A RATIONAL BASIS FOR THE TREATMENT OF GONORRHOEA

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The world-wide recrudescence of gonorrhoea calls for a critical review of all methods of control of dissemination of the disease. Not least of available methods is adequate treatment. Determining the best antibiotic and its dosage can be based on clinical response to currently used antibiotic schedules or it can be based on laboratory studies or both.

In Singapore 600,000 units of P.A.M. (Procaine Penicillin in aluminium monostearate) in one injection for men was replaced in 1969 by a routine dosage of 1·2 mega units of aqueous procaine penicillin. A review of 97 consecutive cases of gonorrhoea in men treated with the schedules showed a failure rate of between 14-25%. The deteriorating clinical response rates prompted the present study.

MATERIALS AND METHODS

During late January and early February, 1970 specimens of pus were obtained from 112 men with acute urethral gonorrhoea. Carbon impregnated swabs were used (Stuart *et al*, 1954). All swabs were placed in individual stoppered plastic (polymopyline) tubes and immediately stored in a Linde liquid nitrogen container (Union Carbide Coy. U.S.A.). Experiments (Reyn, A. personal communication) had shown that controlled rate freezing as used by Brookes and Hedin (1966) was unnecessary. When collection was completed the specimens were flown in the liquid nitrogen container to the World Health Organization International Reference Centre for Gonococci, Neisseria Department, Statens Serum Institut, Copenhagen, Denmark.

On arrival the stoppering of six tubes had "blown". Of the remaining 106 swabs 104 gave positive cultures.

Sensitivity testing against nine anti-bacterials was carried out on all strains. In the case of penicillin, streptomycin, tetracycline, spiramycin and rifampicin plate dilution methods were used (Reyn *et al*, 1963). In the case of sulphathiazole, chloramphenicol, kanamycin and nalidixic acid a disc diffusion method was used (Thomsen, 1962).

RESULTS

Table I shows sensitivity of Singapore's gonococcal population to nine antibacterial drugs. Erythromycin testing was omitted as results are known to correspond very closely to spiramycin findings.

Results from the plate dilution methods are given in micrograms per millilitre as 50% inhibitory concentration (IC_{50}). The minimum inhibitory concentration (MIC) is about twice the IC_{50}. (Reyn *et al*, 1963). The results from the diffusion procedures are given as sensitive, moderately sensitive, less sensitive and resistant. The relation of these degrees to IC_{50} is shown in the legend to Table I.

Eight of the 104 Singapore strains were duplicates, that is, a specimen was taken at the initial visit of the patients and again when they returned showing failure to respond to treatment. The figures in brackets in Table I and II give the results for the 96 unselected strains. The unbracketed figures are the mixed strains. Of special note in Table I is the high percentage of strains relatively insensitive to penicillin and resistant to streptomycin. Cross resistance is marked between the two and other broad spectrum antibiotics.

In Table II these results are compared with those of 43 strains from the Far East examined in 1967/68. These were mixed strains (Reyn, 1969). The latter findings resemble those of more recent studies of other Far East gonococci (Reyn, personal communication). Also compared are the findings in 96 London strains (Philips *et al*, 1970). In the case of rifampicin 100 strains were examined by Philips *et al*. The same applies to erythromycin. Findings with the latter are set alongside spiramycin results. In the last eighteen months in Singapore spiramycin has enjoyed increasing popularity for the treatment of gonorrhoea by private practitioners. Other oral broad spectrum antibiotics have been widely used in varying dosage schedules for some years.

The case notes of the men concerned in the present study were reviewed.

Of 96 cases 26 (27%) failed to respond to the primary treatment employed. The details of all failures are set out in Table III.

