Two-day treatment with metronidazole in vaginal trichomoniasis

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Recent studies have demonstrated that the traditional 7-day course of metronidazole at a dosage of 200 mg. three times a day is not the only schedule effective in trichomoniasis (McClean, 1971; Csonka, 1971; Woodcock, 1972). It was decided to assess the efficacy of metronidazole 400 mg. four times a day for 2 days; this dosage would facilitate its administration with tetracycline 500 mg. four times a day, a schedule sometimes used as an alternative to penicillin in the treatment of gonorrhoea.

Methods
The patients taking part in the trial were attending the St. Mary's Hospital Special Clinic, and were diagnosed by routine darkfield microscopy of the vaginal secretion as having vaginal trichomoniasis. When cervical cytology was investigated this often confirmed the diagnosis, but it was not used as a diagnostic criterion nor as a test of cure. Cultural methods were not used because previous experience of their use in this clinic had shown them to be not substantially more reliable than simple microscopy; nor was any attempt made to diagnose trichomoniasis in the male consorts, many of whom were routinely treated with metronidazole 200 mg. three times a day for 1 week.

Patients were included in the trial whenever the diagnosis was made while the doctor conducting the trial was on duty. The only patients excluded were those who had already been treated for a trichomonal infection in the previous 3 months. The patients were asked to return in 1 week and again after 1 month for repeat tests; further visits were made at the discretion of the patient, but an interval of at least 3 months elapsed before the results for each patient were reviewed.

The criteria for diagnosis and assessment of cure, although satisfactory for routine clinical work, might be judged inadequate for a scientific study. It was therefore decided to establish a control group of patients by the same criteria, and to treat them with the standard course of metronidazole 200 mg. three times a day for 7 days. The use of a control group made the difficult task of distinguishing between treatment failure and re-infection of less importance, as the results were to be judged relatively rather than in terms of absolute success or failure. The controls were patients in whom the diagnosis was made when the doctor conducting the trial was not on duty.

Material
The preliminary data are shown in Tables I and II.

### Table I
Concurrent diagnoses in control and trial groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Gonorrhoea</th>
<th>N.S.U.</th>
<th>Warts</th>
<th>Herpes</th>
<th>Monilia</th>
<th>Syphilis</th>
<th>Phthirus pubis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Patients 32</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Consorts 45</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Patients 25</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Consorts 21</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

### Table II
Marital status and oral contraceptive use in control and trial groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Marital status</th>
<th>On 'pill'</th>
<th>Not on 'pill'</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Married 7</td>
<td>16</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single 26</td>
<td>65</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Married 9</td>
<td>11</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single 28</td>
<td>54</td>
<td>82</td>
<td></td>
</tr>
</tbody>
</table>
TRIAL GROUP (114 patients)
The average age was 23·9 years; 20 per cent. were married, and 28·9 per cent. were taking the contraceptive pill; 32 of the patients and 45 of their consorts were diagnosed as having gonorrhoea, six of the consorts had non-specific urethritis, and a total of eleven other diagnoses was made.

CONTROL GROUP (102 patients)
The average age was 25·3 years, 19·7 per cent. were married and 36·4 per cent. were taking oral contraceptives; 25 of the patients and 21 of their consorts were diagnosed as having gonorrhoea, twelve of the consorts had non-specific urethritis, and a total of ten other diagnoses was made.

Table III shows the results obtained by cytological examination in both groups of patients and in those with and without gonorrhoea. There was no evidence of malignancy in any patient and no significant difference in the reporting of Trichomonas vaginalis from cytology in the different sub-groups.

Results
These are shown in Table IV.

In the trial group, 75 returned for follow-up tests; after 4 weeks there had been eight recurrences (10·7 per cent. of those followed) and a further nine recurrences were revealed by later visits, bringing the total to seventeen (22·7 per cent. of those followed).

In the control group, 68 returned for follow-up tests; after 4 weeks there had been five recurrences (7·3 per cent. of those followed), and later visits revealed a further eight, bringing the total to thirteen (19·1 per cent. of those followed).

