

Gentamicin in the treatment of gonorrhoea in females

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The increasing resistance of *Neisseria gonorrhoeae* to many antimicrobial agents demands a continual search for alternative drugs for its treatment. As more resistant strains emerge, it is conceivable that the required dose of penicillin, even with probenecid, will become too large to be acceptable. The aminoglycosides are among the potential alternatives. Kanamycin has already been shown to be efficacious in investigations by Wilkinson, Race, and Curtis (1967), Hooton and Nicol (1967), and Fischnaller, Pedersen, Ronald, Bonin, and Tronca (1968). Spectinomycin hydrochloride is also proving to be an acceptable alternative to penicillin. *Neisseria gonorrhoeae* has been shown by Finland (1969), Waitz and Weinstein (1969), and Phillips, Rimmer, Ridley, Lynn, and Warren (1970) to be susceptible *in vitro* to gentamicin at concentrations that are readily achieved *in vivo*. Felarca, Laqui, and Ibarra (1971), Siboulet (1972), and Hantschke, Strauss, Linzenmeier, Gahlen, and Heller (1973) have used gentamicin to treat gonorrhoea. In the present study, gentamicin was used successfully to treat females with gonococcal infection.

Material and methods

Women presenting at the Venereal Disease Clinic at the Winnipeg General Hospital with a history suggestive of gonorrhoea, contact with a known case of gonorrhoea, or a known positive cervical culture, had a cervical swab taken for smear and culture, and blood was taken for a VDRL. They were then given 240 mg. gentamicin intramuscularly as a single injection of 6 ml. into the upper outer quadrant of one buttock. No rectal or pharyngeal cultures were taken. Patients were then requested to return for follow-up cultures at 48 hrs, 5 days, and 12

days. At these times, patients were questioned about side-effects, symptoms, and sexual activity.

Cervical swabs were inoculated directly onto a split Thayer-Martin chocolate agar plate and incubated at 35°C. in 5 to 10 per cent. CO₂ for 48 hrs; the Thayer-Martin chocolate agar plate was then examined for oxidase-positive colonies containing Gram-negative diplococci. Such colonies were further identified by the fluorescent antibody technique and by sugar fermentations. 42 isolates were tested for sensitivity to penicillin, streptomycin, kanamycin, tobramycin, and gentamicin using Mueller-Hinton agar (Baltimore Biological Laboratory) with added Isovitalex to give final concentrations in a log₂ dilution series. Penicillin concentrations ranged from 0.005 to 100 i.u./ml., streptomycin from 0.04 to 100 µg./ml., kanamycin from 0.04 to 200 µg./ml., tobramycin from 0.004 to 50 µg./ml., and gentamicin from 0.04 to 25 µg./ml. The tests were performed with a Steers inoculum replicator, approximately 0.002 ml. being transferred as a spot inoculum. The plates were incubated in a CO₂ incubator at 35°C. and read after 24 hrs. The minimum inhibitory concentration of the antibiotic was accepted as the lowest concentration preventing visible growth.

Results

55 women with positive cultures were treated. Four did not return for follow-up. Three made only one follow-up visit at 72 hrs and all had negative cultures. All but six of the remaining 48 women returned twice or more and all 48 made at least one visit 4 or more days after treatment.

Four of the 48 with adequate follow-up had a positive culture after treatment:

(1) **A 23-year-old woman** had had intercourse after treatment with a partner with known gonorrhoea, and was positive on both Day 3 and Day 18 after therapy. After treatment of her consort and re-treatment of the patient with gentamicin, she was negative 15, 22, and 29 days later.

(2) **A 21-year-old woman** had had intercourse after treatment with a partner with known gonorrhoea and was positive on Day 11, but after further gentamicin and concurrent treatment of her consort she was negative 10 days later.

Received for publication September 17, 1973

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(3) A 16-year-old girl known to be promiscuous had a positive culture on Day 5.

(4) A 16-year-old girl had intercourse between follow-up visits; she had a negative culture on Day 3 but was positive on Day 9.

Before therapy, a number of women complained of burning on micturition. In all but one patient this cleared up promptly after treatment. Only one patient had a positive VDRL.

There were no significant side-effects. The women tolerated the injection very well with minimal pain.

