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Single and triple dose treatment of *Trichomonas* infection of the vagina

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Both metronidazole and nimorazole (Naxogin) are highly effective in the treatment of *Trichomonas* infection of the vagina when given orally over a period of 5 to 7 days (Wisdom and Dunlop, 1965; Keighley, 1971; Moffett, McGill, Schofield, and Masterton, 1971; Cohen, 1971; McClean, 1972). However, Moffett and others (1971) consider that only about half those on standard oral therapy adhere correctly to treatment. Even in clinical trials of such courses, the percentage of patients failing to attend for follow-up has tended to be high: 21 per cent. (Evans and Catterall, 1971); 22 per cent. (McClean, 1972); 17 per cent. (Moffett and others, 1971). The aim of the present investigation was to determine the efficacy of metronidazole and nimorazole when given in short high-dose courses.

Patients and methods

Two trials were carried out at the Lideta M.C.H. Centre and at the University Gynaecology Clinics at the Princess Tsahai Memorial Hospital on a total of 258 patients found to be infested with *Trichomonas vaginalis*. The patients were unselected except for the exclusion of those in early pregnancy.

In the first trial, 58 patients were given 3 g. metronidazole and 52 patients 3 g. nimorazole. Both groups were instructed to take 1 g. immediately, 1 g. 6 hrs later and 1 g. the next morning. If the patient arrived too late in the day to comply with the above instructions she was told to take 1 g. of the drug that evening and further doses in the morning and afternoon of the following day.

In the second trial 75 patients were given 2 g. metronidazole, and 73 patients were given 2 g. nimorazole. The drug was administered in the clinic. In this trial the nature of the trichomonicide was not known either to prescriber or to patient, the latter being allocated to one or other treatment groups alternately. Forty of these patients (twenty in each group) were also treated with thorough swabbing of the vagina with a 1 per cent. aqueous solution of gentian violet which was repeated at the first follow-up examination.

Of the 258 patients, 65 per cent. were pregnant, 38 per cent. were single, separated, or divorced, and 59 per cent. were in the age range 21 to 30 yrs. All but six had symptoms, of which vaginal discharge was much the commonest occurring in 240 patients. The composition of the trial groups was very similar in relation to age, gestation, marital status, and symptomatology. Furthermore, the clinical features of the 133 patients treated with metronidazole were similar to those of the 125 patients treated with nimorazole.

Diagnosis was made by immediate microscopic examination of secretion from the posterior vaginal fornix suspended in normal saline. The follow-up procedure aimed at seeing the patient within 1 week of completion of the treatment, with four further examinations spread over a total of 12 weeks from the start of treatment. Concurrent monilial infection was diagnosed by Gram-stain of a smear from the posterior fornix. Moniliasis was not treated unless it appeared to be causing symptoms.

Results

A total of 258 patients was treated, 110 in the 3 g. dosage group and 148 in the 2 g. group. Nine patients (3·5 per cent.) failed to attend for any post-treatment examination; these were spread fairly evenly over the different groups. Thus 249 patients were seen at least once after treatment, of whom nine were found to be positive at the first examination, and 23 developed positive smears subsequently.

Table I (overleaf) shows the duration of follow-up in those apparently cured.

Detailed analysis of the treatment failures is shown in Table II (overleaf), the figures in brackets referring to the numbers of those known to have been exposed to the risk of re-infection. The male partners did not receive any treatment in this trial.

Side-effects encountered in both trials were mainly nausea, vomiting, and abdominal pain. Neither drug had a significant advantage in relation to the incidence of side-effects; on direct questioning 12 per cent. of patients given 3 g. complained of

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TABLE I *Treatment successes*

Trial dosage	*Drug*	*Defaulters*	*No. of negative examinations*					*Cured*	
			1	2	3	4	5	*No.*	*Per cent.*[a]
3 × 1 g.	Metronidazole	3	14	12	7	10	3	46	84
	Nimorazole	2	19	9	8	4	4	44	88
2 g. in one dose	Metronidazole	2	18	16	11	11	6	62	85
	Nimorazole	2	16	17	11	10	11	65	92

[a]Percentage of those followed

TABLE II *Treatment failures*

Trial dosage	*Drug*	*Positive examinations after treatment*					
		1st	*2nd*	*3rd*	*4th*	*5th*	*Total + ve*
3 × 1 g.	Metronidazole	2	4 (1)	1 (1)	1 (1)	1 (1)	9 (4)
	Nimorazole	3	2 (1)	—	1 (1)	—	6 (2)
2 g. in one dose	Metronidazole	3	2 (2)	4 (4)	1 (1)	1	11 (7)
	Nimorazole	1	3 (3)	1 (1)	1 (1)	—	6 (5)

Figures in brackets indicate patients known to have had coitus after treatment

untoward symptoms compared with 19 per cent. of those given 2 g. Only one patient was unable to tolerate the treatment; she vomited both metronidazole and nimorazole tablets when she was given 2 g. in a single dose. One other patient vomited each dose of 1 g., but was able to keep the tablets down when the drug was preceded by chlorpromazine. Both these patients were pregnant.

