

Secnidazole

A 5-nitroimidazole derivative with a long half-life

D. VIDEAU,* G. NIEL,* A. SIBOULET,† AND F. CATALAN‡

From the *Institut de Biopharmacie, Rhône-Poulenc Santé, Paris, †Hôpital St-Louis, Paris, and ‡Institut Alfred-Fournier, Paris

SUMMARY The therapeutic activity of a single 2 g dose of secnidazole was studied in patients with urogenital trichomoniasis. In 140 patients, 97% were cured and the drug was well tolerated. In the laboratory, tests on sensitivity were made and the minimal inhibitory concentration (MIC) and the minimal trichomonacidal concentration (MTC) were determined on cultures that had recently been isolated at the clinic, and the pharmacokinetic properties of secnidazole in man were compared with those of tinidazole. The therapeutic efficacy of all the metronidazole derivatives was reviewed and a single-dose treatment is recommended. Therapeutic and prophylactic treatment is achieved by products with a long half-life. Secnidazole, with a half-life of 14.3 ± 1.3 h (women) and 20.2 ± 3.1 h (men), is particularly suitable for this type of treatment.

Introduction

Urogenital trichomoniasis is a common sexually transmitted disease (STD). Recent studies by French workers in Paris, Corsica, and Senegal showed that 20 to 25% of women and 15% of men who have a non-gonococcal genital infection are infected by this parasite (Nicoli *et al.*, 1964; Ridet and Siboulet, 1974-75, unpublished; Bohbot, 1975).

As a result of this work and because of the current epidemiological need for a single-dose treatment (treatment 'within a minute') (Siboulet and Durel, 1961; Csonka, 1971), the interest of clinicians has been focused on new products.

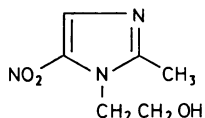
Two studies, one clinical and one laboratory, have been carried out in parallel on a new derivative of 5-nitroimidazole—14-539 RP or secnidazole. In the laboratory study, the biological activity and pharmacokinetic properties of secnidazole were compared with those of metronidazole and tinidazole. The half-life of secnidazole made it especially interesting, particularly for the type of treatment stated above.

Patients and methods

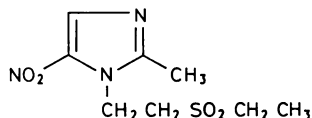
One hundred and forty patients (56 men and 84 women) aged between 15 and 54 years, were treated at two centres with one 2 g dose of secnidazole (4×500 mg tablets). Pregnant women were not included in the trial. To complete the study a larger dose (2.5 g) was given to 110 patients to find out if this improved the rate of cure. Patients in the second group matched patients in the first in respect of mean age, marital state, and the number of sexual partners treated at the same time.

The importance of hygiene and of having an adequate diet was stressed and each patient was told that the partner(s) must be given treatment simultaneously.

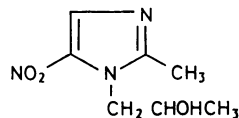
Diagnostic and control samples were taken as previously described (Siboulet *et al.*, 1977). The samples were examined microscopically—phase contrast and May-Grunwald-Giemsa stain—and cultured on Roiron's isolation medium (Durel *et al.*, 1961), before treatment and 48 hours and 15 days after.



Metronidazole



Tinidazole



Secnidazole*

* 1-(2'-hydroxypropyl)-2-methyl-5-nitroimidazole

Address for reprints: D. Videau, Institut de Biopharmacie, Rhône-Poulenc Santé, Paris

Received for publication 31 October 1977

The following biochemical investigations were undertaken to monitor possible adverse effects: blood count, blood urea, prothrombin index, and transaminases.

In vitro estimations of the minimal inhibitory concentration (MIC) and the minimal trichomonacidal concentration (MTC) were made by the method of Wallin and Forsgren (1974), modified by substituting Dubost medium (Cosar *et al.*, 1962) for the Diamond medium (Diamond, 1957), as the latter is too rich and allows too great a growth rate for the sensitivity test. Details of the techniques are given elsewhere (Siboulet *et al.*, 1977). The MIC and MTC estimations were made on 11 strains (one reference standard, maintained in the laboratory for 20 years, and 10 strains freshly isolated from humans) for each of the three drugs—metronidazole, secnidazole, and tinidazole.

In addition we studied serum concentrations for the three products both physicochemically (Populaire *et al.*, 1977, personal communication) and microbiologically (Cosar *et al.*, 1962; Videau, 1972) and obtained the same results. This was carried out by taking blood samples 1, 2, 3, 6, 9, 12, 24, 48, and 72 hours after a single oral dose (2 g) of each drug had been administered to 10 volunteers* (five men and five women). With the assay procedure the standard deviation was 7% and half-lives were calculated according to the methods of Riegelman *et al.* (1968) and Ritschel (1970).

Results

The single 2 g dose was curative at 48 hours in 136 (97.1%) of the 140 patients treated (Table 1). Four patients were cured by further doses—one more dose in three cases and two extra doses in the other. Long-term results (15 days) showed that six of the 136 patients who had been cured after a single dose either had a relapse or were reinfected. With the exception of nausea in 4%, tolerance to secnidazole was excellent. No adverse effects were detected in the control tests.

Table 1 *Distribution of patients treated and clinical results 48 hours after treatment*

Dose (500 mg tablets)	No. of patients	Results	
		Cured	Not cured
Total dose 2 g	140 (56 men 84 women)	136	4
Total dose 2.5 g	110 (53 men 57 women)	105	5

*Dr P. Pasquier, Hôpital de la Croix, St Simon, Paris

Short-term (48 hours) cure was obtained in 105 (95.4%) of the 110 patients given 2.5 g secnidazole. This resembled the cure rate obtained with the lower dose.

