# Treatment of Gonorrhoea

## —The Role of Spectinomycin—

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**Because of increasing resistance of circulating *N. gonorrhoeae* and frequent failures in the treatment of gonorrhoea, intensive work on gonorrhoea has become of paramount importance.**

**During January 1980—April 1984, at the Choong-Ku VD Clinic in Seoul, 3,340 male patients with uncomplicated gonococcal urethritis were treated with various treatment regimens. Diagnosis of gonorrhoea and declaration of a treatment failure were made on the basis of positive urethral culture.**

**In 1984, the prevalence of Penicillinase Producing *N. gonorrhoeae (PPNG)* was about 30%, The pretreatment minimun inhibitory concentration of various antibiotics were quite high. Even for non-PPNG urethritis standard penicillin regimens gave unsatisfactory results. For PPNG urethritis, only spectinomycin, cefoperazone and cefotaxim-probenecid regimens gave satisfactory results. No spectinomycin resistant strain of *N. gonorrhoeae* has been found since 1982 at the Choong-Ku VD Clinic.**

**As an agent of single drug therapy, spectinomycin seems to be one of the most cost effective drugs in the treatment of uncomplicated gonorrhoea in men. (Ann Dermatol 1:69-72, 1989)**

*Key Words:* Gonorrhoea, PPNG, Spectinomycin, Treatment of gonorrhoea

In the face of decreasing susceptibility of *Neisseria gonorrhoeae* to penicillins and many of other antibiotics[1-3] and the high prevalence of Pencillinase Produciong *N. gonorrhoeae* (PPNG) among isolates in many parts of the world,[3] including Korea,[4] spectinomycin has gained more importance in the treatment of gonorrhoea. In 1982, we reported a case of spectinomycin resistant PPNG.[5] We report herein the treatment results of uncomplicated gonococcal urethritis in men with various regimens and the result of screening tests for spectinomycin resistant *N. gonorrhoeae*.

Received November 16, 1988
Accepted for publication August 4, 1989

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This work has been supported in part by a grant from WHO-WP.

## MATERIALS AND METHODS

### *Patients*

Male patients who visited the VD Clinic of Choong-Ku Public Health Center in Seoul, between January 1980 and April 1984, for suspected gonorrhoea were the source of the study. Informed consent was obtained from the patients. For study purposes, the diagnosis of gonorrhoea was made on the basis of urethral smears which showed positive cultures and a history of no subsequent therapy. Only those patients with uncomplicated urethritis were included in the study. A total of 3,340 patients entered the study and 2,437 patients were followed. In age distribution of the patients, an exception was a man aged 70. The age of the rest of patients ranged from 17 to 59 with a mean of 25.8 and a median of 25. 78.5% of patients belonged to 19 to 28 age group.

### *Laboratory tests*

Before treatment, a specimen obtained from the

urethra with a cotton tipped wooden stick was Z-streaked immediately onto the Thayer-Martin media, kept in a candle jar and, within 2 hours, cross streaked and incubated in a candle jar at 36°C for 20-48 hours. Positive oxidase reaction on colonies with typical morphology, composed of Gram negative diplococci, was taken as sufficient evidence of *N. gonorrhoeae*.[6] For detection of beta-lactamase produced by colonies, the chromogenic cephalosporin method was used.[7]

The agar plate dilution method[8] was used for estimation of minimum inhibitory concentration (MIC) for various antibiotics on 121 strains at the Department of Dermatology, Hanyang University Medical College in collaboration with Dr. Kisung Lee, Department of Biology, College of Natural Science, Hanyang University. Disk pre-diffusion method[9] was used on all strains isolated from August 1984 to May 1985 to screen out strains resitant to spectinomycin. Disks containing 100 mcg of spectinomycin were used for study. Strains with inhibition zone greater than 18mm were considered susceptible.

### *Treatment*

Various treatment regimens were tried, some as open treatment trials, some as randomized, comparative trials.

### *Follow-up study*

The patients were instructed to abstain from sexual intercourse and alcoholic beverages and not to use any antibiotic or antibacterial agent until the end of the follow-up period. The patients were asked to return in 3 to 5 days to have a test of cure, culture and Gram stain of urethral smear. The patients of the initial study group who returned for re-examination 3 to 5 days after the treatment, in whom the result of the test of cure culture could be obtained, comprised the final study population in each trial.

