

Gentamicin in the treatment of gonococcal urethritis

A microbiological, pharmacological, and clinical study

G. D. MORRISON*

Department of Venereology, United Bristol Hospitals

AND

D. S. REEVES

Department of Microbiology, Southmead Hospital, Bristol

Gentamicin is an aminoglycoside antibiotic complex derived from two species of *Micromonospora* (Weinstein, 1967). It is chemically similar to neomycin and kanamycin. It is not significantly absorbed from the gastrointestinal tract but intramuscular injections are reported to give peak blood levels within 1 hour with a dose-dependent duration of detectable levels for 6 to 12 hours (Black, Calesnick, Williams, and Weinstein, 1963). The main side-effects are ototoxicity involving the vestibular apparatus, which is largely dose related (Cox, 1970; Jackson and Arcieri, 1971), and, rarely, nephrotoxicity (Falco, Smith, and Arcieri, 1969).

A report by Izzat, Smith, and Knox (1972) confirming work by Holzmann, Tupath-Barniske, and Morsches (1969) showed that gentamicin had no effect on *Treponema pallidum*. When this study was begun in April, 1971, no reports had been published in Great Britain on the treatment of gonorrhoea with gentamicin.

Since this time, however, Siboulet (1972), Felarca, Laqui, and Ibarra (1971), and Hantschke, Strauss, Lenzenmeier, Gahler, and Heller (1973) have reported series from France, the Philippines, and Germany respectively. Theoretically, gentamicin should be a useful addition to the non-treponemidal antibiotics active against the gonococcus, and we considered that a trial of the drug would be of interest.

Clinical methods

85 male patients with acute uncomplicated gonococcal urethritis attending the Bristol venereal diseases clinic between April, 1971, and November, 1972, were treated with gentamicin. The first 39 in the series were given an intramuscular injection of 120 mg. gentamicin on two successive days; the subsequent 46 were given one single injection of 240 mg.

Their ages ranged from 16 to 60 years (average 26.3). 64 patients were from the United Kingdom, sixteen from the West Indies, four from Eire, and one from Cyprus. There was a previous history of sexually acquired disease in 24. The duration of the discharge varied from 1 to 28 days (average 4.4).

The initial diagnosis was made by finding intracellular Gram-negative diplococci in a smear of the urethral discharge. A swab of the discharge was collected into Cooper's transport medium (Cooper, Mayr-Harting, and McLachlan, 1950) and sent to the Public Health Laboratory. Cultural confirmation of the diagnosis was made in 65 (76.5 per cent.) patients; this low rate was later found to be due to the transport medium which has now been replaced by Stuart's medium.

Every patient had routine serological tests for syphilis performed, and only in one West Indian patient were they positive.

Of the first series of 39 patients, 35 had blood taken for gentamicin assay 1 hour after either the first or second injection. Of the second series of 46 patients, 22 had samples of blood taken at varying times after the injection. Assays were performed by the Microbiological Laboratory of Roussel Laboratories Ltd. and by the Department of Microbiology, Southmead Hospital, Bristol.

Each patient had a repeat urethral swab and smear taken 1 week after treatment; at subsequent visits a smear was taken if any discharge was present. Not all patients attended for the full follow-up period (see Tables I and II).

Laboratory methods

Swabs were plated on chocolate agar and a selective medium containing vancomycin, colistin, and nystatin. Presumptive colonies of *Neisseria gonorrhoeae* were identified by biochemical reactions. Isolates of *N. gonorrhoeae*, both from the patients treated with gentamicin and from other male and female patients attending the Bristol Clinic, were tested in

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*Present address: Plymouth General Hospital, Plymouth

pure culture to determine their sensitivity to gentamicin. Gentamicin sulphate was diluted in Oxoid diagnostic sensitivity test agar containing 5 per cent lysed horse blood to give final concentrations in 2 ml. slopes of 0.1, 0.2, 0.4, 0.6, 0.8, 1 and 2 $\mu\text{g./ml.}$ Three colonies from each isolate of *N. gonorrhoeae* were suspended in 2 ml. saline, 0.02 ml. of this suspension being put on to a slope of each concentration of gentamicin and on to a purity plate of a similar agar containing no gentamicin. Incubation was at 37°C. in an atmosphere of 5 per cent. CO_2 for 48 hrs. The minimum inhibitory concentration (MIC) of gentamicin was taken as the lowest concentration of drug at which no growth occurred.

Sera for *gentamicin assay* were tested by a method described elsewhere (McLaughlin and Reeves, 1971; Reeves, 1972).

