Treatment of Females with Acute Gonorrhœa using Cefuroxime

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Gonorrhœa has shown a continuous increase in most parts of the world for the last decade and that in spite of an effective and cheap treatment such as benzylpenicillin. Although in the late 1960s there were many reports of an increasing number of isolates of *Neisseria gonorrhœæ* which were less sensitive to penicillin (that is with an MIC of 0.6–2.0 μg/ml) this was never considered as a very serious threat, since it was possible in most cases to treat the patients harbouring these strains with higher doses of penicillin or with prolonged therapy. The standard treatment for the last 8–10 years in many parts of the world has been ampicillin or its derivatives by the oral route.

In 1971, when it was recommended by the National Board of Health and Welfare in Sweden that ampicillin might be used as an alternative to benzylpenicillin, it was feared (at least by microbiologists) that an oral treatment for gonorrhœa might lead to the development of more resistant strains. This, however, has not happened as can be seen from the cumulative percentage of the sensitivity to ampicillin as determined by the disc diffusion method over the years 1971–1976. The treatment with a single oral dose of 2 g ampicillin plus probenecid has been reported to produce a cure rate of over 98% in Sweden (Eriksson *et al.* 1972).

In March 1976, the first reports on β-lactamase producing gonococci appeared, almost at the same time from Liverpool (Percival *et al.* 1976) and from the United States (MMWR 1976). In Sweden during the last year we have isolated β-lactamase producing gonococci from 7 patients, 1 of whom had contracted gonorrhœa in Ghana, 2 in Bangkok and 2 in the Philippines. Two were secondary cases.

This threat of a wide-spread occurrence of β-lactamase producing gonococci focused interest on alternative drugs. One such drug is cefuroxime which is not inactivated by the β-lactamase in question and to which most strains of *Neisseria gonorrhœæ* are highly sensitive. The clinical results so far have also been favourable, but in the trials reported at the time that the present study was started, they had involved a dosage too large to be given in one injection. It thus seemed desirable to learn if it was possible to cure women with uncomplicated gonorrhœal infection with a single injection of, for example, 1 g. A study on cefuroxime in the treatment of gonorrhœa was therefore started in the summer of 1977 at the Out-patient Clinic for Venereal Diseases at St Goerans Hospital, Stockholm.

In 1976, about 6000 new patients were examined for gonorrhœa and 1900 were treated for the disease at this clinic.

They are representative of metropolitan patients in that many neglect follow-up examinations or may wait several weeks before coming to the first follow-up. A proportion of patients are addicts of alcohol and narcotics and many had been previously treated for gonorrhœa on one or more occasions. The present therapy for uncomplicated gonorrhœa is 1.4 g of pivampicillin with 1 g of probenecid in a single oral dose.

Patients and Methods

In this study only females suffering from uncomplicated gonorrhœa, verified by culture, were included. The patients were over the age of 16, not pregnant and were not known to be allergic to cephalosporins or to penicillins. Samples for direct microscopy and culture were collected from the urethra, cervix and rectum, and culture was taken from the tonsils. The bacteriologically proven cases of gonorrhœa were given an i.m. injection of 1 g of cefuroxime in combination with 1 g of probenecid orally. Cefuroxime was dissolved in 4 ml of water and was given in the proximal lateral quadrant of the buttock.

The patients were instructed to abstain from sexual intercourse until the final follow-up investigation. They were requested to return 7 and 14 days after treatment for bacteriological and clinical assessment in accordance with the recommendations of the Swedish National Board of Health and Welfare. These recommendations stipulate that patients harbouring gonococci with decreased sensitivity for penicillin should be checked 3 times. The study was designed as an open evaluation without controls.

Cultures were taken with charcoaled cotton swabs and sent to the laboratory in transport medium (Gästrin & Kallings 1968). They were cultured on chocolate agar with and without polymyxin and vancomycin; 109 strains were tested for sensitivity to cefuroxime by the plate dilution technique and by paper diffusion to obtain a regression line. At the same time the strains were examined for MICs for benzylpenicillin.

