

Ceftriaxone in the treatment of ordinary and penicillinase-producing strains of *Neisseria gonorrhoeae*

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SUMMARY Ceftriaxone, a third generation cephalosporin, was used in a single intramuscular dose with oral probenecid to treat 124 men with infections due to non-penicillinase-producing *Neisseria gonorrhoeae* (non-PPNG) and 64 men with infections due to PPNG. Three different doses of ceftriaxone were used—125 mg, 62.5 mg, and 32.5 mg. The cure rate for all PPNG infections with the different doses was 100%. The cure rate for the non-PPNG infections with ceftriaxone 125 mg was 100%; those for non-PPNG infections treated with ceftriaxone 62.5 mg and 32.5 mg were 96.2% and 97.3% respectively. The 160 strains of non-PPNG and 60 strains of PPNG isolated were all susceptible to ceftriaxone with minimum inhibitory concentrations of 0.008 µg/ml. These results are compared with those using kanamycin 2 g. Ceftriaxone is a safe and effective treatment for PPNG and non-PPNG infections.

Introduction

The first cephalosporin was isolated in 1955 and since then different generations, each showing advantages over the previous one, have been produced. The newer generations show increasing activity, a broader antimicrobial spectrum, and increased stability to penicillinase.

When compared with other cephalosporins of the same class^{1,2} ceftriaxone, a new third generation cephalosporin, has been found to be highly active against strains of both penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and non-penicillinase-producing *N gonorrhoeae* (non-PPNG). Ceftriaxone is an aminothiazolyl-oxymino-cephalosporin, which is different from other cephalosporins in the nature of the substitution at position 3 of the nucleus (figure). The presence of an enolate axion group at the triazine moiety of the 3-substituent probably contributes to its long plasma half-life.

The bioavailability of ceftriaxone when dissolved in water or 1% lignocaine given by the intramuscular route is about 100%.³ Regardless of the dose administered the half-life of the drug in the plasma is 6.5-8.6 hours in healthy adults. The plasma half-life of all other cephalosporins is relatively short, ranging from 45 minutes to 2½ hours.

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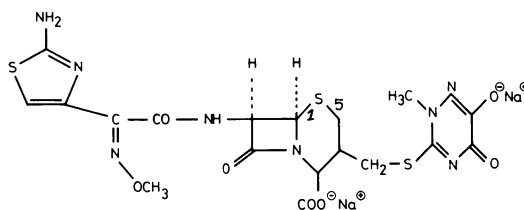


FIGURE Chemical structure of ceftriaxone

In man the drug is not metabolised and about 40% of the unchanged compound is eliminated in the bile; 60% of the injected dose is excreted in the urine.³

A clinical study was performed to determine the effectiveness of ceftriaxone against PPNG and non-PPNG infections in male patients. Comparisons were made with patients treated with kanamycin, the present drug of choice for the treatment of gonorrhoea in Singapore. Different doses of ceftriaxone were administered and the results recorded.

Patients and methods

DIAGNOSIS

Four hundred and eleven male patients with acute gonococcal urethritis were studied. Gonorrhoea was diagnosed when Gram-negative intracellular diplococci were seen on microscopy of a Gram-stained smear and the gonococcus was isolated on modified Thayer-Martin media. Penicillinase production was

tested in all isolated cases by the disc diffusion method using a penicillin disc (10 IU) and confirmed by a rapid iodometric method.⁴ Isolates of *N gonorrhoeae* whose growth was not inhibited by a penicillin disc were examined for the production of β -lactamase by the rapid iodometric method.

TREATMENT

When Gram-negative intracellular diplococci were seen in urethral smears treatment was given. Only those treated patients whose infections were confirmed by culture were included in the study. Two hundred and six patients were given a single intramuscular dose of 2 g kanamycin; 205 were given a single intramuscular dose of ceftriaxone 125 mg or 62.5 mg or 32.25 mg with 1 g probenecid orally. Patients were grouped for study according to the dose of ceftriaxone given.

Group A

Sixty male patients received a single intramuscular injection of ceftriaxone 125 mg and probenecid 1 g orally.

Group B

Eighty-seven patients were treated with a single intramuscular injection of ceftriaxone 62.5 mg and probenecid 1 g orally.

Group C

Fifty-eight patients were treated with ceftriaxone 32.25 mg intramuscularly and probenecid 1 g orally.

Kanamycin group

Two hundred and six men with gonococcal urethritis were treated with kanamycin in a single intramuscular dose of 2 g.

FOLLOW UP AND TEST OF CURE

All patients in the study were reassessed on days 5 and 14 after treatment. A clinical assessment followed by a urethral smear for Gram staining and culture for *N gonorrhoeae* was made on each visit. Any unwanted effects of treatment were noted. Treatment failure was considered if any of the Gram-stained smears or cultures gave positive results. Patients with reinfections were excluded from the study. Post-gonococcal urethritis was diagnosed on day 14 in symptomatic patients with pus cells (≥ 10 high-power field) on the Gram-stained smear and a negative culture result for *N gonorrhoeae*. Chlamydial cultures were not attempted.

ANTIBIOTIC SUSCEPTIBILITY

Antibiotic susceptibility tests were performed on 160 non-PPNG and 60 PPNG strains isolated. The minimum inhibitory concentrations (MICs) of ceftriaxone were determined by the agar plate dilution method.⁵ Twofold concentrations of ceftriaxone from 0.000063 to 0.008 $\mu\text{g/ml}$ were used.