Results

Tables I and II show that the failure rate among those who attended for follow-up in each series was fairly high, four out of 38 (10.5 per cent.) and six out of forty (15 per cent.) respectively. Eight of the failures were diagnosed in the first week, one in the

second, and one in the third week after treatment. In half of the failures, cultures as well as smears were positive.

Sensitivity tests

The sensitivities of the strains of *N. gonorrhoeae* to gentamicin are shown in Table III. All were sensitive to 2 $\mu\text{g./ml.}$ or less.

Serum levels

35 samples of serum taken 1 hour after an intramuscular injection of 120 mg. gentamicin were available for assay. The mean concentration was 6 $\mu\text{g./ml.}$ (S.D. 1.2 $\mu\text{g./ml.}$) with a range of 4.1 to 9.6 $\mu\text{g./ml.}$ No significant difference was found between samples taken after the first injection of 120 mg. (11 samples, mean 6.1 $\mu\text{g./ml.}$) and those taken after a second injection at least 12 hrs later (24 samples, mean 6 $\mu\text{g./ml.}$).

22 samples of serum were available for assay after a single intramuscular injection of 240 mg. gentamicin. A single sample was taken from each patient but at different times in an attempt to discover the time of 'peak' serum concentration of the drug. The results are shown in Table IV (opposite).

TABLE I *Follow up and results in patients treated with two injections of 120 mg. gentamicin*

Days	No. followed	Satisfactory	NGU	Re-infection	Relapse
0	39	—	—	—	—
1-7	38	7	5	2	3
8-14	21	1	1	0	1
15-21	18	0	2	0	0
22-28	16	2	2	0	0
29-35	12	2	0	0	0
36-42	10	1	1	2	0
43-90	6	6	0	0	0
Total	38	19	11	4	4

TABLE II *Follow up and results in patients treated with one injection of 240 mg. gentamicin*

Days	No. followed	Satisfactory	NGU	Re-infection	Relapse
0	46	—	—	—	—
1-7	40	7	0	0	5
8-14	28	2	1	1	0
15-21	24	2	3	1	1
22-28	17	1	0	0	0
29-35	16	1	0	1	0
36-42	14	1	2	0	0
43-90	11	9	1	1	0
Total	40	23	7	4	6

TABLE III *Minimum inhibitory concentrations of gentamicin for N. gonorrhoeae*

MIC ($\mu\text{g./ml.}$)	0.1	0.2	0.4	0.6	0.8	1.0	2.0	Total tested
No. of isolates	6	3	16	22	1	12	5	65

TABLE IV Serum gentamicin concentrations ($\mu\text{g./ml.}$) after an intramuscular dose of 240 mg.

Time since dose (min.)	No. of observations	Mean value	S.D.	Range
11-15	4	7.1	1.0	6.2-8.3
16-30	11	10.2	2.1	6.1-12.6
31-45	6	10.9	2.5	7.2-14.5
67	1	11.3	—	—

Discussion

A comparison with the other non-treponemicidal drugs which may be used to treat gonorrhoea is shown in Table V. Our results are similar to those of other workers using gentamicin in the same dosage, although Felarca and others (1971) have claimed a higher cure rate using a single dose of 280 mg. gentamicin and Hantschke and others (1973) a cure rate of 94 per cent. using a single injection of 5 mg./kg. There is no apparent reason for the relatively poor results obtained, particularly in comparison with the other aminoglycoside, kanamycin. Gentamicin is excreted by glomerular filtration and there seems no practical way of prolonging its action apart from repeated injections.

Our findings on the sensitivity of *N. gonorrhoeae* to gentamicin are in accord with those of other workers. Klein, Eickhoff, and Finland (1964) examined thirteen strains finding a median value of 0.8 $\mu\text{g./ml.}$, while Phillips, Rimmer, Ridley, Lynn, and Warren (1970) found a median value of 1.56 $\mu\text{g./ml.}$ with a range of <0.09 to 6.2 $\mu\text{g./ml.}$ among 96 strains. Waitz and Weinstein (1969) found higher values for 49 strains, only 20 per cent. being inhibited by 5 $\mu\text{g./ml.}$ gentamicin. The reasons for this discrepancy are not apparent. It would certainly appear that the majority of our strains were sensitive to gentamicin at a concentration easily attainable in the blood of patients.