Results

The regression line for cefuroxime may be compared to the line for benzylpenicillin (Fig 1). From this comparison it is clear that the slope fo the curve for cefuroxime is less than that for

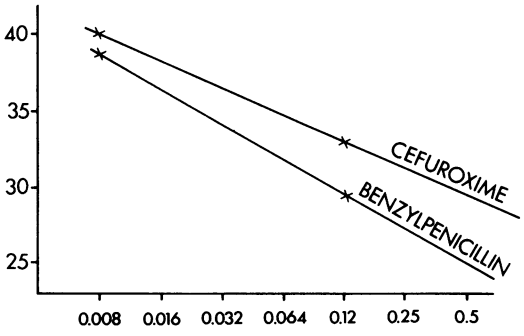

Fig 1 *Regression lines for cefuroxime and benzylpenicillin against 109 strains of* Neisseria gonorrhœæ

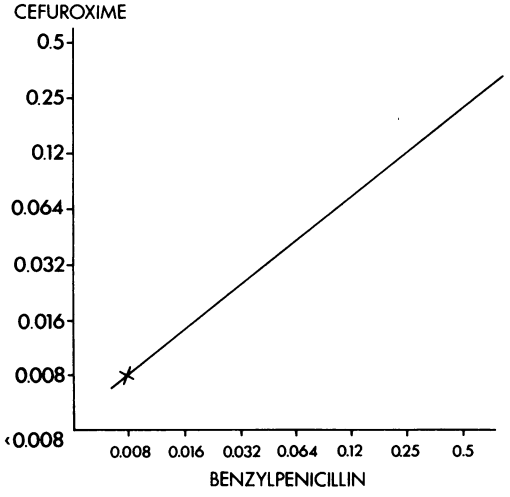

Fig 2 *Regression line for benzylpenicillin against cefuroxime. $r=0.869$, $SD_x=0.14$, $SD_g=0.09$*

benzylpenicillin. To some extent this might be due to the amount of cefuroxime in the discs used (30 μg for cefuroxime and 10 μg for benzylpenicillin). The location of the cefuroxime curve, high above the penicillin curve, is certainly due to this latter fact.

When the MICs for cefuroxime obtained by the plate dilution technique are compared to those for benzylpenicillin, it can be seen that strains with a decreased sensitivity to benzylpenicillin are more sensitive to cefuroxime (Fig 2). The β-lactamase producing strains tested were sensitive to cefuroxime in the range of 0.05–0.1 μg/ml. The distribution of the sensitivities to cefuroxime of the 109 strains tested by the plate dilution shows an unimodal curve with the peak moved towards the more sensitive side, as compared to benzylpenicillin with its usually bimodal curve. The sensitivities of the 40 strains from the patients in the study had the same pattern (Fig 3).

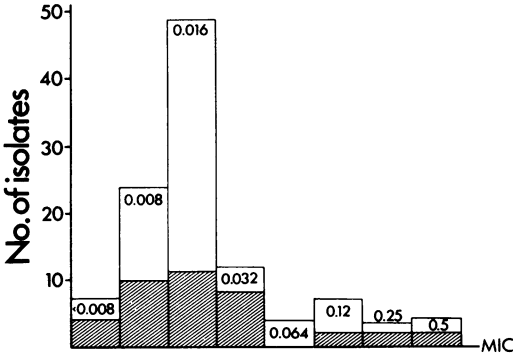

Fig 3 *Distribution of sensitivities among 109 isolates of* Neisseria gonorrhœæ *for cefuroxime* □ *and of isolates from 40 women treated with cefuroxime* ▨

Forty women with uncomplicated gonorrhœa verified by culture have been treated with 1 g of cefuroxime and 1 g of probenecid. Their ages varied from 16–47, the majority being 16–27. All of the patients were Caucasian and no concurrent disease of importance was present in any case. One patient had a history of suspected penicillin rash. Most of the patients had been suffering from their infection for about 1 week and experienced a wide variety of symptoms (Table 1). Twelve patients were asymptomatic. The patients complaining of slight lower abdominal pain were examined by palpation for evidence of salpingitis and erythrocyte sedimentation rate and temperature were controlled. Patients with suspected salpingitis were excluded from the study. Four patients had received therapy prior to cefuroxime for their presenting infection. They had been treated for suspected urinary tract infection, 3 with sulphonamides and 1 with nitrofurantoin.

