

Treatment of trichomoniasis in the female

A comparison of metronidazole and nimorazole

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Forgan (1972) has described the history of the treatment of trichomoniasis culminating in the introduction of metronidazole (Flagyl) in 1959. In the past 15 years metronidazole has established itself as the first effective systemic remedy for trichomonal infection in men as well as women and no drug-resistance has emerged. The standard course of one 200 mg. tablet thrice daily for 7 days is almost completely free of side-effects, and cure rates in excess of 90 per cent have been reported by numerous workers in many countries. Nimorazole (Naxogin) became available in 1969 and the course of treatment recommended was one 250 mg. tablet every 12 hrs for 6 days. Most of the early reports in which this course was used suggested that the results were comparable with those of the standard course of metronidazole and the greater convenience to the patient of its twice-daily administration seemed an obvious advantage (Moffett, McGill, Schofield, and Masterton, 1971). It was therefore decided to compare the two drugs in the Special Clinic, Royal Victoria Hospital, Bournemouth.

Material and methods

With few exceptions, our female patients undergo a genital examination which routinely includes smears and cultures for *N. gonorrhoeae* (from urethra and cervix) and wet drop and culture (from the vagina) for *T. vaginalis* and yeasts. Serological tests for syphilis (cardiolipin Wassermann reaction, Venereal Disease Research Laboratory, and Reiter protein complement-fixation tests) are carried out in all patients at their initial visit and repeated later as indicated. Material from the posterior fornix of the vagina is collected with a sterile cotton-wool swab and mixed in a drop of normal saline on a slide. A cover-slip is added and after brief and gentle warming the preparation is at once examined microscopically under a 1/6 objective. The movement of the flagella and undulating

membrane enables *T. vaginalis* to be identified. When these are numerous the presence of *T. vaginalis* is quickly established but where the number of flagellates is low a prolonged search may be required. Oxoid Trichomonas medium (No. R.27) is inoculated directly with a similarly collected specimen of vaginal secretion and immediately incubated at 37°C. At the end of the clinic session the cultures are transferred to the hospital laboratory where incubation is continued at 35°C. for 36 to 48 hrs. In the 218 female cases in the present study *T. vaginalis* was found by wet drop examination in 214 (98 per cent.) and by culture in 213.

Alternate patients in this series of 218 consecutive female cases of trichomoniasis were treated either with metronidazole (200 mg. thrice-daily for 7 days) or nimorazole (250 mg. 12-hrly for 6 days). No local treatment was prescribed, but a daily bath and the application of talcum powder to vulva and perineum was recommended to the patients with acute vulvitis. The importance of taking the tablets punctually and of avoiding sexual intercourse and alcohol was stressed. The venereal transmission of the infection and its asymptomatic character in the male were explained; the need for simultaneous and similar treatment of their male partner(s) was emphasized and 'contact slips' were issued with a firm request that the male partner should attend within 24 hrs. Every male partner attending was examined but, irrespective of the findings, and after similar explanation, each was started immediately on the same course of the same drug as prescribed for the female. The male consorts were asked about additional female contacts and 'contact slips' were issued as required.

The importance of follow-up examinations was also explained to the female patients on their initial visit and re-attendance was requested 7, 14, 28, and 42 days from the first day of treatment. These intervals were, of course, not always rigidly observed, being reduced or increased for a number of reasons, including menstruation. Overdue patients were sent a reminder by post and a few patients re-attended only after a visit from our social worker. On each attendance our usual routine smears, wet drop, and cultures for *N. gonorrhoeae*, *T. vaginalis*, and yeasts were carried out. At the first follow-up visit the patient was asked if and when she had completed the course of tablets and any complaint of side-effects was noted. Loss of swallowed tablets by vomiting was specifically inquired after. When *T. vaginalis* was found on re-attendance the

case was reviewed in an attempt to decide whether failure of treatment or re-infection was responsible. In those considered to be cases of re-infection the original course of treatment was repeated. Where treatment appeared to have failed the patient was given the alternative drug in standard dosage or re-treated with the original drug using double dosage. Those patients re-treated with metronidazole in double dosage were asked to attend on the third day of the 7-day course and, without prior warning, were asked to provide a specimen of urine. This specimen was sent to our biochemist for a test for breakdown products of metronidazole; a positive test was considered to confirm not only that the tablets had been taken, but also that the metronidazole had been absorbed. It was not possible to make the test a quantitative one.