<table>
<thead>
<tr>
<th>TABLE III</th>
<th>T. vaginalis in cervical cytology in control and trial groups of patients with trichomoniasis and with and without gonorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Genococi</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td>Not found</td>
</tr>
<tr>
<td>Control</td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td>Not found</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE IV</th>
<th>Follow-up and results in control and trial groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of follow-up (wks)</td>
<td>0</td>
</tr>
<tr>
<td>No. followed</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Trial</td>
</tr>
<tr>
<td>No. of recurrences</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Trial</td>
</tr>
<tr>
<td>Cumulative recurrences as percentage of cases followed</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Trial</td>
</tr>
</tbody>
</table>
starting treatment (see below) are also shown. Since most strains of *Trichomonas* are sensitive *in vitro* to levels of 0.25-0.125 μg./ml. (Jennison, Stenton, and Watt, 1961), it can be seen that values considerably above the minimum trichomonicidal level were maintained for at least 54 hours. Comparison with the fall-off of mean levels after single doses of 2 g. metronidazole (Fig. 2) suggests that adequate levels might have persisted for another 24 hours; thus the 2-day course of treatment probably provides effective blood levels for 3 to 4 days.

There was no significant difference in the values obtained.

A review of the case notes of 500 consecutive female patients previously treated with metronidazole for trichomoniasis revealed thirteen who had been taking tetracycline concurrently. Three did not return for follow-up; the remaining ten showed no failures. The original suggestion of antagonism was based on a single case of treatment failure and it seems likely that this was a chance occurrence.

**Discussion**

Since the introduction of metronidazole in 1959, the then recommended regimen has continued to prove so satisfactory in the treatment of trichomoniasis that there has been little impetus for its modification. However, the introduction of different dose schedules for other conditions such as gingivitis (Duckworth, Waterhouse, Britton, Nuki, Sheilham, Winter, and Blake, 1966) and amoebiasis (Powell, Macleod, Wilmot, and Elsdon-Dew, 1966; Powell, Wilmot, and Elsdon-Dew, 1967; Powell, 1969) has led to the recognition that there is nothing sacred about ‘200 mg. three times a day for 7 days’.

In the present trial the results obtained using a dosage of 400 mg. four times a day for 2 days were as good as those obtained by the traditional regime.

The relatively high cumulative recurrence rates of 22.7 and 19.1 per cent. should not be considered in absolute terms; the patients were followed for more than 3 months, allowing ample time for re-infection to have occurred, and no attempt was made to assess whether the regimens were treated adequately or to distinguish between treatment failure and re-infection.

**Summary**

114 women with vaginal trichomoniasis were treated with metronidazole 400 mg. four times a day for 2 days. A control group of 102 patients received metronidazole 200 mg. three times a day for 7 days.

Recurrence rates in those followed up during a period of 3 months or longer were seventeen of 75 (22.7 per cent.) and thirteen of 68 (19.1 per cent.) respectively. No evidence was found of any antagonism between tetracycline and metronidazole.

I am grateful to Dr. F. J. G. Jefferiss and Dr. R. R. Willcox for allowing this trial to be undertaken on patients under their care. Thanks are also due to May and Baker Ltd. for providing the 'Flagyl' as 400 mg. tablets, and in particular to Mrs. O. Sheldon for her helpful advice and to Mr. S. Squires for estimating the serum levels of metronidazole.

**FIG. 2 Comparison of mean serum levels of metronidazole in subjects on four different dosage schedules;**

1. Six on 2 g. stat (Woodcock, 1972)
2. Four on 200 mg. three times a day (Fig. 1)
3. Two on 200 mg. three times a day (8 a.m. specimens) (Kane, McFadzean, Squires, King, and Nicol, 1961)
4. One of the two above (12-hourly specimens)

**METRONIDAZOLE AND TETRACYCLINE**

Whilst the trial was being planned, Szanto (1971) suggested a possible antagonism between oxytetra-cycline and metronidazole. Four of the trial patients who were also taking tetracycline 500 mg. four times daily had blood specimens taken 36 hours after starting treatment. Their serum metronidazole levels are shown in Fig. 1, together with the results at 36 hours for four patients on metronidazole alone.
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Traitement de deux jours par le métronidazole
dans la trichomonase vaginale

SOMMAIRE
114 femmes atteintes de trichomonase vaginale furent
traitées par une dose de 400 mg de métronidazole donnée
4 fois par jour pendant 2 jours. Un groupe témoin de 102
malades reçut 200 mg de métronidazole 3 fois par jour
pendant 7 jours.

Les taux des rechutes chez les malades suivies pendant
trois mois et plus furent respectivement de 17 sur 75
(22,7 pour cent) et de 13 sur 68 (19,1 pour cent). Aucun
antagonisme entre tetracycline et métronidazole ne put
être mis en évidence.