If, at the follow-up study visit, the urethral smear showed no Gram negative diplococci and the cultural results were negative, the patient was considered to be cured. Any patient showing Gram negative diplococci on urethral smear or positive cultural result was regarded as a treatment failure, provided that the patient had not had sexual contact since treatment.

## RESULTS

### *Prevalence of PPNG*

The prevalence of PPNG among the pretreatment isolates was very high. In 1984, 214 (27%) of 791 strains of *N. gonorrhoeae* isolated at the VD Clinic, Choong-Ku Public Health Center in Seoul were PPNGs, a slight decrease from 30.9% in 1982 (Table 1).

### *Susceptibility pattern*

$MIC^{90}$ of various antibiotics is shown in Table 2. Most values are high. Spectinomycin resistant strains were screened on all isolates at the Choong-Ku VD Clinic from August 27, 1984, to May 28, 1985. All of 126 PPNGs and 186 Non-PPNGs were found to be susceptible to spectinomycin by disk pre-diffusion method (Table 3).

**Table 1.** Prevalence of PPNG among isolates at the Choong Ku VD Clinic (1981–1984)
No. of PPNG/No. of isolates

| Year | Jan | Feb | Mar | Apr | May | June | July | Aug | Sep | Oct | Nov | Dec | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 81 | 1/80 | 2/40 | 4/63 | 3/63 | 13/93 | 14/88 | 18/93 | 27/84 | 27/60 | 21/80 | 35/82 | 32/73 | 197/899 |
| | 1.3 | 5.0 | 6.4 | 4.8 | 14.0 | 15.9 | 19.4 | 32.4 | 45.0 | 26.3 | 42.9 | 43.9 | 21.9(%) |
| 82 | 19/77 | 37/69 | 31/69 | 31/98 | 16/57 | 28/94 | 19/69 | 21/86 | 19/72 | 25/76 | 21/64 | 16/58 | 283/916 |
| | 24.7 | 53.6 | 32.3 | 31.6 | 28.1 | 29.8 | 27.5 | 24.4 | 26.4 | 32.9 | 32.8 | 27.4 | 30.9(%) |
| 83 | 20/67 | 26/69 | 21/60 | 9/49 | 16/52 | 16/71 | 17/79 | 14/49 | 14/55 | 5/30 | 14/53 | 6/45 | 178/679 |
| | 29.9 | 37.7 | 35.0 | 18.4 | 30.8 | 22.5 | 21.5 | 28.6 | 25.5 | 16.7 | 26.4 | 13.3 | 26.2(%) |
| 84 | 14/57 | 21/58 | 21/81 | 16/53 | 25/81 | 17/69 | 12/68 | 17/68 | 9/45 | 12/46 | 27/91 | 23/74 | 214/791 |
| | 24.6 | 36.2 | 25.9 | 30.2 | 30.9 | 24.6 | 17.6 | 25.0 | 20.0 | 26.1 | 29.7 | 31.1 | 27.1(%) |

PPNG: Penicillinase-Producing *Neisseria gonorrhoeae*

**Table 2.** Pretreatment $MIC_{90}$ of *N. gonorrhoeae* (Sep. 1982–Mar. 1984) (mcg/ml)

| Antibiotics | Beta-lactamase + | Beta-lactamase − |
|---|---|---|
| Penicillin | >32 | 8 |
| Ampicillin | >32 | 4 |
| Tetracycline | 8 | 8 |
| Thiamphenicol | 4 | 2 |
| Spectinomycin | 16 | 16 |
| Cefobid | 0.25 | 0.25 |
| S/A | 4 | 2 |

S/A: Sulbactam/ampicillin

**Table 3.** Spectinomycin susceptibility pattern of *N. gonorrhoeae* (Aug. 1984–May 1985)
Disk content: 100mcg No. of strains

| Betalactamase | Tested | Susceptible >18mm | Resistant <18mm |
|---|---|---|---|
| Positive | 126 | 126 | 0 |
| Negative | 186 | 186 | 0 |

### *Treatment results with various regimens*

***1) Non-PPNG urethritis:*** The treatment results of non-PPNG urethritis with various regimens are shown in Table 4. Most of regimens did not give satisfactory results including standard penicillin-probenecid regimens. The aqueous procaine penicillin G, 4.8 million units, IM plus probenecid, lg, PO regimen gave a 14.0% failure rate, fortified procaine penicillin G, 4.8 million units, IM plus probenecid, lg, PO regimen resulted in 11.3% failures, fortified procaine penicillin G, 6 million units, IM plus probenecid, lg, PO regimen resulted in 11.7% failures and a regimen of probenecid, lg, PO plus aqueous crystalline penicillin G, 4.0 million unit, s IM, twice, with a 4 hour interval, resulted in 5.8% failures while spectinomycin, 2g, IM gave only a 1.5% failure rate.

