Dose Response Evaluation of Cefuroxime in the Treatment of Gonorrhœa in Male and Female Patients

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In this clinic we have, over the past few years, undertaken various clinical trials to assess the efficacy of standard and new antibiotics. In the light of the appearance of the β-lactamase producing strains of gonococci, reported from centres in the UK as well as abroad, and conscious of data from the Center for Disease Control in Atlanta, we decided that it would be appropriate to evaluate cefuroxime in our patients to establish a single dose that would be most suitable for both male and female patients. The dosages used were planned at the outset. We therefore undertook to give cefuroxime by i.m. injection, to patients presenting with uncomplicated urethral gonorrhœa.

Patients and Methods

Adult male patients suffering from urethral gonorrhœa shown by positive identification of Gram negative diplococci in a Gram stained smear were included in the study, provided that they were not known to be allergic to cephalosporins or to have had a previous anaphylactic reaction to penicillin. Cultures on modified Martin Thayer Medium were incubated for bacteriological identification and MIC determination. Blood tests for syphilis were also taken at the first visit. Treatment was given on all positive microscopic findings. All the patients were instructed to refrain from alcohol for the first week after the injection and from sexual intercourse until completion of the review. Patients were asked to return after 4, 7 and 14 days for follow-up assessment, or at any time if there was a recurrence of the original symptoms.

The first group of male patients treated was given 1 g of cefuroxime alone, the second group 1 g of cefuroxime with 1 g of (oral) probenecid, and the third group 1.5 g of cefuroxime with 1 g of probenecid. In all instances the cefuroxime was given by i.m. injection, the 1 g dose being prepared with 4 ml of water and the 1.5 g dose (2 × 750 mg vials) with 6 ml of water. The larger dose was administered half into each buttock.

At each follow-up visit the patients were questioned about any sexual activity since treatment and samples of urine and deep intraurethral smears were taken for culture and microscopy.

The study was then extended to include female patients with acute uncomplicated gonorrhœa from whom smears and cultures were taken from the urethra, cervix and rectum. Treatment was not given until either a positive smear or a positive culture was found. Follow-up with routine smears and cultures was at 4, 7 and 14 days, as for male patients. Twelve patients had previously received another antibiotic for their presenting gonococcal infection. In 8 of these patients, the antibiotic was ampicillin (6 being treated elsewhere), in one penicillin G and oxytetracycline. In the remaining 3, the identity of the antibiotic was unknown.

Results

The majority of the male patients presented with symptoms of discharge and/or dysuria of less than one week duration. Of the female patients, 48% were asymptomatic and 52% presented with symptoms of discharge, dysuria, irritation and frequency of micturition.

Table 1 shows that 277 patients (219 males and 58 females) have been treated in this series to date.

The majority of the patients were 18–30 year olds; 206 were Caucasian, 61 negroid and 10 Asian. Six patients had a history of previous antibiotic allergy; 4 of these had had a penicillin rash, 1 an allergy to tetracycline, and 1 to sulphonamides.

Table 2 shows the MIC determination of the isolates from 130 of the 277 patients (carried out by the Microbiology Department of Glaxo Research Ltd). Only 7 of the 130 organisms had an MIC greater than 0.1 μg/ml to cefuroxime, but 24 of these isolated had an MIC greater than 0.1 μg/ml to penicillin G.

Bacteriological Assessment

Table 3 shows the bacteriological response. Of the 31 male patients treated with 1 g of cefuroxime alone, only 14 were assessable. The infection was successfully eradicated in 12 which, in this small series, gives a 14.3% failure rate.