The MIC and MTC values for the three products, determined simultaneously in one study, are given in Table 2. The mean values were obtained from duplicate measurements of MIC and MTC values for each drug from 11 clinical strains of trichomonas and were determined for the confidence limits.

The half-life values calculated from the equations for the serum clearance curves, obtained from the mean serum concentrations measured physicochemically, are given in Table 3.

Lastly, the serum drug-clearance curves, obtained after oral administration of 2 g of secnidazole or tinidazole (mean of 10 volunteers) are given with standard error of the mean in the Figure, as well as the curve for metronidazole, for the same 2 g dose, taken from the literature (Wood and Monro, 1975).

Table 2 *Comparison of minimal lethal and inhibitory concentrations ($\mu\text{g/ml}$)*

Product	P=0.05	
	MIC	MTC
Metronidazole	0.60 (0.48–0.71)	0.42 (0.31–0.58)
Secnidazole	0.70 (0.53–0.86)	0.63 (0.44–0.81)
Tinidazole	1.125 (0.88–1.36)	0.75 (0.49–1.00)

Student's *t* test applied to the mean-degrees of freedom 15

Table 3 *Comparison of the pharmacokinetic parameters after a single 2 g dose*

Product (2 g)	Elimination serum half-life (hours)		
	Men	Women	Mean
Metronidazole	—	—	7.3
Secnidazole	20.0	14.0	17.0
Tinidazole	13.0	12.0	12.5

Table 4 *Results of Student's *t* test applied to the comparison of the MIC of two products (degrees of freedom 30)*

Drug	Tinidazole	Secnidazole
Metronidazole	$t = 4.29 > 3.65$ $P < 0.001$	$t = 1.07 > 2.04$
Tinidazole	—	$t = 3.14 > 2.75$ $P < 0.01$

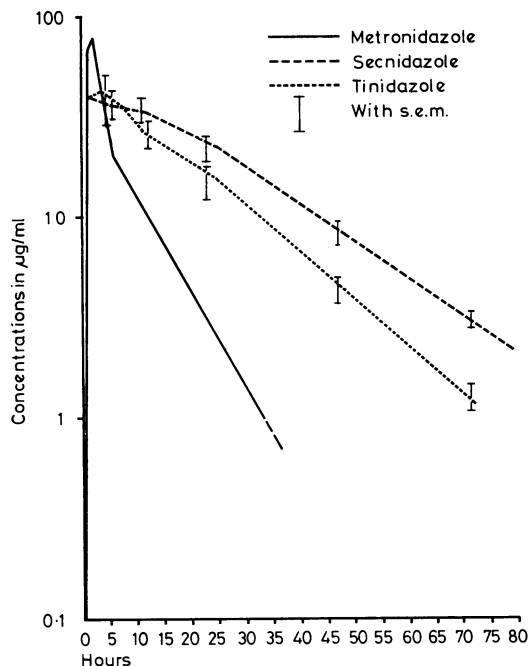


Figure 1 Drug values in the serum after oral administration of 2 g of secnidazole or tinidazole showing mean from 10 volunteers and standard error of the mean. Curve for metronidazole (2 g dose) from Wood and Monro, 1975.

Discussion

With a single 2 g dose, 97% of the patients were cured, while the 3% failures responded to further doses of the drug (Table 1). There were 6–7% long-term relapses (on day 15) which may be related not only to the menstrual cycle and the probable presence of persistent forms of trichomonads but also to reinfection.

The values for metronidazole (90 to 92%) and tinidazole (96%) given by Wallin and Forsgren (1974) and 94% given by Swarz (1974) are comparable with those for secnidazole and the failures undoubtedly occur for the same reasons.

On the other hand, we believe that the different cure rates (which vary between 90 and 100%) reported in the literature for metronidazole-related compounds (for example, tinidazole and ornidazole) may be caused by differences in the patients and not by any therapeutic variations. Knowledge of the pharmacokinetic, trichomonostatic, and trichomonocidal properties of a drug could well be as useful as the cure rates obtained in clinical trials for assessing the efficiency of these drugs.

Statistical analysis by Student's *t* test of the MIC values (Tables 2 and 4) showed that there was no significant difference between the metronidazole and secnidazole MIC values but that there was a significant difference between these drugs and tinidazole, the latter being only approximately half as active. These results are in agreement with the work of Korner and Jensen (1976).

The study of the MTC showed that secnidazole continued to act on the parasite after being subcultured in a fresh medium and that the mean value of the MTC was always lower than that of the MIC. Statistical analysis (Student's *t* test) showed no significant difference in the trichomonocidal effect of the three drugs, but the mean lethal values for each drug bore the same relationship to the MIC values.

We agree completely with Wood and Monro (1975) that to ensure efficacy of a drug after a single dose the pharmacokinetics of the molecule, its half-life, and peak serum level must be understood. For secnidazole and tinidazole, the peak serum values, observed approximately three hours after administration of the dose, reached 40 and 46 µg/ml respectively and did not differ significantly. Nevertheless at between six and 72 hours, the level of secnidazole remained higher than that of tinidazole, and the Student's *t* test showed that the difference in the half-lives of the two products was highly significant ($P=0.05$).

Conclusion

Since the introduction of metronidazole in the treatment of urogenital trichomoniasis, other drugs have also been found to be effective for this disease, but they had different pharmacokinetic properties. Our studies demonstrated the efficacy of secnidazole (*in vitro* activity on *Trichomonas vaginalis* and its half-life in human serum) and showed that it is useful for single dose treatment of trichomoniasis.

The authors wish to thank May & Baker Ltd for help in the translation of this paper.

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