Treatment of acute gonococcal infections in Bangkok with a dose range of the new cephalosporin, cefodizime

A Chitwarakorn¹, C Wongba², E E Dagrosa³ and B Schinzel³

¹Office for Communicable Disease Control, Region 1, Department of Communicable Disease Control, Bangkok, Thailand, ²Venereal Diseases Division, Department of Communicable Disease Control, Bangkok, Thailand and ³Clinical Research Antiinfectives, Hoechst AG, Frankfurt/Main, Germany

Summary: In this randomized dose range study conducted in Bangkok, 326 patients with presumed acute uncomplicated gonorrhoea were treated with a single intramuscular dose of either 0.25 g, 0.5 g, or 1.0 g of a new aminothiazole cephalosporin, cefodizime. One hundred and eighty men and 110 women were evaluable for efficacy. Pathogens were eliminated in all but 4 of these patients resulting in a cure rate of 99%, irrespective of dose, sex, or multiplicity of infected sites. A high percentage of the 290 strains of Neisseria gonorrhoeae isolated from the evaluable patients showed resistance to penicillin, and 40% were penicillinase producing (PPNG). The minimum inhibitory concentration of cefodizime for 90% of the PPNG strains was <0.04 mg/l. No clinically relevant adverse drug reactions were reported. This study demonstrates that a single 0.25 g dose of cefodizime is effective against both PPNG and non-PPNG strains in a geographic region characterized by high endemic antibiotic resistance.

Keywords: Cefodizime, single-shot treatment, acute gonococcal infection, South East Asia, PPNG strains

INTRODUCTION

The introduction of penicillin in the 1940s revolutionized the treatment of gonorrhoea, resulting in a cure rate of greater than 90% with single-dose treatment¹. Within 10 years, however, gonococcal strains began to be isolated which showed partial resistance to penicillin. This initiated a vicious upward spiral of ever-increasing doses and resistance, culminating in the emergency of highly resistant, penicillinase producing strains of Neisseria gonorrhoeae (PPNG) in the 1970s²,³. These strains were classified according to the size of the plasmid which encodes the β-lactamase responsible for resistance. An Asian strain with a 4.4 mD plasmid, and an African strain with a 3.2 mD plasmid were identified⁴. Since then, such strains have spread worldwide, greatly complicating the antibiotic therapy of gonorrhoea.

The Asian strain was first encountered in the United States in 1976 where it had been introduced by American military personnel from the Philippines. In Thailand, the first two cases involving PPNG strains were reported in 1977⁵. One year later a survey showed that such strains accounted for 8.6% of all gonococcal strains isolated⁶. This percentage has increased steadily since then, and in 1982 a study reported that PPNG strains were responsible for 42% of gonococcal infections in Bangkok⁷.

In response to this situation, a number of new antibiotics have been introduced which are active against both PPNG and non-PPNG strains. The cephalosporin and quinolone families of antibiotics are particularly noteworthy⁸,⁹. Nevertheless, there is still a continuing need to develop new, more effective and safer antibiotics capable of overcoming the increasingly resistant pathogenic microbes.

Cefodizime is a new aminothiazole cephalosporin, active against a broad range of bacterial species¹⁰. It is extremely active in vitro against both PPNG and non-PPNG gonococcal strains, with minimum inhibitory concentration for 90% inhibition (MIC) values of between 0.004 and 0.016 mg/l¹⁰,¹¹. High, long-lasting concentrations in both serum and urine¹² make it well suited for use against gonococcal infections. Pilot studies in Bangkok suggested that a single dose as low as 0.25 g would be effective despite the high incidence of PPNG strains in this...
region. Therefore, doses of 0.25, 0.5 and 1.0 g were employed to investigate the lower limit of the effective dose range. This study presents a large-scale clinical evaluation of the efficacy of cefodizime in patients from South East Asia, a region of great epidemiological significance in terms of resistant gonococcal strains.

