

# Comparison of ceftriaxone with cefoxitin in the treatment of penicillin-resistant gonococcal urethritis

T R ZAJDOWICZ, P L SANCHES, S W BERG, S B J KERBS, R L NEWQUIST, AND W O HARRISON

*From the Infectious Diseases Branch, Department of Internal Medicine, and the Clinical Investigation Department, Naval Hospital, San Diego; and the Environmental Health Service, Naval Regional Medical Center, Subic Bay, California, USA*

**SUMMARY** Since cefoxitin has been shown to be an effective alternative to spectinomycin for the treatment of infections due to penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) its efficacy was compared with that of a new cephalosporin, ceftriaxone (R013-9904). One hundred and twenty eight men with culture-confirmed gonococcal urethritis were treated with either 250 mg of ceftriaxone intramuscularly or 2 g of cefoxitin intramuscularly with oral probenecid 1 g. The incidence of penicillin-resistant strains in each group was about 60%. Ceftriaxone was completely effective in treating both penicillin-sensitive and penicillin-resistant gonococcal urethritis. No side effects were noted. Ceftriaxone thus seems to be an effective and safe alternative to either spectinomycin or cefoxitin in the treatment of penicillin-resistant gonococcal urethritis.

## Introduction

Since the first reported cases of infection with penicillinase-producing strains of *Neisseria gonorrhoeae* (PPNG) in 1976<sup>1,2</sup> the world wide prevalence of these strains has increased.<sup>3</sup> PPNG are widely distributed but so far are not a major problem in the United States. In many areas of the Far East, however, 30-60% of *N gonorrhoeae* isolates produce  $\beta$ -lactamase and are resistant to penicillin.<sup>4</sup> The standard treatment for gonorrhoea in US Navy personnel stationed in the Far East is presently with spectinomycin.<sup>5</sup> With the recent report of a case of gonococcal urethritis due to a strain of bacteria resistant to both spectinomycin and penicillin<sup>6</sup> a diminution of the efficacy of spectinomycin in treating PPNG becomes a serious possibility. Thus alternative treatment regimens for treating infections due to penicillin-resistant strains of gonococci must continue to be evaluated.

Ceftriaxone is a third generation cephalosporin with three properties that suggest efficacy in treating gonococcal urethritis caused by PPNG: (a) resistance to the TEM  $\beta$  lactamase produced by PPNG<sup>7</sup>; (b) a prolonged serum half-life<sup>8</sup>; and (c) notable activity in

vitro against PPNG.<sup>9</sup> Information provided by the manufacturer (Hoffman LaRoche, Nutley, NJ) indicated peak serum concentrations of 35  $\mu$ g/ml after a single intramuscular injection of ceftriaxone. These properties led us to use ceftriaxone in a single 250 mg intramuscular dose to treat patients with gonococcal urethritis due to both penicillin-resistant and penicillin-sensitive strains.

## Patients and methods

We studied American military personnel stationed at a naval base in the western Pacific, where 60% of recent cases of gonococcal urethritis were caused by penicillinase-producing strains of *N gonorrhoeae*.<sup>4</sup> Patients were seen by the research investigators if they had signs or symptoms of urethritis. Those who agreed to take part in the study gave informed consent and were then examined and treated. Patients were enrolled if all of the following criteria were met: recent sexual exposure, signs or symptoms of urethritis, and the presence of polymorphonuclear neutrophils and intracellular Gram-negative diplococci in a Gram-stained smear of urethral exudate. Patients were excluded if they had a history of a severe immediate reaction to penicillin or any type of allergic reaction to any of the cephalosporins; hypersensitivity to lignocaine or probenecid; evidence of coexisting syphilis or gonococcal

Address for reprints: Lieutenant Commander T R Zajdowicz, Clinical Investigation Department, Naval Hospital, San Diego, California, 92134, USA

Accepted for publication 8 December 1982

infection other than uncomplicated urethritis; or any disease which might require additional antibiotic treatment.

#### TREATMENT ALLOCATION

Patients were randomly assigned to treatment with ceftriaxone or cefoxitin according to a computer-generated table of random numbers. Treatment with ceftriaxone consisted of a single intramuscular injection of 250 mg. Patients treated with cefoxitin received 2 g intramuscularly together with oral probenecid 1 g. Both antibiotics were reconstituted with 0.5% lignocaine.