Although a great deal of information on the pharmacology of gentamicin has been published, little is known of the blood levels attained after such large single doses given to adults. In a small number of patients receiving 240 or 280 mg. intramuscularly (3.61 to 5.71 mg./kg.), Felarca and others (1971) found mean gentamicin serum levels of 14.0 $\mu\text{g./ml.}$ at 30 min., 13.1 $\mu\text{g./ml.}$ at 60 min., and 8.1 $\mu\text{g./ml.}$

at 120 min. after injection. Our own results suggest a mean peak value of rather less (Table IV), but are similar with regard to the timing of the rise. The similarity of mean serum levels at 30 and 60 min. in their results, and for the time periods 16-30 and 31-45 min. in our results, suggests that either the dose response curve is very flat or there is wide variation in the timing of the peak. Personal observations favour the latter, as do the results of Hantschke and others (1973), although Riff and Jackson (1971) have suggested that some patients may have a flat response curve.

Assuming the half-life of gentamicin to be about 2 hrs in patients with normal renal function, then the blood gentamicin concentration would be above the highest MIC of any of our strains of *N. gonorrhoeae* (i.e. 2 $\mu\text{g./ml.}$) for approximately 3 hrs after doses of 120 mg. and for 5 hrs after doses of 240 mg.

Although we did not attempt to detect objectively any ototoxicity caused by gentamicin, published evidence suggests that it should not arise when only one or two doses of this size are given. Senra del Valle, Imbrogno, and Fernandez (1969) gave 4 to 6 mg./kg. daily to children with no ill effects, while Wersall, Lundquist, and Bjorkroth (1969) were of the opinion that levels of 12 $\mu\text{g./ml.}$ in the blood were acceptable provided the drug was rapidly excreted and that the dose was not repeated. These clinical observations fit in well with experimental observations of animals which show that diffusion of aminoglycoside antibiotics into the perilymph and endolymph of the inner ear is slow (Stupp, Rauch, Sous, and Lagier, 1966). Clinical studies with streptomycin also suggest that ototoxicity depends mainly on the more prolonged 'trough' levels rather than on transitory 'peak' levels. (Line, Poole, and Waterworth, 1970).

TABLE V Comparison of results with other non-treponemicidal drugs

Drug	Authors	Date	No. in series followed	Failure rate per cent.
Cotrimoxazole	Evans, Churcher, and Human	1972	101	18
Kanamycin	Wilkinson, Race, and Curtis	1967	341	2-3
Rifampicin	Willcox, Morrison, and Cobbold	1970	89	11.2
Gentamicin 240 mg.*	Siboulet	1972	105	11.4
Gentamicin 240 mg.*	Felarca and others	1971	45	15.5
Gentamicin 240 mg.*	Present series		40	15.0

*Single injection

Conclusions

As an acceptable cure rate seems to require even larger doses than we used, gentamicin should not be considered a first-line or even a second-line drug in the treatment of gonorrhoea, except in patients with a possible concomitant early syphilitic lesion.

Summary

85 male patients with acute uncomplicated gonorrhoea were treated with intramuscular injections of gentamicin. In 38 patients followed after being given 120 mg. on two successive days, the failure rate was 10.5 per cent. and in forty patients followed after a single injection of 240 mg. the failure rate was 15 per cent.

Serum levels of gentamicin 1 hour after an intramuscular injection of 120 mg. showed a mean of 6 µg./ml.

An attempt was made to find the timing of the peak level after a single injection of 240 mg. gentamicin.

Minimum inhibitory concentrations of gentamicin for 65 strains of gonococci both from patients in the trial and from other patients were determined. Most were sensitive to less than 1 µg./ml. and none required more than 2 µg.

The results are compared with those obtained using other non-treponemicidal antibiotics.

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Traitement de l'urétrite gonococcique par la gentamicine: étude microbiologique, pharmacologique et clinique

SOMMAIRE

85 hommes atteints de gonococcie aiguë non compliquée furent traités par des injections intra-musculaires de gentamicine. Chez les 38 malades suivis après avoir reçu 120 mg deux jours consécutifs, le taux d'échec fut de 10,5 pour cent et chez les 40 malades suivis après avoir reçu une seule injection de 240 mg, le taux d'échec fut de 15 pour cent.

Une heure après une injection intra-musculaire de 120 mg, le taux sérique de gentamicine s'établit à une moyenne de 6 µg/ml.

On s'efforça de déterminer le moment du taux maximal après une injection unique de 240 mg de gentamicine.

Les concentrations minima inhibitrices de gentamicine furent déterminées pour 65 souches de gonocoques provenant soit des malades du présent essai, soit d'autres malades. La plupart des souches furent sensibles à moins de 1 µg/ml, et aucune n'exigea plus que 2 µg.

Les résultats sont comparés avec ceux obtenus avec d'autres antibiotiques non tréponémicides.