Of the forty-five male patients treated with 1 g of cefuroxime plus 1 g of probenecid, 32 patients were assessable bacteriologically and there were no failures. One hundred and forty-three male patients were given 1.5 g cefuroxime plus 1 g of probenecid. In 95 of the 98 assessable patients the

Table 1

Number of patients treated

Dose	*Males*	*Females*	*Total*
1 g cefuroxime	31	—	31
1 g cefuroxime + 1 g probenecid	45	—	45
1.5 g cefuroxime + 1 g probenecid	143	58	201
Total	219	58	277

Table 2
MIC of isolated organisms

		Penicillin G (μg/ml)				
		< 0.06	*0.06–0.1*	*0.11–0.5*	*> 0.6*	Total
Cefuroxime (μg/ml)	< 0.06	98	5	7	—	110
	0.06–0.1	1	2	10	—	13
	0.11–0.5	—	—	6	1	7
	> 0.5	—	—	—	—	—
Total		99	7	23	1	130

Table 3
Summary of bacteriological response in assessable patients

	Success/success with reinfection	*Failure*	*Total*
1 g cefuroxime (males)	12 (85.7%)	2 (14.3%)	14
1 g cefuroxime +1 g probenecid (males)	32 (100%)	—	32
1.5 g cefuroxime +1 g probenecid (males)	95 (96.9%)	3 (3.1%)	98
1.5 g cefuroxime +1 g probenecid (females)	50 (98.0%)	1 (2.0%)	51
Total	189	6	195

gonococcus was successfully eradicated. There were 3 failures, giving a failure rate of 3.1%.

In the female patients at the same dose, 7 of the 58 patients included in the group did not return for assessment, but 50 had had the gonococcus eradicated on smear and culture, including 19 who had had positive rectal cultures.

Clinical Assessment

The clinical assessment was made at the end of a 14-day follow-up period as follows:

Success: complete remission of signs and symptoms.

Improved: symptoms or signs still present but showing improvement.

Unassessable: the patient was initially asymptomatic, or there was no follow-up, or other treatment had been given before the completion of the 14-day treatment period.

Table 4 shows the clinical response to treatment with cefuroxime. When given alone, 14 of the 17 assessable patients were successfully treated. Two were both clinical and bacteriological failures. One patient had post gonococcal urethritis (PGU).

At the 1 g cefuroxime plus 1 g of probenecid dose, 27 of 32 patients had complete remission of symptoms. Five were diagnosed as having PGU (15.6%). When the dose of cefuroxime was increased to 1.5 g, then 89 of the 94 assessable patients were successfully treated; 4 had PGU (4.2%) and 1 failed. With the female patients, many were initially asymptomatic and therefore the clinical assessment could not be made, but of the 27 that were assessable, all had complete remission of signs and symptoms.

It should be noted that the PGU rate was lower (4.2% as compared to 15.6%) in the male patients given the larger dosage of cefuroxime. The number of cases, however, is too small for any conclusion.

The only side effects reported were in 2 females and 1 male receiving 1.5 g of cefuroxime and 1 g of probenecid. One felt faint, a second fainted on injection and the third developed a maculopapular rash the second day after treatment, which responded well to antihistamines.

None of the patients having a history of antibiotic allergy reported any side effects following the use of cefuroxime. Of the 8 patients that were known previous treatment failures, 2 did not return for follow-up and 6 were successfully treated bacteriologically with cefuroxime.

Summary

Two hundred and seventy-seven patients with acute gonorrhœa were treated with a single dose of cefuroxime. The failure rate of 14.3% with the

Table 4
Summary of clinical response in assessable patients

	Success/success with reinfection	*Improved/ PGU*	*Failed*	*Total*
1 g cefuroxime (males)	14 (82.3%)	1 (5.9%)	2 (11.8%)	17
1 g cefuroxime +1 g probenecid (males)	27 (84.4%)	5 (15.6%)	—	32
1.5 g cefuroxime +1 g probenecid (males)	89 (94.7%)	4 (4.2%)	1 (1.1%)	94
1.5 g cefuroxime +1 g probenecid (feamles)	27 (100%)	—	—	27
Total	157	10	3	170

single 1 g dose was quite unacceptable. The results when probenecid was used both with the 1 g and 1.5 g dosages were satisfactory. The ultimate choice of dosage (assuming continued acceptable rates of cure) might well depend on the MIC concentrations of the prevailing strains of gonococci in any given area.