To measure the safety of ceftriaxone haematological and renal and liver function tests were carried out before treatment. Urethral specimens were obtained by inserting a calcium alginate swab 3-4 cm into the urethra. These specimens were examined as in our previous studies.<sup>10</sup> Gram stained smears of urethral exudate were read by both an experienced laboratory technician and one of the investigators. Cultures were examined at 24 and 48 hours. A presumptive diagnosis of *N gonorrhoeae* was based on typical colonial morphology, Gram staining, and a positive oxidase test.  $\beta$ -lactamase activity was tested using the chromogenic cephalosporin assay.<sup>11</sup> Specimens were frozen and subsequently confirmed as gonococci by carbohydrate utilisation. Minimum inhibitory concentrations of the antibiotics used were determined as described.<sup>10</sup>

All patients were interviewed at the time of follow up and asked about the course of their infection, any interim sexual contact, and any adverse reactions after treatment. In addition to a physical examination, repeat urethral cultures were obtained and a Gram stained urethral smear examined if the patient had symptoms. The patients treated with ceftriaxone also had blood and urine tests repeated.

#### Results

Of the 143 patients enrolled in the study 15 were excluded from final analysis, either because *N gonorrhoeae* did not grow on the initial culture or because the patient failed to return for review. Complete data were available on 61 and 67 patients treated with ceftriaxone and cefoxitin respectively. The two treatment groups did not differ in age, duration of symptoms, previous episodes of gonococcal urethritis, or proportion of infections due to PPNG.

All 61 patients treated with ceftriaxone were cured (table I). All had minimal or no symptoms at follow up and test-of-cure urethral culture results were negative for *N gonorrhoeae*. There was only one treatment failure with cefoxitin; the patient was

cured with 2 g spectinomycin given intramuscularly. At follow up this patient was symptomatic and denied interim sexual contact.

The cumulative percentage of isolates (both PPNG and non-PPNG) sensitive to increasing concentrations of ceftriaxone and cefoxitin is shown in table II. All isolates of *N gonorrhoeae* were sensitive to  $\leq 0.03$   $\mu\text{g/ml}$  of ceftriaxone. The PPNG strains were slightly more susceptible to ceftriaxone, but this difference was not statistically significant. The geometric mean minimum inhibitory concentration for penicillin-resistant isolates was 0.42  $\mu\text{g/ml}$  for cefoxitin and 0.003  $\mu\text{g/ml}$  for ceftriaxone, while for penicillin-sensitive isolates these values were 0.59  $\mu\text{g/ml}$  and 0.004  $\mu\text{g/ml}$  respectively.

All patients treated with ceftriaxone reported minimal or no pain at the injection site. Several volunteered that ceftriaxone was the least painful injection that they had received for gonorrhoea. In contrast, several patients receiving cefoxitin had felt moderate or severe pain lasting up to several hours. No serious adverse effects were directly attributable to either ceftriaxone or cefoxitin.

TABLE I Efficacy of ceftriaxone in the treatment of gonococcal urethritis

Isolates	No cured/No treated with:			
	Cefoxitin		Ceftriaxone	
	No	%	No	%
PPNG	38/39	98	36/36	100
Non-PPNG	28/28	100	25/25	100

PPNG = penicillinase-producing strains of *N gonorrhoeae*

TABLE II Cumulative percentage of isolates sensitive to increasing concentrations of ceftriaxone or cefoxitin

MIC ( $\mu\text{g/ml}$ )	Cumulative percentage of isolates in groups treated with:			
	Cefoxitin (n = 67)		Ceftriaxone (n = 68)	
	PPNG (n = 39)	Non-PPNG (n = 28)	PPNG (n = 36)	Non-PPNG (n = 25)
<0.0004			3	5
0.001			14	19
0.002			61	48
0.004			89	67
0.008			97	81
0.015			100	86
0.03				100
0.06				
0.12	8	5		
0.25	46	19		
0.5	69	52		
1.0	100	100		

PPNG = penicillinase-producing strains of *N gonorrhoeae*;  
MIC = minimum inhibitory concentration