Results

The details of the treatment response are given in table I. There were no treatment failures in all three groups of patients infected with PPNG when treated either with ceftriaxone with probenecid or with kanamycin. The overall failure rate with kanamycin in the patients infected with non-PPNG strains was 11%.

POSTGONOCOCCAL URETHRITIS

There was no significant difference in the incidence of postgonococcal urethritis in patients treated with kanamycin or with ceftriaxone. The overall incidence of postgonococcal urethritis in patients treated either

TABLE I Response of patients with gonorrhoea due to PPNG and non-PPNG strains to various doses of ceftriaxone and probenecid compared with kanamycin

Treatment group	No of cases	No defaulted	No completing study		No of treatment failures (%)		No with post-gonococcal urethritis (%)
			Non-PPNG	PPNG	Non-PPNG	PPNG	
1							
Ceftriaxone 125 mg + probenecid 1 g	60	6	35	19	0 (0)	0	3 (5.5)
Kanamycin 2 g	60	6	35	13	6 (14.6)	0	3 (5.5)
2							
Ceftriaxone 62.5 mg + probenecid 1 g	87	7	52	28	2 (3.8)	0	2 (2.5)
Kanamycin 2 g	87	7	52	24	6 (10.9)	0	2 (2.5)
3							
Ceftriaxone 32.25 mg + probenecid 1 g	58	4	37	17	1 (2.7)	0	4 (7.4)
Kanamycin 2 g	59	10	39	10	3 (7.7)	0	5 (10.2)

PPNG = penicillinase-producing *N gonorrhoeae*

TABLE II Susceptibility of *Neisseria gonorrhoeae* to ceftriaxone

Strains	No	Minimum inhibitory concentration ($\mu\text{g/ml}$)							
		0.000063	0.000125	0.00025	0.0005	0.001	0.002	0.004	0.008
PPNG	60	1	1	6	12	23	12	4	1
Non-PPNG	120	1	5	9	42	37	16	7	3

PPNG = penicillinase-producing *N. gonorrhoeae*

with kanamycin or with ceftriaxone was 5.4% and 4.4% respectively.

SIDE EFFECTS

No serious side effects or local reactions to the injections were reported. A few patients had a little discomfort after injections of both kanamycin and ceftriaxone.

ANTIBIOTIC SUSCEPTIBILITY

The results of the antibiotic susceptibility to ceftriaxone are given in table II. All the 120 non-PPNG and 60 PPNG strains were susceptible to 0.008 $\mu\text{g/ml}$ of ceftriaxone. There was no difference in the susceptibility of non-PPNG and PPNG strains. The geometric means of the MICs of the drug for PPNG and non-PPNG strains were 0.00018 $\mu\text{g/ml}$.

Discussion

The effectiveness of the newer cephalosporins (cefuroxime, cefoxitin, cefotaxime) in the treatment of PPNG and non-PPNG infections has been well documented.⁵⁻⁷ Ceftriaxone is a third generation cephalosporin. In this study the clinical response to ceftriaxone in acute gonococcal infection was extremely good. The overall cure rate for the infections due to PPNG strains was 100%. With the 125-mg dose of ceftriaxone the cure rate for the non-PPNG infections was 100%. With doses of 62.5 mg and 32.25 mg ceftriaxone the rates were 96.2% and 97.3% respectively. All these results are acceptable as effective treatment for gonorrhoea.

Although there was a slight difference in the clinical response of the PPNG and non-PPNG strains to ceftriaxone the antibiotic susceptibility in vitro was the same. This differed from the results of our previous study,⁵ in which cefotaxime had a greater inhibitory effect on the PPNG strains. Our experience also differs from that of Thabaut *et al.*,² who suggested that the non-PPNG strains seemed to be more susceptible to ceftriaxone. Nevertheless, our study agrees with others in showing that ceftriaxone has high activity at low levels when compared with all other cephalosporins.^{1,2}

The gonococcus has shown great resistance over the years and needs progressively increasing doses of penicillin to inhibit its growth both in vitro and in vivo. In 1976 totally resistant penicillinase-producing

strains were isolated. The Pacific and South-east Asian regions have shown alarmingly high prevalences of PPNG strains.⁸ At the same time South-east Asian non-PPNG strains have become resistant to several antibiotics and show their robustness by producing greater failure rates to established antibiotics and even newer antibiotics such as cefotaxime and ceftriaxone.⁹ In 1979 in Singapore the success rate with kanamycin 2 g was 100% for all gonococcal infections (Rajan, personal communication). In 1981, in this study, the overall success rate was 91.9% for the non-PPNG strains. Until now, all strains of gonococci in Singapore have been susceptible to kanamycin at 16 $\mu\text{g/ml}$ (Sng, personal communication). Nevertheless, the non-PPNG strains in Singapore are being carefully watched because of their multiple resistance to several antibiotics.

Thus, ceftriaxone in a single dose is safe and effective in treating both PPNG and non-PPNG infections. In the light of the increasing partial resistance of South-east Asian gonococcal strains to several antibiotics the optimum dose should not be less than 125 mg intramuscularly with 1 g probenecid orally.

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