

The activity of rosoxacin, fosfomycin, cefotiam, and spectinomycin on β -lactamase producing *Neisseria gonorrhoeae*

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SUMMARY We measured the activity of rosoxacin, fosfomycin, cefotiam, and spectinomycin against 51 isolates of β -lactamase producing *Neisseria gonorrhoeae*, all of which were susceptible to each drug at sufficient concentrations. The development of strains of penicillinase producing *N gonorrhoeae* (PPNG) which are resistant to spectinomycin can therefore be avoided, as there are alternative drugs.

Introduction

Penicillinase (β -lactamase) producing *Neisseria gonorrhoeae* (PPNG) was first isolated in Liverpool in 1976,¹ and these strains have since been isolated in many other countries of Europe, America, Asia, and Australia. A report from the Centers for Disease Control stated that worldwide in 1981 and 1982 there had been a twofold to sixfold increase in PPNG strains.² These strains are clinically important as they are resistant to penicillin G, the most widely used treatment for gonorrhoea. The susceptibility of PPNG strains to several cephalosporins has been examined, and they have been shown to be sensitive, for example, to cefuroxime and cefoxitin.³ Nevertheless, in many countries the drug of choice for infections with PPNG strains is spectinomycin hydrochloride. As there may be a one step mutation of *N gonorrhoeae* to spectinomycin resistance,⁴ it is of growing concern that spectinomycin has been used more frequently in the past years for the treatment of gonorrhoea. To prevent this resistance, spectinomycin should be used only in special cases, and not as frequently as at present.

The purpose of this study was to examine alternative drugs to spectinomycin for the treatment of infections caused by PPNG strains. We tested the sensitivity to spectinomycin, cefotiam, fosfomycin, and rosoxacin of 51 PPNG strains isolated from different geographical areas.

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Materials and methods

BACTERIAL STRAINS

The 51 PPNG isolates examined came from: England (37), Nigeria (3), Hong Kong (1), Saudi Arabia (2), Cameroon (1), South Korea (1), Philippines (2), and Thailand (4). Deoxyribonucleic acid (DNA) isolation and agarose gel electrophoresis showed that 10 strains carried a 3.2 megadalton (Mdal) β -lactamase inducing plasmid and 41 strains carried a 4.6 Mdal plasmid. Using isoelectric focusing, the β -lactamase produced by all the isolates was shown to be TEM1.

CULTURE MEDIA

Chocolate agar containing 1% haemoglobin (BBL) and vitox enrichment (Oxoid) was used for culture of *N gonorrhoeae*. Twofold dilutions of the following antibiotics were prepared for agar dilution testing: spectinomycin 2-128 mg/l, cefotiam 0.015-16 mg/l, fosfomycin 1-64 mg/l, and rosoxacin 0.007-2 mg/l.

TESTING SUSCEPTIBILITY TO ANTIBIOTICS

To prevent loss of the plasmid, the isolates were grown on chocolate agar containing 1 mg/l ampicillin. Overnight cultures were suspended in prewarmed GC broth⁵ to a 0.5 McFarland standard (10^8 colony forming units (cfu)/ml) and diluted to suspensions of 10^7 and 10^6 cfu/ml. Using a multipoint inoculator, spots of 10^5 , 10^4 , or 10^3 cfu were inoculated on to prewarmed chocolate agar containing the above antibiotics. The strains were incubated at 37°C in a 10% carbon dioxide incubator for 45 hours. The minimum inhibitory concentration (MIC) was the lowest concentration of a drug which inhibited growth completely. A 45 hour incubation

period was chosen as it gave more reproducible results than the usual 20 hours. MICs of rosoxacin, fosfomycin, and spectinomycin were the same after 45 hours as after 20 hours, while that of cefotiam was one dilution higher after 45 hours than after 20 hours.

Results

The figure shows cumulative data on the susceptibilities of PPNG strains to rosoxacin, cefotiam, fosfomycin, and spectinomycin, with the MIC of rosoxacin being the lowest. The table shows the ranges of MICs related to inoculum sizes.