Candida was found at the initial examination in 12 per cent. of cases. The incidence of *Candida* after treatment with the anti-protozoal agents alone was 20 per cent., but in the small series of forty cases which also received gentian violet the fungus was found in only 10 per cent. at follow-up.

We also examined 48 babies of mothers treated during pregnancy. Two were fresh stillbirths after difficult breech deliveries and one was a macerated stillbirth. All the other infants were healthy. This perinatal mortality rate of 6·3 is rather better than the overall rate for the two units concerned.

Discussion

Experimental work with metronidazole and nimorazole has shown that a 250 mg. oral dose of either drug produces a serum level of above 3·5 μg./ml. of active substance and when the dose is increased to 1 g. levels of active substance reach 14 to 16 μg./ml. serum (de Carneri, Cantone, and eight others, 1969). Furthermore, in the case of nimorazole, it has been shown that single doses of 2 g. produce serum levels of 32 μg./ml. which are higher than the level of 24 μg./ml. found when the subjects are given 3 g. in divided doses (Groppi, 1972, personal communication). Similar very high levels are produced after single doses of 2 g. metronidazole (Woodcock, 1972). However, even the lowest of these serum levels is considerably higher than the minimum required to kill *Trichomonas vaginalis* (de Carneri and others, 1969). It appears likely that a high serum level is important because it leads to a lethal level of the anti-trichomonal agent in the vaginal secretion, and there is experimental evidence to show that this in fact occurs (de Carneri, Broccali, and eight others, 1971).

The treatment schedules described in this paper have obvious advantages over those usually employed. The cost per treatment is considerably reduced and short-term therapy is more likely to be properly completed by the patient. On the other hand, these advantages will be diminished if there is a reduction in effectiveness or if there is a greater incidence of side-effects. The results reported here suggest that short-term high-dose therapy is quite as effective in the treatment of trichomonal infection as longer courses but that the incidence of side-effects is probably higher. However, this incidence was investigated by direct questioning and this is likely to lead to far more complaints than would otherwise have been registered. Certainly our patients appear to prefer the shorter course.

The use of a 1 per cent. aqueous solution of gentian violet appears to be of some value in reducing the occurrence of super-infection with *Candida*, but the results in the small trial reported here are insufficient for any definite conclusion to be drawn.

Summary

Nimorazole (Naxogin) is compared with metronidazole in the treatment of vaginal trichomoniasis in two trials involving a total of 258 patients. In one,

the drugs were given in three doses of 1 g. spread over 24 hrs. In the other, a single dose of 2 g. was taken in the clinic in a double-blind trial. In the 3 g. trial the cure rates with metronidazole and nimorazole were 84 and 88 per cent. respectively. In the 2 g. single-dose trial the cure rates were 85 and 92 per cent. respectively. The overall default rate was 3·5 per cent. Over half the apparent cases of failure were probably due to re-infection. Side-effects occurred in 19 per cent. of cases in the 2 g. trial and in 12 per cent. of cases in the triple-dose trial, but in only two cases were they severe enough to interfere with treatment.

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Traitement par dose unique ou par dose triple de la vaginite à trichomonas

SOMMAIRE

Le nimorazole (Naxogine) fut comparé au métronidazole dans le traitement de la vaginite à trichomonas au cours de deux essais concernant un total de 258 malades. Dans le premier, les produits furent donnés en trois doses de 1g réparties sur 24 h.; dans l'autre, une dose unique de 2g fut prise à la clinique, en étude à double aveugle. Dans l'essai des 3g., les taux de guérison avec le métronidazole et le nimorazole furent respectivement de 84 et 88 pour cent. Dans l'essai à dose unique de 2g., les taux de guérison furent respectivement de 85 et 92 pour cent. Dans l'ensemble, la proportion de malades ne s'étant pas fait contrôler fut de 3,5 pour cent. Plus de la moitié des cas d'échecs apparents furent probablement dus à des réinfections. Des effets secondaires furent notés dans 19 pour cent des cas dans l'étude à 2g et dans 12 pour cent des cas dans l'étude de la dose triple; dans 2 cas seulement ils furent suffisamment sévères pour gêner le traitement.