

COMPARATIVE EFFICACY OF PENICILLIN AND DOXYCYCLINE IN GONOCOCCAL URETHRITIS

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Ninety two episodes of gonococcal urethritis treated with one of the following regimens viz : (A) 3 m. u. of fortified procaine penicillin, made by adding 1 m. u. of crystalline penicillin to 2 m. u. of fortified procaine penicillin, intramuscularly with one gram of probenecid orally, (B) 3 m. u. of above fortified procaine penicillin intramuscularly alone, and (C) 400 mg single oral dose of doxycycline produced success rates of 95, 76.2 and 66.7% respectively. Post-gonococcal urethritis was detected in 37% patients. Thirty four (45.94%) of the 74 isolates of *N. gonorrhoeae* were relatively resistant (MIC > 0.12 unit/ml) to penicillin. None of the 74 *Neisseria gonorrhoeae* strains was beta-lactamase producing.

Key words : Gonorrhoea, Treatment, Fortified procaine penicillin, Doxycycline.

Gonorrhoea is reported to be the commonest of sexually transmitted diseases in the world today.¹ Since its introduction in 1940s, penicillin was the mainstay of therapy for gonorrhoea. However, because of rapidly changing antibiotic susceptibility of *Neisseria gonorrhoeae*, increasing relative resistance to penicillin² and emergence of penicillinase producing *Neisseria gonorrhoeae* (PPNG) infections,³ it is imperative to reassess the role of penicillin and look for alternative chemotherapeutic agents for the treatment of gonorrhoea.

Materials and Methods

Male patients with acute, uncomplicated gonococcal urethritis who had not taken any antibiotic or chemotherapeutic agent for a minimum of 2 days before reporting were included in this study. Patients were assigned at random to one of the following schedules of treatment : (A) 3 m.u. of fortified procaine penicillin, made by adding 1 m.u. of crystalline penicillin to 2 m.u. of fortified procaine penicillin giving the final dose of 1.5 m.u. each of procaine and crystalline penicillin, intramuscularly after

a test dose, preceded half an hour earlier by 1 gm probenecid orally, (B) 3 m.u. of above fortified procaine penicillin without probenecid, (C) doxycycline 400 mg in single oral dose. Before the institution of therapy urethral exudate was collected for smear and culture for *N. gonorrhoeae*. Only the patients who showed Gram-negative intracellular diplococci of classical morphology were included. Subsequently, patients were followed on day 3, 7 and 14 following treatment. Patients were instructed to refrain from indulgence in sexual activity and alcohol in any form, and to come for examination holding urine for a minimum period of three hours. On every visit an enquiry was made about the symptoms, and any further sexual exposures, and the patients were examined for the type of urethral discharge, and smear and culture was taken for *N. gonorrhoeae*. Blood for VDRL test was also collected in all the cases. The material for culture was directly inoculated on modified Thayer-Martin medium⁴ and plates were incubated at 37°C in a candle extinction jar for 24 to 48 hours. *N. gonorrhoeae* was identified by colony characteristics, oxidase and sugar fermentation tests. Susceptibility of *N. gonorrhoeae* to penicillin and doxycycline was determined by the plate dilution and the disc diffusion techniques, respectively. WHO

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reference strain VII was used as control. A zone of inhibition measuring more than 19 mm was recorded as sensitive, between 15-18 mm as partially sensitive and less than 14 mm as resistant to doxycycline. The penicillinase production was checked in all the isolates by the rapid iodometric technique.⁵

The patients in whom smear and culture for *N. gonorrhoeae* did not become negative in 48 hours following treatment, or the smear and/or culture for *N. gonorrhoeae* became again positive after it had become negative once, during the 14-day follow-up without a history of further exposure, were designated as treatment failures. And the patients in whom smear and/or culture which had become negative once, became positive again within 14 days and who gave history of further exposure were considered as reinfection. The patient in whom smear and/or culture became negative in 48 hours and remained so for a period of 14 days following treatment were considered to be cured. The post-gonococcal urethritis was suspected in patients in whom meatal inflammation persisted after 7 days and on day 14 the smear and culture for gonococci were negative and smear showed more than 10 pus cells per high power field, a diagnosis of post-gonococcal urethritis was made.

Results

Eighty three male patients were included in this study. Two of these patients had three episodes each and five had two episodes each making a total of 92 episodes of gonococcal urethritis. Seventy six (91.5%) of the 83 patients were between 20-39 years of age, and 51 (61.4%) were unmarried. In majority (86.98%) of the episodes, professionals were the source of infection, and 3.25% patients had acquired infection after homosexual exposures. Most of the patients (80.4%) reported within 10 days of onset of symptoms. Incubation period of less than five days was recorded in 58.7% and 6-10 days in 28.9% cases.