Bacteriological Response

Thirty-eight patients returned for at least 2 follow-up investigations. Two patients with a first negative follow-up, who did not return, were

Table 1

Symptoms

Asymptomatic	12
Vaginal discharge	10
Frequency of micturition and dysuria	2
Vaginal discharge, frequency of micturition and dysuria	8
Slight lower abdominal pain	1
Vaginal discharge and slight lower abdominal pain	4
Vaginal discharge, slight lower abdominal pain, bleeding	1
Vaginal discharge, frequency of micturition and dysuria, slight lower abdominal pain	1
Vaginal discharge, pruritis	1
Total	40

Table 2

Bacteriological response and time after injection of first follow-up

	Time after injection (days)								
Response	*0–7*	*8–14*	*15–21*	*22–28*	*29–35*	*36–42*	*43–49*	*50–56*	*Total*
Successful	27	6	4	—	—	—	1	1	39
Failure	—	—	—	—	—	—	—	—	—
Unassessable	—	—	—	—	1[a]	—	—	—	1
Total assessable	27	6	4	—	—	—	1	1	39

[a] = this patient complained of acute lower abdominal pain after 1 week, which was treated as salpingitis

Table 3

Bacteriological response and time after injection of final follow-up

	Time after injection (days)									
Response	*0–7*	*8–14*	*15–21*	*22–28*	*29–35*	*36–42*	*43–49*	*50–56*	*57–63*	*Total*
Successful	1	20	9	5	—	1	—	1	1	38
Failure	—	1[b]	—	—	—	—	—	—	—	1[b]
Unassessable	—	—	—	—	—	1[a]	—	—	—	1[a]
Total assessable	1	21	9	5	—	1	—	1	1	39

[a] = this patient complained of acute lower abdominal pain after 1 week which was treated as salpingitis; [b] = positive culture in the second follow-up. No reinfection

included in the study. Four patients returned on 3 occasions. The bacteriological response in relation to the time of the first follow-up is shown in Table 2.

At the first control examination, the gonococcal infection had been successfully eradicated within 7 days in 27 patients. In 1 case complications of gonorrhœa developed during the follow-up period. One week after treatment she complained of intense lower abdominal pain which was treated as salpingitis. This could not be assessed bacteriologically.

The patients were evaluated in a similar manner for the last follow-up investigation (Table 3). Gonococci were isolated from 1 patient at the second follow-up. The patient still experienced a vaginal discharge but denied reinfection. She received a second injection of 1 g of cefuroxime and an oral dose of 1 g of probenecid. Two repeat tests were subsequently negative and the patient was considered cured. She is the failure in the table on bacteriological response (Table 4).

Table 4

Bacteriological response (first and final follow-up)

	No. patients
Successful	38
Successful with reinfection	—
Failure	1
Unassessable	1
Total assessable	39

Table 5

Clinical response and time after injection

	Time after injection (days)				
Response	*1–3*	*4–7*	*8–14*	*15–21*	*Total*
Cured	16	8	1	1	26
No improvement		1	1		2
Total assessable	16	9	2	1	28
Symptomless throughout					12
Total					40

Clinical Response

Twelve patients were asymptomatic throughout (Table 5). Twenty-six patients showed complete symptomatic remission after treatment. None of these patients had symptoms requiring further treatment.

The patient with positive bacteriology at the second control examination, and the patient who developed salpingitis, were considered as clinical failures.

Side Effects

No serious side effects were reported in the 40 patients. Transient pain at the site of injection was noted in all cases. In 4 cases, more intense pain was experienced in the leg, lasting for a few hours to 3 days. One patient complained of slight vertigo for a few days after injection. The patient with the history of antibiotic allergy demonstrated no side effects.

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