Cefuroxime and Post-Gonococcal Urethritis

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A recent clinical trial by Fowler and Rahim in Birmingham involving over 500 cases has shown that 1 g i.m. of cefuroxime is highly effective in the treatment of gonorrhœa, with a cure rate of 98%. Side-effects were minimal, but as with most *one shot* treatments for gonorrhœa (Table 1) there was a high incidence of post-gonococcal urethritis (PGU) in males. Fluker & Price (1977) verified these findings and in an attempt to reduce the incidence of PGU, increased the dose of cefuroxime to 1.5 g and administered 1 or 2 g of probenecid at the same time. They found that this treatment was remarkably successful in reducing the incidence of PGU.

As previous experience with penicillin had indicated that a massive increase in the amount of antibiotic combined with probenecid had, at best, only a slight beneficial effect on the incidence of PGU (Hare *et al.* 1969), the findings of Fluker & Price (1977) were unexpected and merited further study. It seemed reasonable, in the first place, to see if the incidence of PGU could be reduced simply by increasing the amount of cefuroxime to 1.5 g. The results of this trial are reported here. These are preliminary findings since a substantial number of cases have not yet completed the observation period.

Post-gonococcal urethritis presents in one of two ways:

(1) Signs of urethritis persist for longer than 7 days after treatment despite the eradication of the gonococcus. In the majority of males, following successful treatment, the symptoms and signs of urethritis disappear within a few days and resolution of the inflammatory process is complete within 7 days.

Table 1

Incidence of post-gonococcal urethritis with *one shot* treatment for gonorrhœa

Year	*Treatment*	*Total cases treated*	*Total cases cured (excluding reinfections)*	*PGU (% cases)*
1973	Spectinomycin 2 g	331	284	13.3 (38)
1974	Procaine penicillin 1.8 Mu	170	127	14.1 (18)
1975/6	Doxycycline 300 or 400 mg	296	219	14.6 (32)
1976	Minocycline 300 mg	191	140	15 (21)
1976/7	Cefuroxime 1 g	375	329	16.7 (55)

(2) Signs of urethritis clear completely within 7 days but recur later, on average after about 3 weeks. In this instance, as in the previous one, exhaustive investigation shows that the gonococcus is not involved.

The ætiology of PGU is uncertain but is widely believed to be of an infectious nature. On occasions, *Trichomonas vaginalis* and, more rarely, the *Herpes simplex* virus Type II can be isolated from the urethra, and presumably are responsible for the inflammatory process. In the majority of cases, no recognized pathogens can be recovered from the lower genito-urinary tract. However, the administration of a wide spectrum antibiotic 2–3 days after penicillin therapy for gonorrhœa produces a 75% reduction in the incidence of PGU (Fowler 1976), suggesting that these cases are due to some infection.

Possible infections responsible for PGU include T-strain mycoplasma (Csonka *et al.* 1966) and *Chlamydia trachomatis* (Richmond *et al.* 1972). Most of the evidence produced so far indicates that it is unlikely that T-strain mycoplasma has any ætiological significance (Hare *et al.* 1969, Fowler & Leeming 1967). It is more probable that *Chlamydia trachomatis* plays a major role in the production of PGU but as yet substantial proof of this is lacking.

It is also widely believed that the infection responsible for PGU is contracted at the same time as the gonorrhœa. However, this is not necessarily so, since Mahoney *et al.* (1946) saw PGU develop in cases infected experimentally with gonorrhœa and under conditions which made it extremely unlikely that another infection could have been introduced. It would seem that if PGU is always due to infection, at times this infection must have been present in the urethra when the gonorrhœa was acquired.

Trial Design

One hundred and fifty-one men suffering from gonorrhœa were treated with one i.m. injection of cefuroxime, 1.5 g. None of the cases had been treated previously for this present infection nor gave any history of sensitivity to the cephalosporins. Apart from this, cases were selected only in so far as those patients who were known from past experience to default immediately after treatment for gonorrhœa were excluded from the trial.

