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*

Group		Gonorrhoea	N.S.U.	Warts	Herpes	Monilia	Syphilis	Phthirus pubis
Trial	Patients	32	—	2	3	3	1	1
	Consorts	45	6	0	0	0	1	0
Control	Patients	25	—	2	3	0	3	0
	Consorts	21	12	0	0	0	2	0

TABLE II *Marital status and oral contraceptive use in control and trial groups*

Group	Marital status	On 'pill'	Not on 'pill'	Total
Trial	Married	7	16	23
	Single	26	65	91
Control	Married	9	11	20
	Single	28	54	82

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).

SERUM LEVELS OF METRONIDAZOLE

Fig. 1 shows the serum levels from four volunteers 3 and 24 hours after the first dose, and 12 hours after the final dose. Serum levels from eight subjects who had a single blood sample taken 36 hours after

FIG. 1 Serum levels of metronidazole in subjects on metronidazole alone (○) and on metronidazole and tetracycline (●)

TABLE III *T. vaginalis* in cervical cytology in control and trial groups of patients with trichomoniasis and with and without gonorrhoea

Group	Gonococci	Cervical cytology (<i>T. vaginalis</i>)		
		Positive	Negative	Not tested
Trial	Found	18	3	11
	Not found	53	18	11
Control	Found	12	5	8
	Not found	40	18	19

TABLE IV *Follow-up and results in control and trial groups*

Length of follow-up (wks)		0	<1	1-4	4-8	8-12	>12	Total
No. followed	Control	34	68	67	50	38	26	102
	Trial	39	75	61	43	33	22	114
No. of recurrences	Control	—	1	4	2	3	3	13
	Trial	—	1	7	3	0	6	17
Cumulative recurrences as percentage of cases followed	Control	—	—	7.3	—	14.6	—	19.1
	Trial	—	—	10.7	—	14.7	—	22.7

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 trichomonocidal 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.

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

- (6) = Six on 2 g. stat (Woodcock, 1972)
 (4) = Four on 400 mg. four times a day (Fig. 1)
 (2) = Two on 200 mg. three times a day (8 a.m. specimens) (Kane, McFadzean, Squires, King, and Nicol, 1961)
 (1) = One of the two above (12-hourly specimens)

METRONIDAZOLE AND TETRACYCLINE

Whilst the trial was being planned, Szanto (1971) suggested a possible antagonism between oxytetracycline 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.

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, Sheiham, 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 consorts 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.

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References

- CSONKA, G. W. (1971) *Brit. j. vener. Dis.*, **47**, 456
 DUCKWORTH, R., WATERHOUSE, J. P., BRITTON, D. E. R.,
 NUKI, K., SHEIHAM, A., WINTER, R., and BLAKE, G. C.
 (1966) *Brit. dent. j.*, **120**, 599
 JENNISON, F. R., STENTON, P., and WATT, L. (1961)
j. clin. Path., **14**, 431
 KANE, P. O., MCFADZEAN, J. A., SQUIRES, S., KING, A. J.,
 and NICOL, C. S. (1961) *Brit. j. vener. Dis.*, **37**, 273
 MCCLEAN, A. N. (1971) *Ibid.*, **47**, 36
 POWELL, S. J. (1969) *Med. Today*, **3**, no. 1, p. 48
 —, MACLEOD, I., WILMOT, A. J., and ELSDON-DEW, R.
 (1966) *Lancet*, **2**, 1329
 —, WILMOT, A. J., and ELSDON-DEW, R. (1967) *Ann.*
trop. Med. Parasitol., **61**, 511

- SZANTO, S. (1971) *Brit. med. j.*, **2**, 467
 WOODCOCK, K. R. (1972) *Brit. j. vener. Dis.*, **48**, 65

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 tétracycline et métronidazole ne put être mis en évidence.