The results of the sensitivity tests are shown in Fig. 1. Penicillin is not shown, but all strains were sensitive to 0.78 i.u./ml. or less. The sensitivity to gentamicin and tobramycin for 42 isolates was similar, with a range of 0.02 to 3.1 $\mu\text{g./ml.}$ (median 1.5) for gentamicin, and a range of 0.01 to 6.2 $\mu\text{g./ml.}$ (median 1.5) for tobramycin. 41 isolates were tested with kanamycin; the range was 0.19 to 12.5 $\mu\text{g./ml.}$ (median 6.2). The gonococcal isolates were divided into two populations on the basis of their susceptibility to streptomycin. 22 strains were sensitive to 25 $\mu\text{g./ml.}$ or less, while nineteen were inhibited only by 100 $\mu\text{g./ml.}$ or more.

Discussion

Gentamicin was successful in eradicating *Neisseria gonorrhoeae* from the cervixes of 44 (92 per cent.) of the 48 women who had an adequate follow-up. Of the four who at some time in the follow-up period had positive cultures, at least two (Cases 1 and 2) were almost certainly re-infected; they responded to gentamicin therapy when their consorts were treated concurrently. Patients 3 and 4 may have been treatment failures, although re-infection in both was possible. The finding of a negative culture on the

third post-treatment day and a positive culture on the ninth day is probably more suggestive of re-infection than relapse. Johnson, Kvale, Afable, Stewart, Halverson, and Holmes (1970) found that 21 of 22 failures were detected in the first 3 days.

Rectal cultures were not taken in this study. This would not obscure the diagnosis as only known cases are reported here, but failures can be missed if rectal cultures are not taken. Schroeter and Reynolds (1972) found that, in 908 women treated by a variety of regimens, treatment failed in 96 (10.6 per cent.), and 29 (30 per cent.) of these failures were detected only by rectal culture. They also found that patients with rectal, or rectal and cervical, gonorrhoea had higher failure rates than patients with cervical gonorrhoea alone.

Kanamycin sulphate may show an even greater discrepancy in the treatment of rectal gonorrhoea. Fluker and Hewitt (1970) found that 15.5 per cent. of ninety males with rectal gonorrhoea treated with 2 g. kanamycin failed to respond. On this regimen, only 3 per cent. failed out of 35 with urethral gonorrhoea alone. It is not known whether similar results are found with females or whether these findings apply to gentamicin.

Felarca and others (1971) treated 37 men with gonococcal urethritis with 280 mg. intramuscular gentamicin; there were no failures in 34 patients who returned for follow-up. Siboulet (1972) treated 105 men with 240 mg. gentamicin; twelve patients (11.4 per cent.) were treatment failures. Hantschke and others (1973) treated 48 females and fourteen males with gentamicin 5 mg./kg. body weight; this treatment failed in three women and one man (6 per cent.).

Serum levels were not measured in our study. Felarca and others (1971) checked the levels in eight

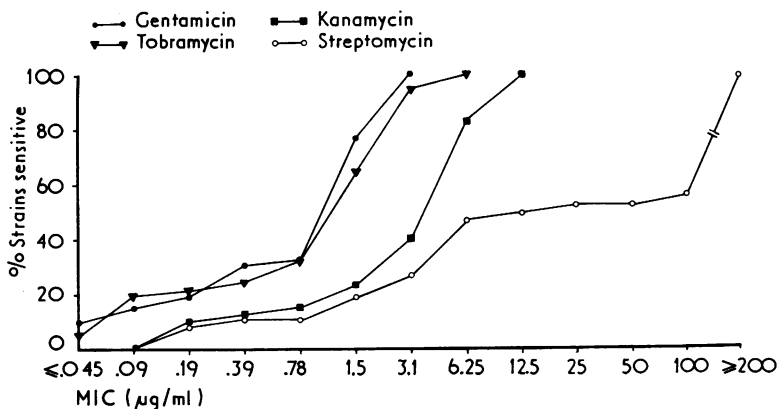


FIG. 1 Sensitivities of *N. gonorrhoeae* to gentamicin, tobramycin, kanamycin, and streptomycin in Mueller-Hinton agar (BBL) with Isovitalex

