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Susceptibility of penicillinase-producing *Neisseria gonorrhoeae* in Ibadan to cefoxitin*

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Summary

The minimum inhibitory concentration (MIC) of fourteen strains of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) isolated in Ibadan to cefoxitin has been determined and compared with that of other antibiotics, viz. penicillin, ampicillin, thiamphenicol, spectinomycin, erythromycin and oxytetracycline. All the strains show high-level resistance to penicillin and ampicillin and the MIC of cefoxitin ranged from 0.5 to 16.0 µg/ml, with 71% of the strains having an MIC of 1.0 µg/ml or less. The data suggest that cefoxitin may be a useful alternative to spectinomycin in the treatment of uncomplicated gonococcal infections, due to either PPNG or non-PPNG strains. However, further experiments and *in vitro* studies are indicated.

Résumé

Une étude comparatoire de la concentration inhibitrice minimale (CIM) de quatorze souches de gonocoque productrice de la pénicillinase d'une part à la cefoxitine et d'autre part aux autres antibiotiques, tels que: la pénicilline, l'ampicilline, le thiamphenicol, la spectinomycine, l'érythromycine et de l'oxytétracycline a été effectuée. Toutes les souches démontrent une résistance élevée à la pénicilline et à l'ampicilline, et les CIM de la cefoxitine va de 0.5 à 16.0 µg/ml, avec 71% des souches ayant une CIM de 1.0 µg/ml ou moins. Ce fait suggère que la cefoxitine peut être un remplaçant utile à la spectinomycine dans le traitement des infections gonococciques non-compliquées dues et à la PNNG et à la non-PPNG. Néanmoins il y a besoins de plus d'expérience et des études *in vitro* sont indiquées.

Introduction

Epidemiological and clinical data have shown that strains of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) are now circulating freely in Nigeria (Osoba *et al.*, 1981; Odugbemi, 1981; Bello, 1982; Osoba & Ogunbanjo, 1983), and in many West African countries (Perine *et al.*, 1979; Piòt, 1977) after their emergence in West Africa in 1976. These strains are resistant to penicillin and other semi-synthetic penicillins by virtue of their penicillinase (β lactamase) production. Surveillance screening of gonococci in Ibadan for PPNG strains has demonstrated an alarming increase from being 2.7% of gonococcal isolates in 1979 (Osoba *et al.*, 1981) to 50% in 1981 (Osoba & Ogunbanjo, 1983; Osoba *et al.*, 1982). At present spectinomycin is the drug of choice for treating infections due to the PPNG. However, there was a recent report of a case of PPNG infection in a traveller returning from South-East Asia to the U.S.A. The isolate was not inhibited by a disc containing 100 µg of spectinomycin (WHO, 1981). The infection was resistant to three courses of spectinomycin and was later successfully treated with cefoxitin (2 g) together with 1 g probenecid. Consequently, there is an urgent need to search for alternative therapy to spectinomycin for PPNG infections.

Recently, two β-lactam antibiotics — cefuroxime and cefoxitin — have been suggested as potentially effective agents in the treatment of PPNG infections, because, firstly, they possess a better *in vitro* activity against *N. gonorrhoeae* than other previous cephalosporin antibiotics

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and secondly, they are resistant to hydrolysis by β lactamase (penicillinase) (Siegel *et al.*, 1979). Cefoxitin is a chemically modified form of a member of a new family of β-lactam antibiotics — the cephamycins. Although cefoxitin resembles the cephalosporins, its main biochemical difference is its remarkable degree of resistance to all β lactamases. This resistance provides the antibiotic with a broad antibacterial spectrum, and it is effective against most bacterial pathogens normally sensitive to the cephalosporins and many strains of Gram-negative bacteria that have become refractory to other β-lactam antibiotics (Birnbaum, 1978). It is a cell-wall active agent and is bactericidal in its action. As is the case with other β-lactam antibiotics, the serum $t_{1/2}$ of cefoxitin is increased by the simultaneous administration of probenecid (Siegel *et al.*, 1979; Birnbaum, 1978).

In view of the advantages of cefoxitin, this study was undertaken to compare the *in vitro* susceptibility of PPNG isolated in Ibadan to cefoxitin with other antibiotics such as penicillin, ampicillin, thiamphenicol, spectinomycin, erythromycin and oxytetracycline.