Results

The comparative study was terminated after a total of 218 consecutive female cases of trichomoniasis had been treated. As no selection was exercised, a few patients who were only temporary residents were included, even although it was appreciated that they could not attend for follow-up examination. These itinerants and some who defaulted for other reasons reduced the number of cases available for comparison to 100 treated with metronidazole and 97 treated with nimorazole. Ninety-five (95 per cent.) of the patients given metronidazole and 80 (82 per cent.) of the patients given nimorazole were considered cured (Table I). First follow-up tests were made between 7 and 9 days from the first day of treatment in 67 females receiving metronidazole and in 77 females receiving nimorazole and *T. vaginalis* was found in one (1.5 per cent.) and nine (11.7 per cent) respectively (Table II). These ten cases are regarded as primary failures. At follow-up examinations after 10 to 14 days three out of forty (7.5 per cent.) treated with metronidazole and five out of 35 treated with nimorazole (14.3 per cent.) were positive; these eight positive cases are regarded as probable primary failures. Thus post-treatment examination between 7 and 14 days after starting therapy indicated failure in four out of 100 females given metronidazole (4 per cent.) and in fourteen out of 97 females given nimorazole (14.4 per cent.).

First re-examinations were not made in some cases until 15 to 28 days from the start of treatment, and in this group treatment failure was diagnosed in one patient given metronidazole and in four given nimorazole although re-infection cannot be ruled out completely in these five women.

TABLE I *Follow-up and results in the two treatment groups*

Drug	Total no. treated	Followed up		Cured		Failures	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Metronidazole	109	100	92	95	95	5	5
Nimorazole	109	97	89	80	82	18	18

TABLE II *Number, time, and results of follow-up examinations*

Time of examination (days from starting treatment)	Results of follow-up tests			
	Treated with metronidazole		Treated with nimorazole	
	T. vag. +	T. vag. -	T. vag. +	T. vag. -
7-9	1	66	9	68
10-14	3	37	5	30
15-28	1	56	4	60
Over 28	0	40	0	43

Table III shows the precise day of the first follow-up examination in those patients giving positive results. We were able to treat the male consort in three of the five positive after metronidazole and in twelve of the eighteen positive after nimorazole.

Table III includes two girls (one treated initially with metronidazole and one initially with nimorazole) who failed to respond to re-treatment with both metronidazole and nimorazole in double the standard dosage; both were eventually cured with local treatment (nifuratel pessaries). Of the four other metronidazole failures, two were cured with a double dosage of metronidazole and one with nimorazole in standard dosage. Of the seventeen other nimorazole failures, nine were cured with metronidazole in standard dosage, five with nimorazole in a double dosage, and three with metronidazole in a double dosage.

The finding of *T. vaginalis* later than 14 days from the start of treatment suggests the possibility of re-infection as a possible cause of apparent failure. It is normal practice to give simultaneous trichomonocidal treatment to the male partners, and in the present study this was achieved in the cases of 68 per cent. of the females treated with metronidazole and 72 per cent. of those receiving nimorazole.

Re-infection was diagnosed in eight patients (Table IV), the criteria being one or more negative follow-up tests following *re-treatment with the same drug in the same dosage*: further sexual exposures were admitted in all cases.

No significant side-effects arose from either drug and none of the patients was pregnant.

Discussion

The encouraging results recorded in the early reports of the use of metronidazole as a purely oral treatment

TABLE III *Time of first test in cases classified as failures*

Drug	Days from start of treatment										
	7	8	9	10	11	12	14	15	16	17	19
Metronidazole	1			1		1	1				1 ^a
Nimorazole	4 ^b	3	2		2	1	2	1	2	1	

^aThis girl's tests were negative on Day 7 but further testing on Day 19 gave a positive culture; she proved unresponsive to both nimorazole and metronidazole in double dosage: her consort lived abroad and was not treated

^bOne girl failed to respond to both metronidazole and nimorazole in double dosage

TABLE IV *Cases classified as re-infections*

Treatment (standard dosage)	Follow-up tests (days)		Negative tests following repeat of original treatment (days)	Consort	
	Negative	Positive		Treated	When
Nimorazole	7	38	7, 21	Yes	Same day
Nimorazole	10	29	7, 28	No	—
Nimorazole	7	35	7	Yes	3 days
Nimorazole	7	14	7, 14, 28	Yes	After Day 14
Nimorazole	7 and 14	28	Defaulted	No	—
Nimorazole		24	7, 21, 28	Yes	Same day
Metronidazole	7	19	26, 56, 87	No	—
Metronidazole		18	28, 42	Yes	5 days

for trichomoniasis (*e.g.* Rodin, King, Nicol, and Barrow, 1960; Davey and Laird, 1960) have since been fully confirmed and 200 mg. given thrice daily for 7 days has become the standard course for infected females and their male consorts. Most reports record a primary failure rate of about 5 per cent. Secondary failure rates occurring after apparent cure are much influenced by the care and duration of follow-up examinations and the sexual activity, admitted or otherwise, of the patients. Simultaneous treatment of the current male partner is widely used, but this policy will not prevent re-infection if the female is unfortunate enough to choose an asymptomatic carrier as her next male partner. Many patients attending V.D. clinics are unreliable in their statements, in taking prescribed tablets, in attending for follow-up tests, and in avoiding sexual activity during the period of surveillance, but we believe that time spent in simple but detailed explanation is often rewarded by greater patient-cooperation and is essential in any comparative drug trial. To minimize the effects of these human factors it is important to use a sufficiently large number of *consecutive* cases and to maintain strictly the giving of each drug to alternate patients. The results in our present study, with cure in 95 of the 100 women followed-up after the standard course of metronidazole, are very much in keeping with those of special studies reported in the past.