METHODS

Study population
All patients included in the study were between 17 and 61 years old (with one exception, a 14-year-old woman) and suffered from presumed acute, uncomplicated urogenital and/or rectal gonorrhoea. This study was carried out at the Venereal Diseases Division, Bangpak Hospital, Bangkok, Thailand. Pregnant or lactating women were excluded from participation as were patients with the following conditions: disseminated gonococcal infections, early syphilis or chancroids; hepatic or renal disease; recent bowel surgery, inflammatory bowel disease or carcinoma of the colon; known to be allergic to penicillin or cephalosporins; or treated recently with antimicrobials (excluding metronidazole or tinidazole), probenecid or immunosuppressant agents. All participants were requested to refrain from sexual intercourse until 7 days after treatment. Patients were randomized to one of three groups receiving either 0.25, 0.5 or 1.0 g cefodizime as a single intramuscular injection of 4 ml with 1.0% lidocaine-HCl. The study protocol was approved by the Ethical Clearance Committee on Human Rights, Mahidol University, Bangkok and the Ministry of Public Health of Thailand. Informed verbal consent was obtained from each patient in the presence of a witness.

Study design
At the initial visit, detailed medical and sexual histories were taken and patients underwent a standard physical examination. Laboratory investigations consisted of standard biochemistry, general haematology, and urinalysis. Additional blood samples were drawn for syphilis serology (Venereal Diseases Research Laboratory [VDRL], Treponema pallidum haemagglutination [TPHA] and fluorescent treponemal antibody [FTA]). Specimens were collected from the urethra in men and the urethra, cervix, rectum and oropharynx in women. The corresponding cultures were prepared and the Gram-stain smears were examined for Gram-negative intracellular diplococci. Urinary sediment was tested for the presence of leucocytes in males, where a count of greater than 10 per field (250-fold magnification) was defined as urethritis. All tests except syphilis serology were to be repeated at the first follow-up examination 7 days after drug administration and at the second follow-up examination 14 days after drug administration (in cases of treatment failure).

Laboratory methods
Cultures were diagnosed in the following manner. Specimens were immediately inoculated into modified Thayer-Martin medium and incubated at 35°C in candle extinction jars. Each culture was examined after 24 and 48 h. Identification of *N. gonorrhoeae* was based on colony morphology, presence of Gram-negative diplococci in stained smears, positive oxidase test, and rapid sugar fermentation reaction. PPNG strains were identified by the nitrocefin test. Sensitivity to cefodizime and spectinomycin was investigated using the disc diffusion assay (30 and 10 mg, respectively). For each isolated strain, the MIC was determined for cefodizime and 6 other antibiotics: ceftaxime, ceftriaxone, ofloxacin, tetracycline, penicillin and spectinomycin. MIC determinations were performed using the standard agar plate dilution assay (twofold dilution steps of antibiotic concentrations from 0.004 to 64.0 mg/l).

Assessment of efficacy and tolerance
Efficacy was based on bacteriological findings. Response was defined as either cure or failure, depending on whether the pathogen was still present at the follow-up examination. Efficacy was determined separately for single and multiple site infections because multiple site gonococcal infections are more often resistant to antibiotic treatment. Symptoms were assessed by patient questioning and physical examination; clinical findings were evaluated but were not used in the determination of efficacy. Tolerance was also assessed by questioning and physical examination. Only descriptive statistical methods were used for the evaluations of efficacy and tolerance. MIC$_{50}$ and MIC$_{90}$ were calculated after a logarithmic transformation of the raw data.

RESULTS
Altogether, 326 patients were enrolled with presumed uncomplicated gonococcal infection. *N. gonorrhoeae* cultures were negative in 17 patients, 15 patients were lost to follow-up and 4 patients were reinfected by sexual contact between treatment and the follow-up examination and were thus withdrawn from efficacy evaluation. A total of 290 evaluable patients therefore remained: 180 men with a median age of 24.3 years and 110 women with a median age of 25.8 years. All patients were ethnic Thais. All three treatment groups were comparable in terms of age, weight and male : female ratio (3 : 2).