Materials and methods

The materials consisted of fourteen strains of PPNG isolated on Thayer-Martin medium from patients with urethritis attending the Special Treatment Clinic of the University College Hospital, Ibadan. Penicillinase production was confirmed by resistance of the isolates to 10 units penicillin disc and chromogenic cephalosporin test. Sensitivities to antibiotics was determined by the agar plate dilution method (WHO, 1978), using the GC agar with 1% haemoglobin and 1% isovitalex. The inoculum consisted of approximately 10^8 colony-forming units from a suspension of organisms in proteose peptone broth (Difco). Inoculated plates were incubated at 35–36°C in a candle extinction jar for 18–24 h. Reference strains were included in each batch of tests. The minimum inhibitory concentration (MIC) was regarded as the lowest concentration of antibiotic that permits the growth of no more than one colony (WHO, 1978). The sensitivities of the fourteen PPNG were determined against cefoxitin, penicillin, ampicillin, thiamphenicol, spectinomycin, erythromycin and oxytetracycline. The strains used were further lyophilized and sent to the Institute of Alfred Fournier in Paris for confirmation and the determination of their MIC.

Results

The cumulative percentage of the MIC in μg/ml of the fourteen strains tested against cefoxitin and the other antibiotics is shown in Table I. As expected, all the strains showed high-level resistance, especially against penicillin and ampicillin. The MIC of cefoxitin ranged from 0.5 μg/ml, with 71% of the strains having an MIC of 1.0 μg/ml or less. Of the isolates tested, 21% had MIC of 2.0 μg/ml of cefoxitin or more. All the isolates were sensitive to spectinomycin with MIC of 32.0 μg/ml or less and to tetracycline with MIC of 2.0 μg/ml or less.

Discussion

Although a few strains of PPNG have been tested in this study, the study nevertheless confirms the marked sensitivity of the West African strains of PPNG to cefoxitin, even though some of the strains show high-level resistance to cefoxitin. In a similar study (Siegel *et al.*, 1979) where the MIC of forty-five PPNG isolates collected through surveillance in the U.S.A. was determined, 87.5% had MICs of 1.0 μg/ml or less, while 13.3% had MIC of 2.0 μg/ml or more. The corresponding figures for the isolates tested in this study are 71 and 21%. Similarly, all five PPNG strains by Philips (1978) had MIC to cefoxitin of 1.0 mg/ml or less. It appears that more strains here showed a higher level of resistance than in the U.S.A. or the U.K.

The result of this susceptibility testing suggests that cefoxitin will be effective in the treatment of gonococcal infections due to the PPNG, since the drug is not hydrolysed by the TEM-type β lactamase mediated by R plasmids in *N. gonorrhoeae*.

However, in the study by Siegel *et al.* (1979), it was found that resistance to cefoxitin was correlated highly with resistance to penicillin in non-PPNG strains. They therefore concluded that cefoxitin would be a poor choice for retreatment if the patient failed initially to be

Table 1. Susceptibility of fourteen penicillinase-producing *N. gonorrhoeae* strains to seven antimicrobial agents

Antimicrobial agent	Cumulative percentage of MIC (μg/ml)								
	0.125	0.25	0.5	1.0	2.0	4.0	8.0	16.0	32.0
Penicillin G						100			
Ampicillin						100			
Cefoxitin			14	71	79	93	93	100	
Thiamphenicol			14	14	50	86	86	93	100
Spectinomycin								7	100
Erythromycin			14	21	43	86	86	100	
Oxytetracycline			7	21	100				

cured by penicillin and was infected with non-PPNG strain. The resistance to penicillin and other antibiotics demonstrated by non-PPNG strains is thought to be a chromosomal-mediated resistance. Although we did not include non-PPNG strains in this study, our previous studies have shown that over two-thirds of the non-PPNG strains encountered in most African countries have marked diminished sensitivity to penicillin and to many other antimicrobial agents, unlike the non-PPNG strains encountered in the U.S.A. (Osoba, 1981; Osoba *et al.*, 1977). Consequently, more *in vitro* studies are indicated, particularly in developing countries of Africa, to determine the activity of cefoxitin against the circulating non-PPNG strains as well as the PPNG strains.

In conclusion, our data suggest that cefoxitin may be a useful alternative to spectinomycin in the treatment or uncomplicated gonococcal infections, due to either PPNG of non-PPNG strains. However, further experience is still required on the treatment of gonococcal infections, particularly in areas with high prevalance of PPNG and non-PPNG strains. There is also a need to determine the efficacy of cefoxitin in the treatment of uncomplicated gonococcal infection in females and in complicated infections in both sexes.

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