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TABLE I

SENSITIVITIES OF 104 MIXED STRAINS* OF GONOCOCCI FROM SINGAPORE – EXAMINED FEBRUARY - MARCH 1970

Antibiotic	Method	Definition of Sensitivity	Sensitive	Moderately Sensitive	Less Sensitive	Resistant
Penicillin	Plate dilution (4 fold dilution steps)	IC_{50} 0·088 IU/ml. (0·053 mcg./ml.) or less less sensitive	14(14)*	Nil	90(82)	Nil
Streptomycin	One plate 25 mcg. ml.	IC_{50} is 25 mcg./ml. or more resistant	33(32)	Nil	Nil	71(64)
Tetracycline	Plate dilution (4 fold dilution steps)	IC_{50} is 1·13 mcg./ml. or more less sensitive	42(42)	Nil	62(54)	Nil
Spiramycin	Plate dilution (4 fold dilution steps)	IC_{50} is 1·13 mcg./ml. or more less sensitive (Arbitrary value)	38(37)	Nil	66(59)	Nil
Rifampicin	Plate dilution (4 fold dilution steps)	IC_{50} is 0·25 mcg./ml. or more less sensitive (Arbitrary value)	41(40)	Nil	63(56)	Nil
Sulphathiazole	Disc diffusion 238 mcg. in disc. See leged below		93(89)	8(4)	2(2)	1(1)
Chloramphenicol	Disc diffusion 50 mcg. in disc	IC_{50} is 0·25 mcg./ml. or more less sensitive (Arbitrary value)	63(53)	40(42)	1(1)	Nil
Kanamycin	Disc diffusion 50 mcg. in disc	IC_{50} is 0·25 mcg./ml. or more = less sensitive (Arbitrary value)	17(16)	79(73)	8(7)	Nil
Nalidixic Acid	Disc diffusion 50 mcg. in disc	IC_{50} is 0·25 mcg./ml. or more — less sensitive (Arbitrary value)	104(96)	Nil	Nil	Nil

Zone diameters used to judge sensitivity.	Sulphathiazole	Chloramphenicol	Nalidixic Acid	Kanamycin
Sensitive	<5·0	<1·0	<4·0	<4·0
Moderately Sensitive	⩾5·0 - 15·0	⩾1·0 - 5·0	⩾4·0 - 10·0	⩾4·0 - 15·0
Less Sensitive	>15·0 - 100·0	5·0 - 50·0	10·0 - 25·0	>15·0 - 50·0
Resistant	>100·0	>50·0	>25·0	>50·0

*Figures in brackets concern 96 unselected strains.

TABLE II

COMPARISON OF SINGAPORE SENSITIVITY SPECTRUM COMPARED WITH SIMILAR STUDIES

	104 (96)* Singapore strains. % less sensitive or resistant 1970	43 mixed Far East** strains. % less sensitive or resistant 1967/1968	96 mixed London† strains. % less sensitive or resistant
Penicillin	87(84)	90·7	40
Streptomycin	70(65)	79·1	33
Tetracycline	57(55)	74·4	30
Spiramycin	63(62)	79·1	1[1]
Rifampicin	60(58)	Not done	20
Sulphathiazole	2(3)	Nil	55[2]
Chloramphenicol	1	Nil	Nil
Kanamycin	7	Nil	7
Nalidixic Acid	Nil	Nil	Nil

1 Erythromycin. 2 Sulphamethoxazole.
*104 mixed and 96 unselected strains.
**Reyn, A. (1969) Bull. Wld. Hlth. Org., 40, 257.
†Philips *et al*, 1970.

Ten patients were treated with 600,000 units of P.A.M. and 7 (70%) failed to respond.

Sixty-one patients received 1·2 mega units of aqueous procaine penicillin as primary treatment. Thirteen (21%) failed to respond. In addition 10 patients received this schedule as second line treatment and 5 (50%) failed to respond satisfactorily.

Where 2·4 mega units of aqueous procaine penicillin was used as second choice, that is in 9 cases, it failed once. It was given in 4 cases which had failed to respond to 1·2 mega and itself failed once.

Benzyl penicillin, 5 mega units was primary choice in 14 cases. There was one failure.

Eleven patients received other antibiotics for reasons including penicillin sensitivity and drug trials.

Table IV shows that of the 70 patients who responded to primary treatment 49 (70%) were infected with strains in the less sensitive, or more resistant range. That is they required serum levels