When nimorazole became available, the recommended course was one tablet (250 mg.) every 12 hours for 6 days. The reported cure-rates have shown some variation. Cohen (1971) obtained 98 per cent. cures in 63 females who completed a satisfactory surveillance and almost half of the male partners were treated concurrently. Moffett and others (1971)

treated 92 selected females, and in 76 patients who attended after treatment the primary failure rate was 6.6 per cent. and the minimal secondary failure rate was 9.4 per cent.; they were able to give concomitant treatment to the male consort in 31 per cent. of cases and all the treatment failures occurred in women whose consorts remained untreated. Evans and Catterall (1971), using nimorazole in standard dosage (250 mg. 12-hrly for 6 days) in a randomized double-blind trial, considered that cure resulted in only 68 per cent of 57 women available for follow-up tests. McCann, Mahony, and Harris (1972), comparing the two drugs in standard dosage, obtained cures in 90 per cent. (of 52 patients) with metronidazole and 78 per cent. (of 48 patients) with nimorazole.

In our study, nimorazole in standard dosage gave a primary failure rate (within 14 days of starting treatment) of 14.4 per cent. in 97 patients available for follow-up as compared with a rate of 4 per cent. in 100 cases treated with metronidazole (Tables I, II, III). After 14 days, failure was diagnosed in the case of one patient treated with metronidazole and in four treated with nimorazole (Tables II and III). The overall cure rates are thus 95 per cent. for metronidazole and 82 per cent. for nimorazole (Table I).

There are several possible causes of primary treatment failure:

(1) Any oral therapy will fail if the patient does not take the drug in correct dosage and at the prescribed intervals, or having followed instructions loses the drug through vomiting before it has been absorbed. In this study especial care was taken regarding instructions to the patients and on the first return visit they were carefully cross-examined to establish that all the tablets had been taken, that the time

schedule had been observed, and that no vomiting had occurred.

(2) Failure of absorption may arise from intrinsic biological causes or from physical factors in the formulation of the drug preparation. In our failed cases the urine was tested without advance warning during re-treatment with metronidazole, and all such patients were found to be excreting metabolites of the drug. Cohen (1971) has reported finding by spectroscopic studies in one female patient with trichomoniasis, who failed to respond both to metronidazole and nimorazole, that both drugs were metabolized into non-active constituents before they could reach the trichomonads in the vagina. Nicol, Evans, McFadzean, and Squires (1966) described local inhibition of metronidazole by the vaginal flora. These factors may account for two of our failures in women in whom re-treatment with metronidazole and nimorazole in double dosage also failed, but in whom subsequent local vaginal treatment with nifuratel pessaries was curative.

(3) Dosage should broadly be related to the patient's body-weight and we have noticed that many of our primary treatment failures occurred in large and overweight women. In some of these primary failures, re-treatment with the same drug but in double dosage was effective. This dose-weight relationship has been ignored in the recommended standard courses of both metronidazole and nimorazole and we think that this may well be a significant factor in failure to cure female cases. It is probably of even more importance in treatment of the male partners in whom the presence of *T. vaginalis* is difficult to prove even before treatment on epidemiological grounds. One is inclined to assume that treating the male partner with either metronidazole or nimorazole in standard dosage will prevent re-infection, but it may well be that such dosage is inadequate in men weighing 170 lb. or more. The recent trend of giving either metronidazole or nimorazole in higher dosage over shorter periods (Campbell, 1972) or in a single dose (Morton, 1972; Jones, 1972) may owe much of its reported success to the higher dose/body-weight ratio achieved.

(4) Drug resistance is a common cause of treatment failure in cases of bacterial infection but, fortunately, there is no evidence so far of drug resistance in the case of *T. vaginalis*.

Summary

The effectiveness of metronidazole (Flagyl) and nimorazole (Naxogin) has been compared by using these drugs in the recommended dosage in alternate patients in a series of 218 consecutive cases of vaginal trichomoniasis. Follow-up tests in 100 patients treated with metronidazole and 97 treated with nimorazole indicated cure-rates of 95 and 82 per cent. respectively. Male consorts were examined and given treatment on epidemiological grounds in about 70 per cent. of both treatment groups. Both drugs were free from significant side-effects.

The causes of treatment failure in trichomoniasis are discussed and the desirability of relating dosage to the patient's body-weight is suggested. This factor may be especially important in deciding the dosage given on epidemiological grounds to the male consorts. It may also be an important advantage in the current trend of treating trichomoniasis in both sexes with larger doses over a much shorter time.

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