Single infected site
All 180 evaluable male patients had single site, urethral gonorrhoea (Table 1). Urogenital gonorrhoea alone was diagnosed in 66 of 110 evaluable women. The causative pathogen was eradicated in all patients
Table 1. Bacteriological efficacy of three different cefodizime treatments

<table>
<thead>
<tr>
<th>Cefodizime treatment</th>
<th>Clinical form</th>
<th>Sex</th>
<th>Total no. treated</th>
<th>No. non-evaluable</th>
<th>Total evaluable</th>
<th>Cure</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>single</td>
<td>F</td>
<td>20</td>
<td>1</td>
<td>19</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>64</td>
<td>3</td>
<td>61</td>
<td>62</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>multiple</td>
<td>F</td>
<td>18</td>
<td>3</td>
<td>15</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>0.50 g</td>
<td>single</td>
<td>F</td>
<td>28</td>
<td>3</td>
<td>25</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>61</td>
<td>4</td>
<td>57</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>multiple</td>
<td>F</td>
<td>15</td>
<td>1</td>
<td>14</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>1.00 g</td>
<td>single</td>
<td>F</td>
<td>24</td>
<td>2</td>
<td>22</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>62</td>
<td>2</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>multiple</td>
<td>F</td>
<td>17</td>
<td>2</td>
<td>15</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>single</td>
<td>F</td>
<td>72</td>
<td>6</td>
<td>66</td>
<td>66</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>187</td>
<td>7</td>
<td>180</td>
<td>179</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>multiple</td>
<td>F</td>
<td>50</td>
<td>6</td>
<td>44</td>
<td>41</td>
<td>3</td>
</tr>
</tbody>
</table>

with single site gonorrhoea except for one man, infected by a non-PPNG strain and treated with 0.25 g.

Multiple infected sites

Of 110 evaluable women patients, 44 (40%) had multiple infected sites (Table 1). This involved either urogenital and rectal (37); or urogenital, rectal and oropharyngeal (7) gonococcal infections. There were three treatment failures, one failure for each dose. In each case the persistent pathogen was a non-PPNG strain. All patients with three infected sites (urogenital, rectal and oropharyngeal) were cured: four with 0.25 g, one with 0.5 g and two with 1.0 g.

Considering all patients as a group, since there were no relevant differences between treatment groups, there were only four bacteriological failures in the treatment of 290 evaluable patients, an overall cure rate of 99%.

Clinical symptoms were present in 179 of 180 (99%) male patients. Of these, 46 patients had urethral discharge alone, three patients had dysuria alone, and 130 patients had both. Within 5 days after treatment, 150 male patients had no remaining symptoms and 29 still had some or all of the original symptoms. The one man who experienced a bacteriological failure had urethral discharge which had improved at follow-up.

Clinical symptoms were present in 96 of 110 (87%) female patients. Various symptoms were reported: 80 cases of purulent vaginal discharge, 31 cases of dysuria, 15 cases of pruritus of the sexual organs, two cases of sore throat, one case of urethral discharge and one case of infectious diarrhea. Of those female patients reporting symptoms, 64 patients had only one symptom, 29 (one bacteriological failure) had two and three patients had three. Within 5 days of treatment, 84 patients had no remaining symptoms, 11 (two bacteriological failures) still had some or all of their original symptoms and for one patient the clinical outcome was not recorded. Two of the three bacteriological failures had both purulent vaginal discharge and dysuria; when examined after 5 days, one showed complete remission and the other showed an improvement for both symptoms. The third failure had vaginal discharge alone and it had improved after 5 days.

Considering all patients as a group, all symptoms disappeared in 234 of 274 patients (85%) that were clinically assessable at the follow-up examination.

Out of the 290 N. gonorrhoeae strains isolated from evaluable patients, 173 were non-PPNG and 117 were PPNG. All strains were sensitive to spectinomycin, although a relatively high MIC$_{90}$ of 32 mg/l was required. The high degree of resistance of the non-PPNG strains is reflected in the high MIC$_{90}$ values for penicillin and tetracycline (Figure 1).

No relevant difference in inhibition pattern was found between the 3 cephalosporins and ofloxacin as shown by the sensitivity distribution of all 309 isolated strains (Figure 2).

None of the antibiotics tested showed any relevant difference in MIC values for PPNG versus non-PPNG strains (the MIC values of the 290 strains from evaluable patients are shown in Table 2).

All 326 patients receiving cefodizime were evaluable for local tolerance. Two kinds of events were reported: pain on injection (36%) and induration (6%). Three-quarters of the patients reporting pain on injection described it as mild, whereas all the reports of induration were mild. No dose relationship with cefodizime was found (there were less than half as many reports with 0.5 g as with 0.25 g).