TABLE III

TREATMENT FAILURES — 26 OF 96

Patient's No.	Treatment	Failure Diagnosed-Days After Treatment	Re-Treatment	Response to Re-Treatment	Remarks
357/70	600,000 units P.A.M.*	2	2·4 mega Aq. P.P.**	Satisfactory	Later reinfection
704/70	600,000 units P.A.M.*	1	1·2 mega Aq. P.P.	Failed (4 days)	
			2·4 mega Aq. P.P.	Satisfactory	
828/70	600,000 units P.A.M.*	2	2·4 mega Aq. P.P.	Satisfactory	
4323/69	600,000 units P.A.M.*	23	1·2 mega Aq. P.P.	Unknown	Doubtful failure
8842/69	600,000 units P.A.M.*	3	1·2 mega Aq. P.P.	Satisfactory	
342/70	600,000 units P.A.M.*	16	1·2 mega Aq. P.P.	Satisfactory	
3514/64	600,000 units P.A.M.*	9	1·2 mega Aq. P.P.	Failed (9 days)	Later reinfection
			Tetracycline mgs. 250 qds. × 4 days	Satisfactory	
2802/69	1·2 mega Aq. P.P.	10	2·4 Aq. P.P.	Satisfactory	Later reinfection
284/70	1·2 mega Aq. P.P.	7	1·2 Aq. P.P.	Failed (9 days)	
			2·4 Aq. P.P.	Satisfactory	
323/70	1·2 mega Aq. P.P.	6	2·4 Aq. P.P.	Failed (3 days)	
			Tetracycline mgms. 250 qds. × 3 days	Failed (5 days)	
			Tetracycline mgms. 500 qds. × 5 days	Failed (5 days)	
			Spiramycin mgm. 250 qds. × 5 days	Failed (5 days)	
			Gabromicina*** 1 gm. I m. × 3 days	Satisfactory	Later reinfection
1020/69	1·2 mega Aq. P.P.	2	2·4 Aq. P.P.	Satisfactory	
887/70	1·2 mega Aq. P.P.	2	2·4 Aq. P.P.	Satisfactory	
896/70	1·2 mega Aq. P.P.	2	2·4 Aq. P.P.	Satisfactory	
2947/67	1·2 mega Aq. P.P.	16	Tetracycline mgms. 500 qds. × 3 days	Satisfactory	Doubtful failure
317/70	1·2 mega Aq. P.P.	9	2·4 Aq. P.P.	Satisfactory	
327/70	1·2 mega Aq. P.P.	9	1·2 Aq. P.P.	Failed (3 days)	
			2·4 Aq. P.P.	Satisfactory	
589/70	1·2 mega Aq. P.P.	9	2·4 Aq. P.P.	Satisfactory	
1154/68	1·2 mega Aq. P.P.	4	2·4 Aq. P.P.	Satisfactory	Later reinfection
1096/70	1·2 mega Aq. P.P.	9	2·4 Aq. P.P.	Failed (9 days)	
			Archromycin mgms. 250 qds. × 5 days	Satisfactory	
10369/68	1·2 mega Aq. P.P.	6	2·4 Aq. P.P.	Satisfactory	
B.M.H. 11	5 mega units Benzyl Pen.****	7	Kanamycin 2 gms. i.m.	Satisfactory	Doubtful failure
B.M.H. 10	Kanamycin 2 gms. i.m.	3	Kanamycin 2 gms. i.m.	Satisfactory	
9419/68	Tetracycline mgms. 250 qds. × 3 days	2	1·2 Aq. P.P.	Failed (3 days)	
			2·4 Aq. P.P.	Failed (3 days)	
			Tetracycline mgm. 500 qds. × 2 days	Satisfactory	
876/70	Vibramycin mgms. 300 stat.	3	1·2 Aq. P.P.	Satisfactory	
1080/70	Vibramycin mgms. 300 stat.	7	1·2 Aq. P.P.	Satisfactory	
B.M.H. 17	Kanamycin	2	Kanamycin 2 gms. i.m.	Satisfactory	

* P.A.M. = Procaine Penicillin in aluminium monostearate.

** Aq. P.P. = Aqueous Procaine Penicillin.

*** Gabromicina (Farmatilia) is Aminosidine sulphate.
It is a member of the Streptomycin/Kanamycin group of antibiotics.

**** Crystalline Benzyl Penicillin.

TABLE IV

PENICILLIN SENSITIVITY FINDINGS IN 96 UNSELECTED STRAINS
— 26 TREATMENT FAILURES AND 70 REMAINDER

	0.007-0.053 0.011-0.088	0.075-0.150 0.125-0.25	0.30 0.50	0.47 0.71	0.6 1.0	0.71 1.19	0.85 1.41	1.0 1.68	1.20 2.0	1.42 2.38	mcg./ml. iu./ml.
Failures (26)	2947/67 (0·38-0·063)	Nil	8842/69 317/70 327/70*	4323/69	Nil	2802/69 284/70*	B.M.H. 11 B.M.H. 17 323/70*† 589/70 896/70 1096/70	B.M.H. 10 3514/64* 1154/68 342/70 828/70	357/70 704/70* 876/70 887/70 1080/70	9419/66* † 10369/68 1020/69	
	1	Nil	3	1	Nil	2	6	5	5	3	
Remainder (70)	21	17	7	1	2	1	10	7	4	Nil	
Cumulative Failures* † (33)	1	Nil	4	1	Nil	3	7	6	6	5	

* Failed with 1·2 mega Aqueous Procaine Penicillin as second choice of treatment.