***2) PPNG urethritis:*** The treatment results of PPNG urethritis with various regimens are shown in Table 5. Here the results were more disappointing. However, the cefoperazone, lg, IM regimen and cefotaxim, lg, IM plus probenecid, lg, PO regimen resulted in no failures. The sulbactam/ampicillin, 1 to 2 vials, IM plus probenecid, lg, PO regimen gave a 2.2% failure rate.

**Table 4.** Treatment regimens used for uncomplicated male non-PPNG urethritis (Jan. 1980–April 1984)
No. of patients (percentage)

| Regimen | Followed | Failed |
|---|---|---|
| APPG, 4.8 mega u. IM/BEN, 1g, PO | 291 | 39(14.0) |
| FPPG, 4.8 mega u. IM/BEN, 1g, PO | 124 | 14(11.3) |
| FPPG, 6.0 mega u. IM/BEN, 1g, PO | 495 | 58(11.7) |
| ACPG, 4 mega u. IM/BEN 1g, PO | 108 | 22(20.4) |
| BEN, 1g, PO/ACPG, 4 mega u. IM then 4 hours later, ACPG, 4 mega u. IM | 171 | 10(5.8) |
| AMP, 3.5g, PO/BEN, 1g, PO | 87 | 16(18.4) |
| Peracillin, 2g, IM/BEN, 1g, PO | 59 | 13(22.0) |
| Talampicillin, 2.5g, PO/BEN, 1g, PO | 43 | 11(25.6) |
| Kanamycin, 2g, IM | 316 | 58(18.4) |
| Gentamicin, 160mg, IM | 45 | 23(51.1) |
| Tetracycline, 0.5g, PO×4/D×5 | 51 | 40(78.4) |
| Thiamphenicol, 2.5g, PO | 108 | 38(35.2) |
| BEN, 1g, PO/cefadroxil, 2g, PO then 4 hours later, cefadroxil, 2g, PO | 48 | 11(22.9) |
| Spectinomycin, 2g, IM | 68 | 1( 1.5) |

BEN: Probenecid
APPG: Aqueous procaine penicillin G
FPPG: Fortified procaine penicillin G
ACPG: Aqueous crystalline penicillin G
AMP: Ampicillin

**Table 5.** Treatment regimens used for uncomplicated male PPNG urethritis (Jan. 1981–April 1984)
No. of patients (percentage)

| Regimen | Followed | Failed |
|---|---|---|
| FPPG, 4.8 mega u. IM/BEN, 1g, PO | 58 | 58(100.0) |
| FPPG, 6.0 mega u. IM/BEN, 1g, PO | 49 | 47(95,9) |
| BEN, 1g, PO/ACPG, 4 mega u. IM then 4 hours later, ACPG, 4 mega u. IM | 14 | 14(100.0) |
| Kanamycin, 2g, IM | 129 | 35(27.1) |
| Gentamicin, 160mg, IM | 10 | 7(70.0) |
| Chloramphenicol, 2g, PO | 38 | 32(84.2) |
| Cefotaxim, 1g, IM/BEN, 1g, PO | 34 | 0( 0.0) |
| Cefoperazone, 0.5g, IM | 29 | 2( 6.9) |
| Cefoperazone, 1g, IM | 42 | 0( 0.0) |
| Thiamphenicol, 2.5g, PO | 44 | 25(56.8) |
| Spectinomycin, 2g, IM | 33 | 2( 6.1) |
| BEN, 1g, PO/cefadroxil, 2g, PO then 4 hours later, 4 mega u. PO | 19 | 4(15.8) |
| Sulbactam/AMP*, 1-2 vials, IM/BEN, 1g, PO | 45 | 1( 2.2) |

*: Sulbactam, 0.5g plus ampicillin, 1g

## DISCUSSION

In the treatment of gonorrhoea, the single visit, on the spot treatment is preferred.[1,11] Over the years, penicillins have long enjoyed the place of the first choice despite the decreasing sensitivity of *N. gonorrhoeae* to this drug.[1,2,12,13] However, the emergence and rapid spread of PPNG changed the situation, especially in developing countries, particularly, in Far-East Asia.

