minimum inhibitory concentrations of ornidazole are shown in Fig. 2. Two isolates were inhibited by 10 µg/ml only; 24 were inhibited by 0.63 µg/ml. Four strains were inhibited by 0.08 µg/ml. The minimum inhibitory concentration values of ornidazole, tinidazole, metronidazole, and nitrimidazine for the 13 *T. vaginalis* strains are shown in Fig. 3. All isolates were inhibited by 5.0 µg/ml of each drug. Nine strains were inhibited by 0.63 µg/ml of ornidazole, which is about the same result as for nitrimidazine, tinidazole, and metronidazole.

The influence of the four investigated drugs on the normal serum bactericidal effect is shown in Fig. 4 for one individual. As can be seen neither 10 nor 40 µg/ml of any drug reduced the serum bactericidal

### Number of strains inhibited

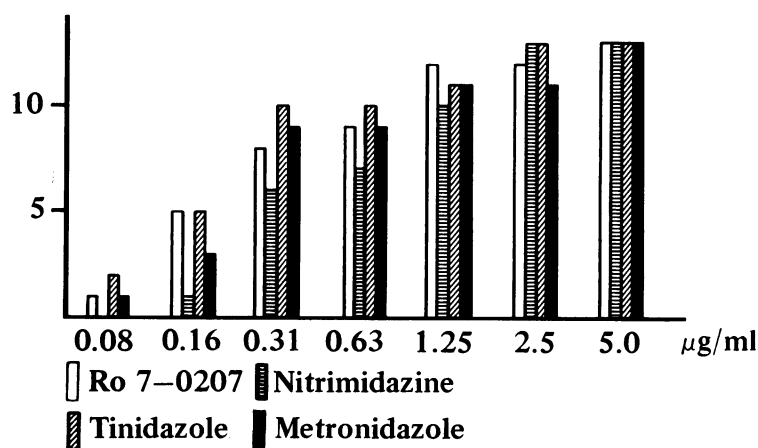


Fig. 3 Minimum inhibitory concentration values of ornidazole, tinidazole, metronidazole, and nitrimidazine for 13 strains of *T. vaginalis*.

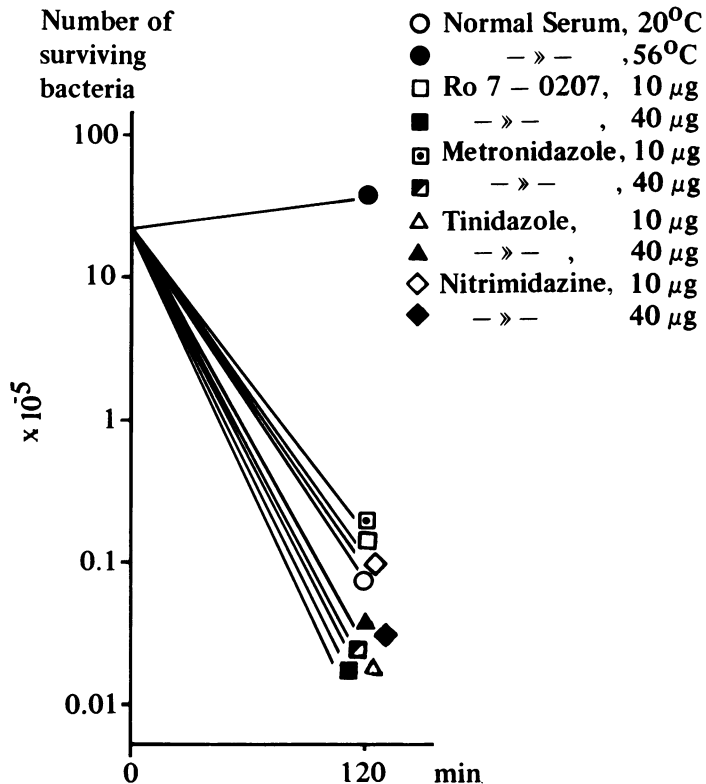


Fig. 4 Influence of ornidazole, tinidazole, metronidazole and nitrimidazine on the normal serum bactericidal effect.

effect. All investigated sera gave almost identical results.

The plasma peak-level of unchanged ornidazole was reached within two and four hours after administration and varied between 26.6 and 42.2 µg/ml, mean value 36.8 µg/ml, ± 6.0 (Fig. 5). The mean half-life was determined as 12.6 hours ± 1.1.

**Discussion**

Judged clinically and by the negative cultures of *T. vaginalis* a single 2 g dose of ornidazole was successful in curing infection in all 20 patients treated. Nevertheless leucocytic reaction persisted in 14 out of 16 patients who had showed this feature before treatment.

Wallin (1974) suggested that leucocytic reaction of the cervical smear was related to infections caused by *Neisseria gonorrhoeae* and *T. vaginalis*. Our impression is, however, that this is a very unspecific reaction probably also indicating other pathogenic agents—for example, those causing post-gonococcal urethritis and non-gonococcal urethritis. It may also be a physiological finding in many women.

Eight women complained of side-effects, fatigue and dizziness being the most common. Since the

peak of plasma levels of ornidazole was found to be between five and eight times greater than the minimum inhibitory concentration for trichomonads

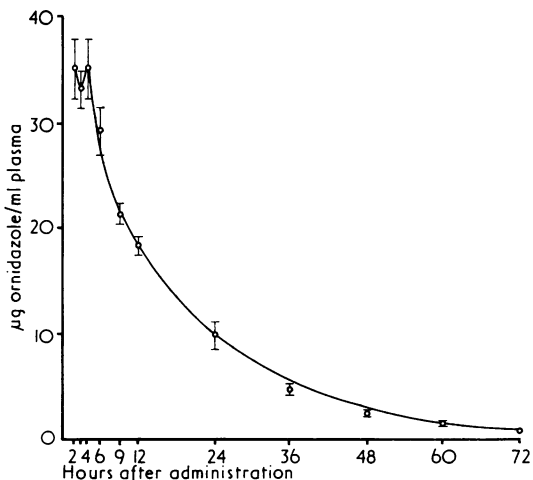


Fig. 5 Mean plasma concentrations and SEM of ornidazole in five healthy female volunteers after a 2 g single dose.

and these levels were still high 36 hours after ingestion, it may be possible to give a smaller dose of ornidazole with a maintained trichomonocidal effect but fewer side-effects. Further studies are in progress.

In our study the minimum inhibitory concentration value of ornidazole does not diverge much from that of other nitroimidazole derivatives on the 13 strains examined.

The clinical results of this study compare favourably with other nitroimidazole derivatives investigated, also given in a single dose of 2 g. For example, Csonka (1971) found a success rate of 94% using metronidazole although of the same compound, while Woodcock (1972) obtained only 85%. Rösemann and Vaughan (1973) and Wallin and Forsgren (1974) using tinidazole obtained cure rates of 90% (31 patients) and 96% (47 patients) respectively. With ornidazole Warnnissorn (1974) achieved 100% cure (36 patients), the same as in our series.

Thus, in conclusion ornidazole appears to have great promise as a trichomonocidal drug. However,

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more clinical studies are necessary, especially with regard to lessening the side-effects.

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