The diagnosis was based on the presence of Gram negative diplococci morphologically identical to gonococci in films of the urethral discharge and/or of gonococci cultured on modified Thayer-Martin medium. Films and cultures were examined in every case. Treatment was given immediately if the microscopic evidence was indicative of infection.

Follow-Up

Patients were asked to refrain from alcohol and sexual intercourse for at least 2 weeks after the signs of urethritis had cleared and to return for examination 2–3 days after treatment, then 7 days later and finally at intervals of 14 days, 4 weeks and 8 weeks. At the initial follow-up visit any urethral discharge present was examined in films and cultures. If there was no obvious urethral discharge films and cultures were taken from urethral scrapings. On subsequent visits tests were not taken for bacteriological examination unless the history, clinical examination or examination of the urine suggested that the urethritis was still present.

Results

Of the 151 patients treated, 24 did not return for further examination while another 5 had to be removed from the trial since they had inadvertently been given prophylactic treatment for PGU 3 days after cefuroxime.

In the 122 patients followed there was one definite treatment failure and 8 cases which were considered to be reinfections. Three of these had negative tests for gonococci at the first follow-up examination, while another had negative tests at both first and second follow-up visits. These cases presented again with acute gonorrhœa 12 or more days after their last visit. All gave a history of exposure to reinfection. The other cases did not attend for the first or second follow-up examination. In these cases the condition had apparently cleared following treatment and recurred after re-exposure to infection.

Post-gonococcal urethritis developed in 18 (15%) of the 113 cases in which the gonococcal infection responded satisfactorily to cefuroxime therapy and there was no reappearance of the infection during the follow-up period.

Discussion

There is little need to discuss these findings at length. The efficacy of cefuroxime in gonorrhœa is confirmed. It would seem that a simple increase in the dose of cefuroxime has no effect on the incidence of PGU. It remains to be seen whether the addition of probenecid can effectively reduce this incidence.

Finally it should be mentioned that in this clinic the incidence of PGU following penicillin therapy increased by 6% between 1970 and 1974. The slight increase in the incidence of PGU following spectinomycin therapy in 1973 and that with cefuroxime in 1977 (Table 1) might well be a natural phenomenon and not attributable to treatment.

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DISCUSSION

Professor W Brumfitt (*London*) asked Dr Moberg what dosage and route she had employed.

Dr Moberg said that 1 g of cefuroxime in water had been given in the upper lateral quadrant of the buttock, together with 1 g of probenecid orally.

Dr Percival (*Chairman*) said that it was clear from the data presented that cefuroxime *in vitro* was more active than benzylpenicillin against strains relatively insusceptible to the latter. It was clear from Dr Thornsberry's findings that of the 4 cephalosporins which were not inactivated by β-lactamase, cephexalin, cephradine, cefoxitin and cefuroxime, the last named was the most active, being at least 10 times more active than cefoxitin. This was true both for strains positive and negative for penicillinase.

As to treatment, Dr Fowler had reported good cure rates with 1 g cefuroxime without probenecid. Dr Fluker had used higher doses together with probenecid. His own observations had involved 10 women and 4 men who had been completely cured of their β-lactamase producing gonococcus by 1 g of cefuroxime i.m. without probenecid. This included 3 negative follow-ups with rectal cultures in the women. Cefuroxime at a dose of 1 g would therefore eradicate gonococci even from the rectum.

Dr O V Renkonen (*Helsinki*) asked what effect cefuroxime had on oral gonococcal strains.

Dr A J Evans (*Plymouth*) had 2 patients with positive throat infections both of whom responded to 1 g of cefuroxime plus 1 g of probenecid with negative throat cultures afterwards.

He asked for any comparative figures between penicillin and cefuroxime with regard to the incidence of post-gonococcal urethritis. He had

been treating gonorrhœa on alternate days either with cefuroxime and probenecid or with penicillin and probenecid and had found a significantly higher incidence of post-gonococcal urethritis in cases treated with cefuroxime.