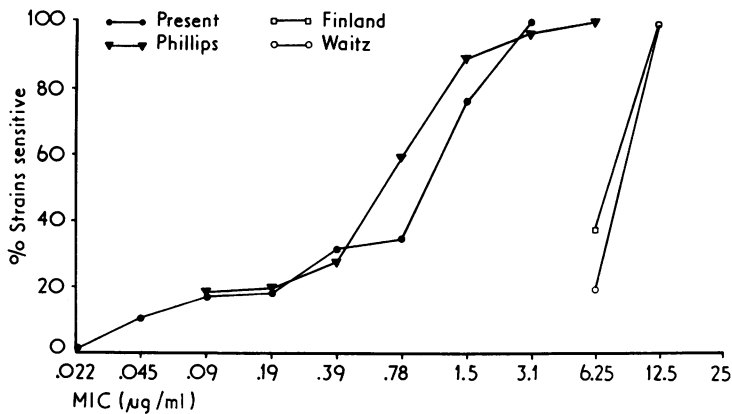


FIG. 2 Sensitivity of *N. gonorrhoeae* to gentamicin in this study and in the literature

patients; they had received doses of 3.61 to 5.71 mg./kg. and attained serum levels of 10.5 to 18.5 µg./ml. at 1 hr, 7.25 to 10.0 µg./ml. at 2 hrs, and minimal levels at 12 hrs. In five patients receiving 5 mg./kg. gentamicin, Hantschke and others (1973) noted mean levels of 24 µg./ml. at 1 hr and hardly measurable levels at 12 hrs.

The dose range in our study was 3.24 to 4.71 mg./kg. with a mean of 3.93 mg./kg. These amounts may be within the range in which ototoxicity could develop, but there is no evidence that a single peak serum level of 10–20 µg./ml. maintained for 1 to 2 hrs is toxic. None of our patients noted otological side-effects. However, careful vestibular and auditory studies of eighth nerve function were not carried out. Hantschke and others (1973) carried out such studies in all their 62 patients but did not find any evidence of ototoxicity.

Few studies have reported the sensitivity of *N. gonorrhoeae* to gentamicin (Fig. 2). Finland (1969) reported on 62 isolates gathered from several laboratories and noted that 37 per cent. were sensitive to 5 µg./ml. and that all were sensitive to 10 µg./ml. Waitz and Weinstein (1969) reported on 49 isolates tested by a tube-dilution method. Some of these isolates may have been included in Finland's study; 20 per cent. were sensitive to 5 µg./ml. and all to 10 µg./ml. Our results on Mueller-Hinton agar with added Isovitalex are very similar to the results of Phillips and others (1970) on Oxoid agar with added lysed horse blood. The median MIC of the 96 isolates tested by Phillips and others (1970) was 0.78 µg./ml., all being inhibited by 6.2 µg./ml. In the present study, the median MIC of the 42 isolates was 1.5 µg./ml., all being inhibited by 3.1 µg./ml.

The sensitivities to kanamycin and streptomycin *in vitro* are comparable with published data. The sensitivity to tobramycin *in vitro* was very similar to that of gentamicin.

There are few clinical situations in which gentamicin can be used, penicillin or penicillin derivatives being the agents of choice. In patients with penicillin allergy, spectinomycin is at present the best alternative (Pedersen, Wiesner, Holmes, Johnson, and Turck, 1972). However, gentamicin would be useful in patients with suspected concomitant syphilis as it would not mask the presence of the latter.

Gentamicin fulfils many of the criteria of a useful agent for gonorrhoea, but it is far from ideal. It is expensive and, despite the absence of significant overt side-effects in this study, the possibility of auditory and renal toxicity has not been excluded. It is effective, easily administered, and requires only a single dose. It does not eradicate incubating syphilis (Izzat, Smith, and Knox, 1972) and follow-up studies must include tests for syphilis.

Summary

Gentamicin, in a dose of 240 mg. intramuscularly, was used to treat 55 women with cervical gonorrhoea. Of the 48 who returned for adequate follow-up, 44 were considered to be cured. Of the four patients with recurrences, two were almost certainly re-infected. Thus, the success rate was at least 92 per cent.

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La Gentamicine dans le traitement de la gonococcie féminine

SOMMAIRE

La Gentamicine, à la dose de 240 mg intra-musculaire, a servi au traitement de 55 femmes présentant une gonococcie cervicale. Sur les 48 qui revinrent pour une surveillance appropriée, 44 furent considérées comme guéries. Chez les 4 malades ayant présenté une reprise, 2 furent presque certainement réinfectées. Ainsi, le taux de succès fut au moins de 92 pour cent.