Because of the lack of follow-up data for some patients, evaluation of general tolerance and of clinical chemistry was based on 310 and 306 patients, respectively. Two moderate increases in transaminases occurred, both with the 1.0 g treatment. In one case, considered probably drug related (according to Karch and Lasagna), both serum glutamic oxaloacetic transaminase (SGOT) and
serum glutamic pyruvic transaminase (SGPT) levels increased concomitantly, whereas in the other case, considered possibly drug related, only SGPT increased. Both patients were young men (ages 22 and 29 years) who had no concomitant diseases or other aggravating factors. No adverse drug reactions were reported. No statistically significant or clinically relevant trends in laboratory values were observed.

DISCUSSION

Although antibiotics such as penicillin and tetracycline continue to be effective against gonorrhoea in some areas, the increase in PPNG strains and the overall resistance encountered in South East Asia has compelled the use of β-lactamase insensitive compounds. The relatively high cost of these antibiotics has tended to discourage their use as first-line treatment. However, when all costs of diagnosis, treatment and follow-up are considered, together with the expenses generated by the further care required by treatment failures, these more effective antibiotics can be less expensive. The highly effective and fast-acting third generation cephalosporins, for example, are more economical provided that a low but effective dose is used. It is therefore imperative that minimum effective doses be ascertained for those antibiotics intended for use in regions of high resistance.

The cure rate in this study was close to 100% for all treatments, even the single dose of 0.25 g. There were only 4 treatment failures which were evenly distributed among all treatment groups. In male or female patients with single-site gonococcal infections pathogens were completely eliminated in all but one case. The other three failures occurred in females with multiple infection sites, one for each dose. It is especially noteworthy that all 7 evaluable cases with concomitant urogenital, rectal and oropharyngeal gonorrhoea were cured (4 with 0.25 g).

These results are similar to those obtained in a clinical study of cefodizime therapy for gonorrhoea performed in the Netherlands, which compared doses of 0.5 and 1.0 g cefodizime with a reference treatment of 1.0 g cefotaxime. It demonstrated a 100% cure rate for both cefodizime doses. Although the Dutch patients did not differ significantly from the Thai patients in demographic details, the resistance of the isolated strains was quite different. The percentage of PPNG strains isolated in the

---

Table 2. Minimum inhibitory concentrations (MIC, mg/ml) of antibiotics for gonococcal isolates of the 290 evaluable patients

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Strain*</th>
<th>MIC range</th>
<th>(\text{MIC}_{50})</th>
<th>(\text{MIC}_{90})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefodizime</td>
<td>non-PPNG</td>
<td>&lt;0.004-0.250</td>
<td>0.014</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>PPNG</td>
<td>&lt;0.004-0.125</td>
<td>0.012</td>
<td>0.039</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>non-PPNG</td>
<td>&lt;0.004-0.250</td>
<td>0.012</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>PPNG</td>
<td>&lt;0.004-0.125</td>
<td>0.010</td>
<td>0.031</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>non-PPNG</td>
<td>&lt;0.004-0.256</td>
<td>0.007</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>PPNG</td>
<td>&lt;0.004-0.063</td>
<td>0.007</td>
<td>0.022</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>non-PPNG</td>
<td>&lt;0.004-0.500</td>
<td>0.020</td>
<td>0.049</td>
</tr>
<tr>
<td></td>
<td>PPNG</td>
<td>&lt;0.004-0.125</td>
<td>0.021</td>
<td>0.051</td>
</tr>
</tbody>
</table>

*Strains: 173 non-PPNG, 117 PPNG

---

Figure 1. Minimum Inhibitory Concentration (for 50% and 90% inhibition of all tested strains) for penicillin and tetracycline for PPNG and non-PPNG strains from the 290 evaluable patients. Data from Bangkok (open columns, this study) compared with data from Rotterdam (shaded columns, adapted from van der Willigen et al.); exact penicillin MICs for PPNG strains cannot be given as they were only determined up to >4 mg/l.

Figure 2. The in vitro sensitivity distribution of all 309 isolated N. gonorrhoeae strains to: cefodizime (CDZ), cefotaxime (CTX), ceftriaxone (CTRX), ofloxacin (OFX), and spectinomycin (SPEC)
Rotterdam study was much lower (8%) than in the present study (40%); moreover, the strains isolated in Bangkok were more resistant to tetracycline (Figure 1). In addition, the non-PPNG strains from Europe were also less resistant to both penicillin (10-fold) and tetracycline (3-fold). From this comparison, it is evident that cefodizime is equally effective in the more stringent setting of greater antibiotic resistance in Thailand, even at the lower dose of 0.25 g.