Results of therapy with different schedules of treatment are shown in table I. Of the 74 isolates of *N. gonorrhoeae* which were tested for susceptibility to penicillin, 45.94% were relatively resistant (MIC>0.12 units/ml) (Table II) to penicillin. All but one strain of *N. gonorrhoeae* were sensitive to doxycycline and one was partially sensitive. Serology for syphilis was negative in all the patients.

Table I. Results of therapy with different schedules of treatment.

Schedule of treatment	Number of cases			
	Treated	Followed-up	Cured %	PGU (%)
A	34	21	19 (95.0)	8 (42.1)
B	27	22	16 (76.2)	4 (25.0)
C	31	21	14 (66.7)	6 (42.8)

Table II. Susceptibility of 74 isolates of *N. gonorrhoeae* to penicillin.

MIC (unit/ml)	Number	(%) of sensitive strains
0.03	12	(16.22)
0.06	14	(18.92)
0.12	14	(18.92)
0.25	14	(18.92)
0.50	11	(14.86)
1.00	5	(6.76)
2.00	2	(2.70)
4.00	2	(2.70)
Total	74	(100.00)

Comments

Procaine penicillin has conventionally been recommended in dosage of 2.4 or 4.8 m.u. for the treatment of uncomplicated gonococcal urethritis. A failure rate of 15.4% was obtained in our clinic with 2.4 m.u. of procaine penicillin.⁶ Hence, the dosage of penicillin was increased to 3 m.u. as there is step-wise increase in the resistance of *N. gonorrhoeae* to penicillin.²

In the present study, failure rate with penicillin plus probenecid was 5%. Similar results have been reported by other workers.⁷⁻⁹ Holmes et al⁷ and Rajan et al⁹ reported failure rates of 2.9 and 4.0% respectively employing 2.4 m.u. of procaine penicillin with probenecid. Rajan et al⁹ reported 100% cure rate with 3.0 m.u. of procaine penicillin with probenecid. Thin⁸ reported a failure rate of 4.2% employing Distraquine fortified (1.8 m.u. procaine penicillin with 0.6 m.u. of crystalline penicillin) with probenecid.

With penicillin alone our failure rate was 23.8%. Holmes et al⁷ obtained failure rate of 29.0% employing 2.4 m.u. of procaine penicillin alone, and Kandhari et al⁶ had reported a failure rate of 15.4% with 2.4 m.u. of procaine penicillin alone, suggesting that 3.0 m.u. of procaine penicillin alone is not adequate for New Delhi males. The only failure given 3 m.u. procaine penicillin with probenecid was in a patient who had acquired the infection in Bangkok and the strain of *N. gonorrhoeae* isolated from him had MIC of 4 units/ml. However, it was not penicillinase producing *N. gonorrhoeae*.

Doxycycline has generally been used as 300-400 mg in a single oral dose. Failure rates of 0-40% have been reported with 300 mg doxycycline.^{10,20} Equally varying failure rates (5.0%¹⁰ and 53.0%¹⁸) have been reported with 400 mg doxycycline also. In the present study, a failure rate of 33.3% was obtained with 400 mg doxycycline and hence it cannot be recommended.

There was a relatively high incidence of post-gonococcal urethritis (PGU) in this study viz. 42.1, 25.0 and 42.8% with penicillin with probenecid, penicillin alone and doxycycline respectively compared to the reported incidence of 0-17% PGU by other workers.^{9,12,15} Hence, it is essential that the patients of gonorrhoea should be carefully followed up and investigated for PGU.

In the present study, 74 strains of *N. gonorrhoeae* were isolated and 34 (45.95%) were relatively resistant to penicillin. Nine strains had MIC > 1 unit/ml. However, none of the strains produced beta-lactamase. Relative resistance to penicillin reported from different parts of India has been in 43.12%²³ and 90%²¹ isolates in Madras, 52.1% in Kerala,²² 56% in Bombay,²³ 34% in Poona²⁴ 50.5% in New Delhi²⁵ and in 64% isolates in Chandigarh.²⁶

All but one strain of *N. gonorrhoeae* were sensitive to doxycycline. Steenbergen¹² from Netherlands found all but one strain sensitive to doxycycline in a study of 132 cases by disc diffusion method. Moffett et al²⁷ in United Kingdom found all 144 strains sensitive to doxycycline. However, no consistent correlation in vitro sensitivity and therapeutic response was seen. In five out of the six failures to doxycycline, the isolated strains of *N. gonorrhoeae* were fully sensitive to it. Similar findings were reported by Steenbergen¹² and Oller et al.¹⁵ Since majority of strains of *N. gonorrhoeae* isolated even in failures were sensitive to doxycycline, the drug given over 2-3 days in a twice a day schedule should be more effective and needs evaluation.

Though there are stray reports of penicillinase producing gonococci in India,^{26,28,29} the exact incidence of PPNG infections is not known and procaine or crystalline penicillin in doses varying from 3 to 5 m.u. with probenecid remains the first line of therapy in gonorrhoea.

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