Nitrimidazine Compared with Metronidazole in the Treatment of Vaginal Trichomoniasis

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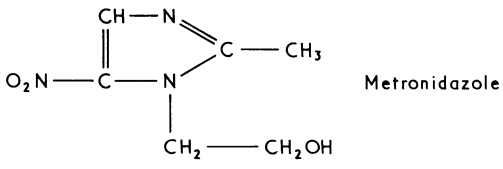
Summary

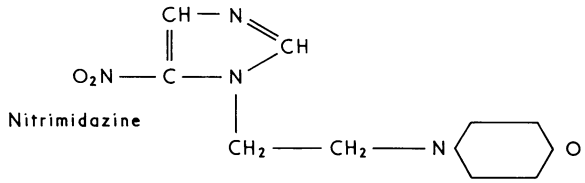
A new substituted nitroimidazole, nitrimidazine (Naxogin), is compared with the established drug, metronidazole (Flagyl), for the treatment of vaginal trichomoniasis in a randomized double-blind trial. Nitrimidazine cured 39 (68%) out of 57 patients and showed no undesirable effects other than nausea in one patient. Metronidazole cured 51 (89%) out of 57 patients and also caused nausea in one patient; this cure rate corresponds with that previously reported in other trials. In the recommended dosage nitrimidazine is inferior to metronidazole, but is sufficiently effective to be useful in cases of intolerance to metronidazole.

Introduction

The standard treatment for vaginal trichomoniasis during the past 10 years has been oral metronidazole (Flagyl); this drug is a substituted nitroimidazole, (1-(2-Hydroxyethyl)-2 methyl-5-nitroimidazole) (see formula).



Metronidazole



Nitrimidazine

Nitrimidazine (Naxogin), introduced in 1968 as a systemic trichomonacide, is also a substituted nitroimidazole (1-*N* (β-ethylmorpholine)-5-nitroimidazole) (see formula).

Clinical trials on the Continent have claimed a success rate of 96% following oral use of this drug (Emanueli and de Carneri, 1969); gastrointestinal side effects were noted in 7% of cases.

The results of two uncontrolled clinial trials have recently been published in Britain. Both report cure rates of over 90% and no side effects (Cohen, 1971; Moffett *et al.*, 1971). Nitrimidazine is compared with metronidazole in the present investigation.

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Patients and Methods

The trial was carried out on 142 women attending a clinic for sexually transmitted diseases who were found consecutively to be infested with *Trichomonas vaginalis*. A random sequence chart was used to allot each patient to one of two treatment groups, designated group A and group B, the nature of which was unknown to both prescriber and patient. Nitrimidazine was administered in the manufacturer's recommended regimen of one 250-mg tablet twice daily for six days, while metronidazole was prescribed in the standard dose of 200 mg three times daily for seven days. White cell counts were carried out before and immediately after treatment in 40% and 47% of cases respectively.

Analysis of the group studied showed an age range of 16-47 years, with 90% between 18 and 30 years of age; 82% of the group were single. Vaginal discharge was present in 73%; 20% were symptomless. Oral contraception was used by 47%, and 44% did not use any contraceptive method.

Diagnosis was made by darkground microscopical examination of a saline suspension of secretion from the posterior vaginal fornix. A few cases were diagnosed only by culture, with the Feinberg-Whittington medium, and two cases in the nitrimidazine group were discovered from cervical smears. These were excluded from the trial on the grounds that this examination is not a routine diagnostic method of established reliability. Patients who defaulted completely after treatment were, of course, also excluded.

The follow-up procedure aimed at obtaining a minimum of two further sets of genital tests to exclude the coexistence of other genital infections, particularly gonorrhoea, and up to a total of five follow-up tests to establish the eradication of *T. vaginalis*. Patients who continued to attend regularly were kept under observation for a period of 12 weeks from the start of treatment. *Candida albicans* was detected by Gram-stained smears from the vaginal wall and by culture on Sabouraud's medium, and gonorrhoea was diagnosed by examination of Gram-stained secretions from the endocervix and urethra and by culture on Columbia blood agar medium.

Results

A total of 142 patients were treated—70 in group A and 72 in group B. Group A patients were treated with nitrimidazine and group B with metronidazole. In the nitrimidazine group there were 11 (16%) defaulters who failed to attend for posttreatment examination and two diagnosed only from cervical smears. Of the remaining 57, 39 (68%) could be regarded as cured on the evidence of one or more sets of follow-up tests (Table I). Nine were found still to be infested at the first posttreatment examination and nine at a second examination (Table II). Fifteen (21%) of the metronidazole group failed to return for posttreatment ex-

TABLE I—*Test of Cure*

Treatment Group	No. of Negative Examinations						Patients Cured
	1	2	3	4	5	6	
Nitrimidazine ..	15	10	12	1	—	1	39
Metronidazole ..	14	21	9	5	1	1	51

TABLE II—*Treatment Failures*

Treatment Group	Positive Examination after Treatment								Total
	1st		2nd		3rd		4th		
	Slide	Culture	S.	C.	S.	C.	S.	C.	
Nitrimidazine ..	9	—	8	1	—	—	—	—	18
Metronidazole ..	1	—	4	1	—	—	—	—	6

amination, leaving 57 patients who were re-examined. Cure was established in 51 (89%) on the minimum basis of a single examination (Table I); one patient had persistent trichomonal infestation at the first examination and five were infested at their second follow-up test (Table II).