## Discussion

In this study men with uncomplicated gonococcal urethritis were treated with either ceftriaxone or cefoxitin. Both antibiotics were highly effective against both penicillin-sensitive and penicillin-resistant strains of *N gonorrhoeae*. This is the first evaluation of the use of ceftriaxone in an area where PPNG is highly endemic. As predicted by in vitro sensitivity testing and other workers' clinical experience, ceftriaxone was extremely effective and well tolerated in these patients. In this study strains of gonococci were associated with a pronounced prevalence of both chromosomal and plasmid-mediated resistance to penicillin. All 61 men so treated, including 36 infected with penicillinase-producing strains, were cured with ceftriaxone. This efficacy, together with the small amount of injected drug required and the striking absence of pain associated with treatment, indicated that ceftriaxone may be recommended as an alternative treatment for gonococcal urethritis. Cefoxitin is also highly effective against both penicillin-sensitive and penicillin-resistant strains and has been used more and more in the western Pacific area. The first bacteriological failure in our series of more than 350 cases of gonorrhoea treated with cefoxitin is a matter of concern.<sup>12</sup>

It is thus encouraging to find an alternative to both spectinomycin and cefoxitin which is both highly effective and well tolerated by the patient. Ceftriaxone appears therefore to be an appropriate antibiotic for treating gonococcal urethritis caused by penicillin-resistant strains.

This study was supported in part by the US Navy Bureau of Medicine and Surgery Clinical

Investigation Program (Study 81-16-1616) and by Hoffman-LaRoche Pharmaceutical Laboratories.

The opinions or assertions expressed in this paper are ours and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or of the naval service at large.

## References

1. Ashford WA, Golash RG, Hemming VG. Penicillinase-producing *Neisseria gonorrhoeae*. *Lancet* 1976;ii:657-8.
2. Percival A, Rowlands J, Corkill JE, et al. Penicillinase-producing gonococci in Liverpool. *Lancet* 1976;ii:1379-82.
3. Centers for Disease Control. Global distribution of penicillinase-producing *N gonorrhoeae* (PPNG). *Morbidity and Mortality Weekly Report*. 1982;31:1-3.
4. Lancaster DJ, Berg SW, Harrison WO, Ockermann KO. Treatment of penicillin-resistant gonorrhoea with cefotaxime. *Drug Therapy* 1981;suppl:87-90.
5. US Navy Bureau of Medicine. Notice, paragraph 6222. Washington DC: Department of the Navy, August, 1981.
6. Ashford WA, Potts DW, Adams HJU, et al. Spectinomycin-resistant penicillinase-producing *Neisseria gonorrhoeae*. *Lancet* 1981;ii:1035-7.
7. Angehrn P, Probst PJ, Reiner R, Theu RL. RO 13-9904, a long-acting broad-spectrum cephalosporin: in vitro and in vivo studies. *Antimicrob Agents Chemother* 1980;18:913-21.
8. Patel IH, Chen S, et al. Pharmacokinetics of ceftriaxone in humans. *Antimicrob Agents Chemother* 1980;20:634-41.
9. NG S, Chan PY, Arnold K. In vitro susceptibilities of *Haemophilus influenzae* and *Neisseria gonorrhoeae* to RO-13-9904 in comparison with other beta-lactam antibiotics. *Antimicrob Agents Chemother* 1981;19:925-6.
10. Berg SW, Kilpatrick ME, Harrison WO, McCutchan JA. Cefoxitin as a single-dose treatment for urethritis caused by penicillinase-producing *Neisseria gonorrhoeae*. *N Engl J Med* 1979;301:509-11.
11. O'Callaghan CH, Morris A, Kirby SM, Shingler AH. Novel method for detection of  $\beta$ -lactamase by using a chromatographic/cephalosporin substrate. *Antimicrob Agents Chemother* 1972;1:283-8.
12. Sanches PL, Wignall FS, Harrison WO, Berg SW. One gram of cefoxitin cures uncomplicated gonococcal urethritis caused by penicillinase-producing *N gonorrhoeae*. *Proceedings of the 21st Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington DC: American Society for Microbiology, 1981:616.