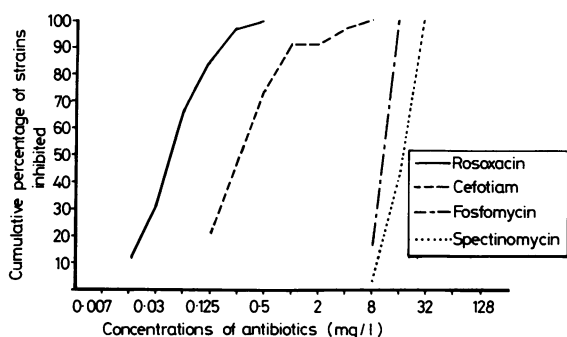


FIGURE Antibiotic susceptibilities of 51 PPNG strains using 10^5 cfu/inoculum

Discussion

Our data corresponded with susceptibility figures already published. MICs of fosfomycin of 8-32 mg/l for non-PPNG strains have been reported,⁶ but there are no data for PPNG strains. The reported MICs of cefotiam⁷ vary from 0.007 to 0.5 mg/l (PPNG strains) and 0.12 to 0.5 mg/l (non-PPNG strains); those in our study ranged from 0.03 to 8 mg/l depending on inoculum size. Reported MICs of rosoxacin vary from 0.007 to 0.06 mg/l (PPNG

strains) and 0.007 to 0.5 mg/l (non-PPNG strains);⁸ those for our isolates were 0.015 to 0.5 mg/l. Resistance to spectinomycin of 4-16 mg/l (PPNG strains) and 0.5-31 mg/l (non-PPNG strains) has been reported;⁸ our results showed MICs of 8-32 mg/l.

Bacteria inhibited by concentrations of <16 mg/l fosfomycin were considered to be susceptible, and strains inhibited by concentrations of >64 mg/l were interpreted as being resistant.⁸ The half life of fosfomycin is 2½ hours, and serum concentrations after administration of 5 g are between 157 mg/l after one hour and 39 mg/l after six hours.¹⁰ Acute gonorrhoeal infections have been cured successfully using a single dose of 4 g fosfomycin.¹¹ The half life of cefotiam is 45 minutes, and serum concentrations after a single dose of 1 g are between 30 mg/l after 30 minutes and 0.7 mg/l after five hours. Strains inhibited by concentrations of <8 mg/l cefotiam are considered to be susceptible, and those inhibited by concentrations of >32 mg/l to be resistant, according to data given by the manufacturer. The half life of rosoxacin is 3.4 hours, and peak serum concentrations are between 4.6 and 4.9 mg/l.¹³ If it is administered orally as a single dose of 300 mg, serum concentrations are between 4.9 mg/l after two hours and 0.5 mg/l after 15 hours.¹³ Calubiran reported 100% cure rates of uncomplicated gonorrhoea using a single dose of 300 mg rosoxacin.¹⁴ Strains of *N gonorrhoeae* inhibited by <32 mg/l spectinomycin are interpreted as being sensitive.^{8,15} We concluded, therefore, that the PPNG strains tested were susceptible to fosfomycin, cefotiam, rosoxacin, and spectinomycin provided there is sufficient diffusion of the drugs.

This report shows the possibility of treating infections caused by PPNG strains with rosoxacin, cefotiam, fosfomycin, or spectinomycin. An advantage of treatment with rosoxacin is that it can be administered orally. The development of mutant strains resistant to spectinomycin can therefore be avoided, as alternative drugs are available.

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TABLE Minimum inhibitory concentrations (mg/l) of four antibiotics to 51 PPNG strains tested on chocolate agar using three inoculum sizes

| Antibiotics | Inoculum sizes | | |
|---------------|-----------------|-----------------|-----------------|
| | 10^3 cfu/spot | 10^4 cfu/spot | 10^5 cfu/spot |
| Rosoxacin | 0.015-0.5 | 0.015-0.5 | 0.015-0.5 |
| Cefotiam | 0.03-4 | 0.06-8 | 0.125-8 |
| Fosfomycin | 8-16 | 8-16 | 8-16 |
| Spectinomycin | 8-32 | 8-32 | 8-32 |

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