The incidence of 40% of PPNG strains found is similar to that of an earlier study conducted in Bangkok in 1982(2) (42%) and suggests that the incidence of PPNG strains in Bangkok may have stabilized. Nevertheless, this very high percentage makes it inadvisable to use penicillin to treat gonococcal infections in this region. Somewhat surprisingly, despite reports of spectinomycin-resistant strains of N. gonorrhoeae(16,19), no truly resistant strains were isolated in this study. The MICs for spectinomycin, however, were considerably higher than those from strains in other parts of the world(19). Cefodizime, the other two cephalosporins tested and the quinolone ofloxacin were all similarly inhibitory at low concentrations in vitro against the strains isolated.

Determining clinical efficacy in gonococcal infections is often difficult. In women, many cases are asymptomatic (although this study included a relatively high percentage of women with symptoms). Furthermore, symptoms often persist in patients due to additional Chlamydia, Mycoplasma or Trichomonas infections which do not respond to cephalosporins. Drugs active against these pathogens usually require longer treatment regimens and therefore efficacy cannot be evaluated concurrently. Nevertheless, there was a complete disappearance of all symptoms in 85% of the patients with symptoms. In accordance with the usual criteria for clinical evaluation, symptoms remaining in those patients with a bacteriological cure are considered to be non-gonococcal in origin.

All 3 doses of cefodizime were safe and well tolerated. Mild pain on injection was reported more frequently than is expected and than previously observed with cefodizime(17). Mild induration was also reported. Neither of these events was dose related. They were most likely due to the rupture of muscle fibres caused by the rapidity of the injections (4 ml within 10 seconds, not slowly as stipulated). There were no major anomalies in clinical chemistry. The two cases of transaminase increases were considered drug related because beta-lactam antibiotics are known to induce occasional increases in transaminase levels (although an over-indulgence in alcohol cannot be ruled out).

A number of other new antibiotics have been used in clinical studies against gonorrhoea in regions of South East Asia with a high incidence of PPNG strains (ofloxacin(20), ceftriaxone(21), cefuroxime(22), norfloxacin(23,24), and cefoxitin(25)) and all display cure rates of almost 100%. None of these treatments show significant advantages over a single dose of 2 g spectinomycin now employed throughout the region. However, reports of spectinomycin resistant strains(19) and a high in vitro frequency of mutation to resistance(26), together with widespread spectinomycin use, indicate a need for constant vigilance against outbreaks of resistance. Indeed, the Centers for Disease Control treatment guidelines for gonorrhoea recommend the use of third-generation cephalosporins in all PPNG-endemic areas(27). The United States Armed Forces also now use cephalosporins in the Republic of Korea(19).

As demonstrated by this study, cefodizime appears to be an attractive alternative treatment. It is safe and well tolerated. It is effective against PPNG and non-PPNG strains at low single doses in both men and women with urogenital and rectal infections. Although greater numbers of patients need to be studied, it appears that the usual difficulties in treating infections of the pharynx do not diminish the effectiveness of cefodizime. It is current practice with gonorrhoea in areas with a high incidence of resistant strains to administer double the minimum effective dose of an antibiotic(25).

Although a single dose of 0.25 g cefodizime was highly effective, double this dose (0.5 g) must be recommended for South East Asia as long as single doses lower than 0.25 g have not yet been tested.

In conclusion, 0.25 g cefodizime has been shown to be an effective and safe antibiotic for the treatment of acute N. gonorrhoeae infections, regardless of sex, multiplicity of infected sites, the production of beta-lactamases or general antibiotic resistance.

Acknowledgements: We would like to thank Dr B Drees for his invaluable assistance in the preparation of the manuscript.

References

9 Barry AL, Jones RN, Thornsberry C, Ayers LW, Gerlach EH, Sommers HM. Antibacterial activities of ciprofloxacin, norflo-
17 van der Willigen AH, Wagenvoort JHT, Schalla WO, et al. Randomized comparative study of 0.5 and 1 g of cefodizime (HR 221) versus 1 g of cefotaxime for acute uncomplicated urogenital gonorrhea. *Antimicrob Agents Chemother* 1988;32:426-9