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DISCUSSION

Professor W Brumfitt (*London*) said that he understood from Professor Milton Salton in New York that the plasmid replicates within the cell to give an increasing rate of penicillinase production. He wondered whether it was the penicillinase or the inability of the antibiotic to penetrate the cell that constituted the major problem.

However, he believed that cefuroxime had an extremely valuable place not least since it could be given as a single dose. Patients failed to return and this was a distinct advantage over multi-dose treatments.

Dr Thornsberry said that Professor Salton's statement about replication within the cell was entirely reasonable. It was indeed the production of β-lactamase not the question of penetration that was of major importance. In strains that did not have the plasmid and that did not produce β-lactamase, MIC values were very low.

Dr Percival (*Chairman*) said that β-lactamase negative variants of the Liverpool strain had MICs to benzylpenicillin of 0.12 μg/ml and with some American strains this figure was 0.06. It seemed that in those strains the β-lactamase had been superimposed on gonococci already having some degree of penicillin susceptibility. This had been shown to be associated with reduced binding of radioactively labelled penicillin to the cells, according to the published work of Rodriguez and Saz. But this was a chromosomally mediated penetration problem which Professor Sparling had shown to be occasioned by the passage of DNA from one strain to another.

He agreed with Professor Brumfitt's suggestion that along with the transfer of a so-called R-factor there might also be an alteration in the membrane. If the organisms were to go on becoming more innately resistant and if the possession of penicillinase were superimposed on that property, there might be a problem. Dr Thornsberry had mentioned that approximately 5% of gonococci had MICs of cefuroxime above 2 μg/ml.

Dr Thornsberry said that they were really considering *relative* resistance. The innate resistances were still very low but they were relatively greater than they had been 30 years previously.

Dr L D Sabath (*Minneapolis*) commented on the well-known diphasic curves of the MICs of gonococci to penicillin G, which, of course, existed long before the introduction of the β-lactamase plasmid into the gonococcus. With the MICs of cefuroxime, there was a uniphasic distribution suggesting that in addition to its resistance to β-lactamase, the unique feature of cefuroxime was that there was only one population of gonococci with respect to the drug. This might have much to do with its usefulness, whether the organisms produced β-lactamase or not.

Data which were presented of the distribution of MICs to cefuroxime showed half the normal distribution curve. This was presumably because dilutions to lower concentrations had not been performed, but he wished to confirm that there was a normal distribution curve of cefuroxime MICs.

Dr Piot said that he and Dr Phillips a year previously had reported on the activity of cefuroxime and other cephalosporins against *Neisseria gonorrhœæ*. He had suggested that for cefuroxime too there was a bimodal distribution but the data were limited and he now believed that there was probably only one population. As to higher dilutions, Dr Sabath was right to assume that they had simply not pursued the problem.

Dr Thornsberry said that his own two-fold dilution data suggested a normal curve.

Dr Percival (*Chairman*) said that the MICs they had found in Liverpool varied between 0.125 and 0.25 μg/ml. He believed that the β-lactamase producers were a single clone because they all had the same auxotype. However, the American isolates were a mixture of auxotypes and not necessarily a single clone.

Dr T Tupasi (*Philippines*) said that of 31 isolates tested for β-lactamase production only 1 was positive, a rate of approximately 3%. The patient with this infection was successfully treated with a single dose of 1.5 g of cefuroxime given 1 h after 1 g of probenecid orally. Mr Westbrook, who had performed a more extensive survey in another area of the Philippines, had reported an incidence of 31% among his isolates. MIC figures for penicillin G had been very similar to those presented by Dr Thornsberry. Susceptibility tests to cefuroxime among 334 isolates showed an incidence of 98.8% sensitivity to the drug.