One patient in each group reported anorexia and nausea while under treatment; there were no other adverse effects. No evidence of depression of leucocyte production was found with either drug.

Gonorrhoea, confirmed by culture and fermentation tests, was found before treatment in 10 (14%) patients who received nitrimidazine and in 13 (18%) treated with metronidazole. A further case of gonorrhoea was found at the first post-treatment examination two weeks after beginning metronidazole. However, no more cases of gonorrhoea were diagnosed in a total of 211 sets of genital tests. Gonorrhoea recurred in two patients in both groups.

Candida albicans was isolated on the initial examination in 12 (17%) patients who received nitrimidazine and in 13 (18%) given metronidazole. Treatment with nystatin pessaries was given only to those patients who had unequivocal candidiasis on Gram-stained vaginal material in all cases, subsequently confirmed by culture on Sabouraud's medium.

One patient was completely refractory to treatment and firmly maintained that she had never had sexual intercourse. After initial failure with metronidazole, which made her nauseated, she failed successively to show any response to nitrimidazine, hydrargaphen pessaries, and chloramphenicol pessaries. Metronidazole given at the clinic as a single 4-g dose together with 800 mg into the vagina did not eradicate the organism. Further investigation carried out in conjunction with the manufacturer showed a serum metronidazole concentration of 2·3 μg/ml one hour after 200 mg by mouth; this is considered the minimum level consistent with adequate absorption (Kane *et al.*, 1961). The strain of *T. vaginalis* isolated was sensitive to the drug (minimal inhibitory concentration 1 μg/ml), and there was no inactivation of metromonidazole after incubation with the patient's vaginal flora. Metronidazole (1·2 g daily) was then combined with chloramphenicol pessaries (Ginetris) one nightly for one week, but, despite temporary symptomatic improvement, the organism was still found three weeks later. She was then admitted to hospital where this regimen was repeated under supervision and produced a cure; metronidazole tablets were administered crushed in milk. It was concluded that this was a case of inconsistent consumption of the drug owing to gastrointestinal intolerance coupled with reduced absorption.

Discussion

Failure to respond to metronidazole seems to occur in less than 10% of cases though it is never possible to exclude the patient's failure to have taken the drug as prescribed or to have avoided reinfection (Rodin *et al.*, 1960; Watt and Jennison, 1962; Csonka, 1963; Wisdom and Dunlop, 1965). The report by Keighley (1971) from a prison community is of particular relevance; she found a 98% cure rate with metronidazole under conditions where medication was seen to be administered and reinfection by heterosexual intercourse was, presumably, not possible. Nevertheless, her cases received a larger daily dose (800 mg) than normally prescribed to fit in with the twice daily treatment routine in prison. Inadequate absorption and low serum levels probably account for some drug failures (Kane *et al.*, 1961). Neither primary nor acquired resistance has been reported after eight years of clinical use (McFadzean *et al.*, 1969). However, Nicol *et al.*, (1966) described inhibition of metronidazole by vaginal flora in some patients showing no response to the drug. These forms of therapeutic failure may be countered by doubling the standard dose and, if necessary, combining local antibiotic treatment to alter the vaginal flora.

Nevertheless, in the treatment of vaginal trichomoniasis metronidazole approaches the therapeutic ideal in ease of administration, freedom from unwanted effects, and high cure rate. Substances of similar chemical structure are being produced. The present one under trial claims the advantage of twice-daily administration for a course one day less than metronidazole; thus the daily dose of nitrimidazine recommended (500 mg) is less than that of metronidazole (600 mg). Clearly this will be invalidated by any loss of therapeutic efficiency such as is shown by the present figures in which nitrimidazine cured only 68% of patients whereas metronidazole cured 89%. The latter figure is in agreement with the results of previous trials (Wisdom and Dunlop, 1965; Evans and Catterall, 1970).

References

Cohen, L. (1971). *British Journal of Venereal Diseases*, **47**, 177.
Csonka, G. W. (1963). *British Journal of Venereal Diseases*, **39**, 258.
Emanueli, A., and de Carneri, I. (1969). Sixth International Congress of Chemotherapy, Tokyo.
Evans, B. A., and Caterall, R. D., (1970). *British Medical Journal*, **2**, 335.
Keighley, E. E., (1971). *British Medical Journal*, **1**, 207.
Kane, P. O., McFadzean, J. A., and Squires, S. L. (1961). *British Journal of Venereal Diseases*, **37**, 273, 276.
McFadzean, J. A., Pugh, I. M., Squires, S. L., and Whelan, J. P. F. (1969), *British Journal of Venereal Diseases*, **45**, 161.
Moffet, M., McGill, M. I., Schofield, C. B. S., and Masterton, G. (1971). (1969). *British Journal of Venereal Diseases*, **45**, 161.
Nicol, C. S., Evans, G. J., McFadzean, J. G., and Squires S. L. (1966). *Lancet*, **2**, 44.
Rodin, P., King, A. J., Nicol, C. S., and Barrow, J. (1960). *British Journal of Venereal Diseases*, **36**, 147.
Squires, S. L., and McFadzean, J. G. (1962). *British Journal of Venereal Diseases*, **38**, 218.
Watt, L., and Jennison, R. F. (1962). *British Medical Journal*, **1**, 276.
Wisdom, A. R., and Dunlop, E. M. C. (1965). *British Journal of Venereal Diseases*, **41**, 90.