Dr Percival (*Chairman*) said that MIC values for *Chlamydia trachomatis* were very high for cefuroxime, in the order of 200 μg/ml, whereas for benzylpenicillin they were 0.1 and for cephaloridine 1.0. A small number of patients with *Chlamydia* infections would therefore be cured by the traditional *one-shot* penicillin treatment but not by cefuroxime. This suggested that cefuroxime either did not penetrate inside mammalian cells very well or that having penetrated it was unable to pass through the matrix surrounding the *Chlamydia*. This finding might be relevant to the question of non-gonococcal urethritis.

Dr Percival repeated that investigators in London, including Dr Oriel, had shown in an *in vitro* system that *Chlamydia* was relatively insusceptible to cefuroxime although penicillin G and cephaloridine were active against it and *Chlamydia* did have a peptidoglycan in their cell wall.

Professor W Brumfitt (*London*) asked why it was possible to eliminate the gonococcus from the throat with a single dose of cefuroxime whereas to eliminate the β-hæmolytic *Streptococcus* group A which was sensitive to 0.01 μg/ml of penicillin it was necessary to continue treatment for 10 days.

Dr L D Sabath (*Minneapolis*) said that this question was fundamental to the therapy of bacterial infection. The effective cure of pharyngitis or any other infection due to β-hæmolytic *Streptococcus* group A was related to the time necessary to eradicate the organism, 10 days. These organisms were unusual in their susceptibility to β-lactam antibiotic in that they were killed without lysis. Gonococci on the other hand were lysed even more rapidly than pneumococci and it was necessary to have the drug present for only a few hours, possibly even 1 h in treating gonococcal urethritis. The difference was not therefore a question of MIC of the organism. It depended on the growth phase of the organisms, and on the entirely different complex of autolytic enzymes in gonococci and streptococci.

Dr Percival (*Chairman*) said that serotyping of pneumococci had shown that these organisms also persisted in the throat after 5-day courses of penicillin, although they had autolytic enzymes.

Dr L D Sabath (*Minneapolis*) said the same was true for the *Meningococcus* and it was well known that penicillins were not an appropriate choice for eradicating these organisms.

Dr Percival (*Chairman*) made several additional remarks. First, spectinomycin which was effective against β-lactamase producing gonococci was known not to abort incubating syphilis in experimental animals and in man. If it were used in the Far East as a primary drug it was possible that syphilis might increase. It had not yet been shown, but one might expect that cefuroxime would be cidal against *Treponema pallidum* and therefore have a comparative advantage.

Second, he wished to consider the so-called resistance to tetracyclines. There were strains that had β-lactamase that were also relatively insusceptible to tetracycline, with MIC values of 1.0–2.0. This was unusual in Liverpool, in non-β-lactamase producing gonococci, but it had been associated with a significant failure of treatment. Even when tetracycline had been given at a dose of 500 mg 6 hourly for 5–7 days there had been a 30% failure rate when the MIC was 1.0–2.0. He noticed from Dr Thornsberry's figures that penicillinase producing strains from the Far East with MIC values of 2–4 were showing a failure rate of 40%. In his view this had important implications for antimicrobial chemotherapy overall. The phenomenon may not be universal, but even a slight shift in the MIC could be significantly associated with higher failure rate when the margin between the blood level and the MIC was critical. In the Liverpool patients on tetracyline therapy, the blood level rarely exceeded 2 μg/ml. This was the sensitivity level associated with a higher failure rate.

Dr Thornsberry concluded by describing the recommendations of the Venereal Disease Control Divison of the Centre for Disease Control, Atlanta, Georgia for the treatment of gonorrhœa. They believed that the incidence of resistant strains was so low in the United States that they had not changed the basic recommendation that gonorrhœa should be treated with 4.8 million units of procaine penicillin with 1 g of probenecid. It was recommended that follow-up cultures should be taken and if there were failure the recommendation was to treat with spectinomycin because the latter had been effective in treating failures due to β-lactamase. He believed that if his patients had contacts with individuals known to have β-lactamase producing gonococci then they should be treated with 2 g spectinomycin.