† Failed with 2·4 mega Aqueous Procaine Penicillin as second and third choice of treatment.

of 0·075 mcg./ml. (0·125 iu./ml.) or more of penicillin. Of the 26 failures 25 (96%) were in the less sensitive range. If the sensitivity level 0·71 mcg./ml. or above is taken the correlation between clinical failure and sensitivity determination is even more marked. Twenty-one (81%) of the failures were in this less sensitive range compared with only 22 (31%) of the 70 in the remainder of the series.

DISCUSSION

The facts presented in Table I underline the dynamically progressive nature of increasing penicillin resistance. Also emphasised is the development of cross resistance. For example, 64 (66%) of 96 unselected strains were completely resistant to streptomycin, whereas of 82 strains selected as less sensitive to penicillin, 71 (86·6%) were completely resistant to streptomycin. There is little doubt that in terms of cure rates the effectiveness of treatment as a gonorrhoea control measure shows a deteriorating situation.

Table II gives some measure of this when London and Far East strains are compared with those in Singapore. The London study (Philips *et al*, 1970) also shows a lesser degree of cross-resistance between penicillin and other anti-bacterials than does the other two studies. More recent studies of Far East strains, from Penang and Saigon confirm the 1967-68 findings (Alice Reyn, personal communication). Singapore's findings fall between those of Far East and London with a marked bias towards the Far East spectrum. Singapore is therefore in a marginally favourable position to benefit from any rationally based schedule of therapy and this applies both to the individual patient and epidemiologically. In other words high cure rates may halt the dangerous trends in resistance and cross resistance.

Table III shows the degree of inadequate dosage in individual clinical terms. Table IV sets out the reasons why the schedules were inadequate. There is a well defined correlation between clinical failure and lessened penicillin sensitivity.

The questions therefore arise. What is the ideal antibiotic in the Singapore situation and what should its dosage be?

The ideal antibiotic in gonorrhoea should be such that it can be given in one dose at the time of diagnosis. It should be cheap and safe. It should be so effective as to offer 100% chance of cure even where gonococci of a relatively marked degree of resistance are circulating. It is not yet possible to meet all these criteria by orally administered dosages of any broad spectrum antibiotic. Oral antibiotics in multiple dosage have many serious shortcomings (Morton in the press).

Olsen and Lomholt (1970) working in Greenland changed the schedule of their penicillin routine in gonorrhoea from a mixed penicillin (benzyl, procaine and benzathine penicillins) to a single injection of 5 mega units of benzyl penicillin given in 8 ml. of 0·5% lidocaine. To maintain the high serum concentration, kidney excretion of the drug was delayed by giving 1 gm. of probenecid half an hour before the "one shot" therapy. Cure rates rose to nearly 100%. All the criteria of the ideal treatment were met. Furthermore the incidence of relatively penicillin resistant strains fell from 54% to 19% in Greenland. Over 200 men and women have now been treated with this regime in Singapore with all but 100% success. The dosage used, the serum levels attained and the maintenance of these by probenecid more than matches the sensitivity of local gonococci. The new regime meets all the criteria of the ideal treatment.

It is planned to repeat the sensitivity survey in a year or so. Clearly the more widely the new regime is employed in public, forces and private sectors the more certainly will the present dangerous trends be halted and the dissemination of relatively resistant strains be reduced.

SUMMARY AND CONCLUSIONS

This study shows a correlation between failures from inadequate antibiotic therapy in gonorrhoea and the antibiotic sensitivity of locally circulating gonococcal strains.

The situation in terms of the latter in the Far East gives cause for serious concern. In the same terms Singapore has a slight advantage. A potentially alarming situation could be forestalled.

A scientifically based "one shot" schedule of treatment meeting all the criteria of the ideal therapy is already proving itself highly effective in the individual and is recommended for use wherever possible.

Used on a wide scale it could have epidemiological advantages and make a substantial contribution and the control of gonorrhoea not only in Singapore but in the Far East generally.

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