The sudden and steep rise of prevalence of PPNG in Korea experienced in 1981 had alarmed all concerned.[4] A strain of spectinomycin resistant PPNG, isolated by us in 1982,[5] caused a great fear that it might be the signal of an end of the spectinomycin era. But, up to now, we have not experienced any more spectinomycin resistant cases and the screening tests we performed on strains isolated at the Choong-Ku VD Clinic did not disclose any strain which is resistant to spectinomycin. The overall failure rate of the spectinomycin, 2g, IM regimen in the treatment of uncomplicated male gonococcal urethritis was 3.0% (3/101), which is in accord with the result obtained by Finger.[14]

In an area where pencillin and other inexpensive drug regimens give unsatisfactory results, spectinomycin may be used as the first line treatment regimen for uncomplicated genital gonorrhoea. The price of spectinomycin, 2g in Korea, as of March 1985, is ₩5,500 or US$6.47, which may not be cheap but is not as expensive as some of other drugs which are effective for both PPNG and non-PPNG urethritis.

In view of above observations, it is clear that spectinomycin, 2g, IM is one of the best regimens in the treament of uncomplicated gonococcal urethritis and, as of 1985, one of the most cost effective single drug regimens in the treatment of gonorrhoea.

## REFERENCES

1. World Health Organization Technical Report Series 616: *Neisseria gonorrhoeae and gonococcal infections. World Health Organization Geneva 1978: 77-61.*
2. Reyn A: *Antibiotic sensitivity of gonococcal strains isolated in the South-East Asia and Western Pacific Regions in 1961-68. Bull WHO 40: 257-262, 1969.*
3. Perine PL, Marton RS, Piot P: *Epidemiology and treatment of penicillinase producing Neisseria gonorrhoeae. Sex Trans Dis 6 (Suppl): 103, 1979.*
4. Kim JH, Junn JW, Chun JH, Hong SW: *Sudden spread of Penicillinase Producing Neisseria gonorrhoeae (PPNG) in Korea. J Korean Med Assoc 25: 163-169, 1982.*
5. Kim JH, Han GC, Hong SW, Junn JW: *Spectinomycin resistant penicillinase producing Neisseria gonorrhoeae. J Korean Med Assoc 25: 1117-1120, 1982.*
6. Martin JE, Armstrong JH, Smith PB: *New system of cultivation of Neisseria gonorrhoeae. Apll Microb 27: 802-805, 1974.*
7. Thornsberry C: *CDC Laboratory update (CDC-78-42). Detection of penicillinase producing Neisseria gonorrhoeae. U.S. Department of Health Education, Welfare. Public Health Service. Centers for Disease Control, Atlanta, 1982.*
8. Reyn A: *Drug susceptibility pattern of Neisseria gonorrhoeae. a world-wide review. Asian J Infect Dis 1: 1-14, 1977.*
9. Kirby WMM, Yoshihara GM, Sundested KS, Warren JH: *Clinical usefulness of a single disc method for antibiotic sensitivity testing. Antibiot Annual 1956-57, p 892.*
10. Lind I: *WHO Collaborating Centers for Reference and Research on Gonococci (Copenhagen). Personal communication.*
11. Brando FN: *Single dose treatment of gonorrhoes. Lancet 2: 885, 1972.*
12. Kim YT, Kim JH, Choi YK: *The sensitivity of Neisseria gonorrhoeae to antibiotics and its relationship to the treatment results. J Hanyang Med Coll 4: 425-443, 1984*
13. Neu HC: *Penicillins. In Kagan BM (ed): Antimicrobial Therapy. 3rd ed, WB Saunders Co, pp 20-34, 1980.*
14. Finger AH: *Spectinomycin in the treatment of gonorrhoea in females and males. Brit J Vener Dis 51: 38, 1975.*