

Effects of minocycline and tetracycline on the vaginal yeast flora

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SYNOPSIS Two groups of women with non-specific genital infection were treated for two weeks with tetracycline 250 mg six-hourly and minocycline 100 mg twice daily respectively. Cultures for yeasts were performed before treatment and at the end of the first and second weeks. Before treatment yeasts, mostly *Candida albicans*, were recovered from 13% of the women. After one and two weeks' treatment yeasts were isolated from 22 and 29% of women treated with tetracycline, and from 19 and 29% of women treated with minocycline. It is concluded that despite inhibition of the growth of yeasts shown by minocycline *in vitro*, there is no evidence of any significant difference between the actions of tetracycline and minocycline on the vaginal yeast flora.

Minocycline is a recently introduced semi-synthetic tetracycline. Unlike other tetracyclines it has been shown to inhibit the growth of *Candida albicans in vitro* in relatively low concentrations; a disc containing 30 µg produces a zone of inhibition about 13 mm in diameter, though this inhibition is much affected by the composition of the medium (Waterworth, 1974).

It has been known for many years that therapy with tetracyclines may be accompanied by an overgrowth of yeasts, particularly *C. albicans*, in the intestinal and lower urogenital tracts (Winner and Hurley, 1964). This overgrowth is often asymptomatic but may at times be accompanied by clinical signs such as stomatitis, pruritus ani or vulvovaginitis. The cause is uncertain; the suppression of inhibitory bacteria by tetracyclines may allow the overgrowth of yeasts, or alternatively low concentrations of tetracyclines may directly potentiate yeast replication.

In view of the inhibitory effect shown by minocycline against *Candida* spp. *in vitro* it might be hoped that less yeast overgrowth would occur in patients treated with this drug than with other tetracyclines. We have investigated this possibility by comparing the effect of oral tetracycline and minocycline on the vaginal yeast flora.

Subjects and Methods

The patients studied were women attending the

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Department of Genito-Urinary Medicine, University College Hospital with the diagnosis of non-specific genital infection (NSGI). They usually came because they were sexual contacts of men with non-specific urethritis. After excluding infection with *Neisseria gonorrhoeae* and *Trichomonas vaginalis* it is our practice to treat these women with a course of a tetracycline.

CLINICAL EXAMINATION

Patients were examined in the lithotomy position. The external genitalia were inspected and the vagina and cervix examined after the insertion of a Cusco speculum. Vulvovaginitis was defined as vulval or vaginal erythema with or without vulval scaling, oedema or excoriation and with or without the presence of vaginal plaques.

Specimens were collected from patients on first attendance as follows:

- 1 Cervical and urethral material was spread on glass slides, and culture plates for *N. gonorrhoeae* were inoculated.
- 2 Vaginal material was suspended in a drop of normal saline and covered with a cover slip; culture medium for *T. vaginalis* was also inoculated.
- 3 A further vaginal specimen was collected on a cotton wool swab which was broken into 1.0 ml sterile water in a bijou plastic container with a close-fitting cap for yeast culture.

MICROBIOLOGICAL EXAMINATION

Wet preparations were examined immediately for

T. vaginalis. Urethral and cervical smears were stained by Gram's method and examined for intracellular Gram-negative diplococci. Selective culture media were used for the isolation of *N. gonorrhoeae*, and Feinberg-Whittington medium was used for culture of *T. vaginalis*. Cultures for *Candida* spp. were examined as follows:

The water containing the vaginal swab was well mixed, then a full 4 mm loopful was transferred to a plate of Sabouraud's medium containing 25 µg/ml chloramphenicol. The inoculum was streaked across the sides of the plate in turn without intervening flaming of the loop. Cultures were incubated overnight at 37°C. *C. albicans* was identified by the germ-tube test (Mackenzie, 1962); any yeasts not producing germ-tubes after four hours' incubation in serum were sent to Dr D. W. R. Mackenzie for identification.

TREATMENT

Women who had gonorrhoea, trichomoniasis or candidal vulvovaginitis which required immediate treatment with an antifungal agent were all excluded from the project. The remainder were assigned at random to one of two treatment groups. Women in the first were given tetracycline 250 mg six-hourly, and in the second, minocycline 100 mg twice daily. Treatment continued for two weeks; patients were re-examined at the end of the first and second weeks and further cultures for *Candida* were prepared; any side effects of the antibiotics were recorded on each attendance.

Results

A group of 204 women with NSGI was studied. Before treatment 27 of them (13%) yielded yeasts on vaginal culture: 24 isolates were *C. albicans* and three were *T. glabrata*. Five of the 27 yeast-positive women and 11 of the 177 yeast-negative women showed vulvovaginitis. Of the 204 women, 99 were treated with tetracycline 250 mg six-hourly and 105 with minocycline 100 mg twice daily. The results were as follows.

TREATMENT WITH TETRACYCLINE

At the end of the first week of treatment three of the 99 women given tetracycline had stopped taking the drug because of side effects, and 28 had defaulted, leaving 68 patients still available for study. Of these 68, 15 now yielded yeasts on culture (22%); all the isolates were *C. albicans* (table I). Four of the 15 women with positive cultures showed vulvovaginitis, as did two of the 53 women with negative cultures.

After the second week of treatment no more patients had experienced side effects, but a further

Days after Treatment	No. Attending	No. with Positive Cultures	% Positive
0	99	14	14
7	68	15	22
14	51	15	29

Table I Vaginal yeast culture results before and after tetracycline therapy

17 had defaulted, so that 51 women were now available for study. Of these, 15 (29%) yielded yeasts on culture (table I); all the isolates were *C. albicans*. Six of these 15 patients exhibited vulvovaginitis.

The effects of a course of tetracycline on the vaginal yeast flora are summarized in table II. After one week's treatment, 53 of 68 women (78%) remained yeast-negative and 10 (15%) yeast-positive. On the other hand, five women (7%) initially yeast-negative were now yeast-positive. After two weeks' treatment, 35 of 51 women (69%) remained yeast-negative and seven (14%) yeast-positive. However, eight women (16%) who were free from yeasts before treatment now yielded isolates, and one woman (2%) had reverted from yeast-positive to yeast-negative during treatment.

Isolation Sequence	Period of Observation			
	1 week		2 weeks	
	No.	% of total	No.	% of total
Neg → Neg	53	78	35	69
Neg → Pos	5	7	8	16
Pos → Pos	10	15	7	14
Pos → Neg	0	0	1	2
Total	68		51	

Table II Effect of tetracycline on vaginal yeast flora

It is of interest that only a minority of patients who appeared to have become carriers of yeasts because of tetracycline therapy showed any evidence of vulvovaginitis, and this was rarely severe.

TREATMENT WITH MINOCYCLINE

A group of 105 women with NSGI was treated with 100 mg minocycline twice daily. Side effects were more noticeable than with tetracycline. At the end of the first week's treatment, 15 women had stopped taking the drug for this reason. A further 26 had defaulted, so that 64 were now available for study. Of these 64 women, 12 now yielded yeast isolates (19%); 10 of these were *C. albicans* and two were *T. glabrata*. Three of the 12 with positive cultures showed vulvovaginitis, as did two of 52 women with negative cultures.

Days after Treatment	No. Attending	No. with Positive Cultures	% Positive
0	105	13	13
7	64	12	19
14	48	14	29

Table III Vaginal yeast culture results before and after minocycline therapy

After the second week of observation three more women had stopped treatment because of side effects and a further 13 had defaulted, so that 48 were now available for study. Of these, 14 (29%) yielded yeasts on culture; nine of the patients yielded *C. albicans*, three *T. glabrata*, one *C. albicans* together with *T. glabrata*, and one *C. parapsilosis*. Of the 14 patients with vaginal yeasts, four had vulvovaginitis, as did one of 34 patients with negative cultures (table III).

The effect of minocycline on the vaginal yeast flora is summarized in table IV; the overall effects are similar to those of tetracycline. After one week's treatment 50 of 64 women (78%) remained yeast-negative and five (8%) remained yeast-positive; seven women (11%) initially yeast-negative were now yeast-positive and two (3%) had reverted from yeast-positive to yeast-negative. After two weeks' treatment 32 of 48 women (67%) remained yeast-negative and three (6%) remained yeast-positive since their first attendance. However, 11 patients (23%) who were free from yeasts before treatment now gave positive cultures and two (4%) had reverted from yeast-positive to yeast-negative.

Again only a minority of women who developed a drug-induced mycosis had any clinical evidence of infection.

Isolation Sequence	Period of Observation			
	1 week		2 weeks	
	No.	% of total	No.	% of total
Neg → Neg	50	78	32	67
Neg → Pos	7	11	11	23
Pos → Pos	5	8	3	6
Pos → Neg	2	3	2	4
Total	64		48	

Table IV Effect of minocycline on vaginal yeast flora

Discussion

The appearance of vulvovaginitis during tetracycline therapy is of clinical importance; for this reason, and because of the ease of collecting vaginal specimens for yeast culture, we chose this area for study rather than the anal canal favoured by other investigators (Smits, Prior, and Arblaster, 1966).

Yeast isolates from the vagina were obtained before treatment from 27 of 204 women (13%). The proportion of positive results was lower than in some other studies; for example, Oriol, Partridge, Denny, and Coleman (1972) recovered yeasts from 26% of a group of young women attending a department of venereology. This difference may be accounted for by variation in age, oral contraception and other factors which we did not investigate here. Like others (Oriol *et al.*, 1972; Hurley, Leask, Faktor, and de Fonseka, 1973), we found *T. glabrata* to be the second commonest yeast isolated after *C. albicans*.

Both tetracycline and minocycline appear to have a definite effect on yeast isolation, the isolation rate being approximately doubled after a two-week oral course. There was no significant difference between minocycline and tetracycline in this respect, and our hopes that minocycline might be less liable to cause yeast overgrowth were not fulfilled. Perhaps the effect of minocycline on commensal bacteria leading to an alteration in vaginal yeast flora is of more importance than any direct inhibitory action of the antibiotic against yeasts.

It was of interest that only a minority of patients in whom tetracyclines had apparently caused an overgrowth of yeasts exhibited clinical evidence of yeast infection. Similarly, other workers (British Tuberculosis Association, 1968) have found that the proliferation of *Candida* in the bowel following the administration of tetracycline makes little difference to the frequency of side effects; in this study *Candida* was grown from rectal swabs in 37 and 38% respectively of those with and without gastrointestinal symptoms. The reasons for the appearance of symptoms and signs of genital mycosis in only some patients harbouring yeasts are obscure at present, and it may well be that the factors affecting the appearance of actual clinical disease in these patients are quite different from those causing simple yeast overgrowth.

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