SHORT REPORT

# Which cephalosporin for gonorrhoea?

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The recommended treatment for gonorrhoea in the United Kingdom has, until recently, included the fluoroquinolone, ciprofloxacin, which consequently was used by most genitourinary medicine clinics. In 2002 national surveillance data showed that resistance to ciprofloxacin had risen to a prevalence of 9.8% (9% in 2003), indicating that the target of >95% efficacy in first line therapy was no longer achievable. The third generation cephalosporins, ceftriaxone (intramuscular) or cefixime (oral), are the recommended alternatives, but recent audit data reveal other cephalosporins are currently being used to treat gonorrhoea, notably including cefuroxime (intramuscular or, often, oral). A pharmacodynamic analysis was undertaken to determine whether all these regimens were equally potent. Ceftriaxone, 250 (or 500) mg intramuscularly, or cefixime, 400 mg orally, were calculated to give free drug concentrations above the $MIC_{90}$ for 22–50 hours post dose whereas the cefuroxime regimens being used were pharmacodynamically borderline, achieving this target for only 6.8–11.2 hours and raising the spectre that continued use may select for stepwise increases in resistance, as occurred with penicillin. We therefore underscore that ceftriaxone or cefixime should be the agents of choice to replace ciprofloxacin, as recommended in the new treatment guidelines, and that cefuroxime is a poor substitute.

Gonorrhoea is predominantly diagnosed at genitourinary medicine (GUM) clinics in the United Kingdom. The presumptive diagnosis is based on microscopy, especially in known contacts of infected people, and is confirmed by culture, often after treatment has been given. The choice of treatment is made with reference to national guidelines (www.bashh.org) and aims to achieve cure in more than 95% of patients. These guidelines are informed by local and national surveillance data on the prevalence of resistance, which have been provided since 2000 by a national programme (GRASP, Gonococcal Resistance to Antimicrobials Surveillance Programme), covering England and Wales. GRASP tests consecutive gonococcal isolates from 26 representative centres over a 3 month period each summer.[1]

Ciprofloxacin has been the antimicrobial agent of choice for gonorrhoea in recent years, and was routinely used by 74% of clinics in 2001, though a minority preferred ampicillin.[2] Until 2001, fewer than 3% of the gonococci collected under the ambit of GRASP were resistant to ciprofloxacin, and most of these few were from infections acquired overseas. In 2002, the proportion of ciprofloxacin resistant isolates jumped to 9.8%[1] and remained over 9% in 2003[3]; moreover, local transmission of resistant strains has become frequent.[4] Most ciprofloxacin resistance is high level, with minimum inhibitory concentrations (MICs) of 16–32 mg/l—values associated with clinical failure.[5]

Fluoroquinolones consequently cannot any longer be relied upon to achieve the target of more than 95% efficacy, and replacement therapies must be sought. Since about 10% of UK gonococci are resistant to penicillin, half of them with β lactamase, penicillins are only an option if good local surveillance data are available to support their continued use. Azithromycin has been suggested because of its broad spectrum activity against other STIs, such as *Chlamydia trachomatis* and *Treponema pallidum*, but despite reports of efficacy,[6] clinical failure has been noted[7] and small but significant increases in resistant isolates were found during GRASP 2003.[3] The remaining, and obvious, alternatives to fluoroquinolones therefore are the cephalosporins and spectinomycin. This report examines the use of different cephalosporins for the treatment of gonorrhoea and considers differences in their potential efficacy.

## METHODS

Information on the choices of antimicrobial therapy for gonorrhoea was obtained from the North Thames Audit Group (unpublished data) and from GRASP 2003.[3]

Based on these surveys we undertook a pharmacodynamic analysis, using published pharmacokinetic parameters to model time above MIC of free drug ($fT > MIC$), which is the critical predictor of β lactam efficacy.[8] The susceptibility parameters used (table 1) were the $MIC_{50}$ and $MIC_{90}$ values published, based on multiple studies, by Wiedemann and Grimm[9] and the top MICs ($MIC_{max}$) published by Rice and Knapp,[10] who tested cefuroxime, cefixime, and ceftriaxone in parallel against some of the most cephalosporin resistant gonococci so far recorded.

The $fT>MIC$ value was estimated using MODLAB version 3.32 (Mediware, Maasstricht, Netherlands) assuming a one compartment model with the parameter values as shown in table 2. Since the absorption coefficient was not always available the values shown were estimated from published literature data.[11–16]

## RESULTS

An audit of 179 patients with gonorrhoea attending GUM clinics in the North Thames area between September and November 2003 revealed 87 were given fluoroquinolones; 16 amoxicillin; 15 spectinomycin, and 64 a cephalosporin, all as single dose therapy. A few patients received more than one of these agents simultaneously and many received concurrent courses of tetracyclines or macrolides, directed primarily against concurrent non-gonococcal infection but potentially effective also against gonorrhoea. Among the cephalosporin treated patients, 20 received 250 mg intramuscular ceftriaxone and one received ceftriaxone 500 mg; 15 received 400 mg oral cefixime; 13 received 1.5 g intramuscular cefuroxime and 15 received oral cefuroxime axetil, five of them at a dose of 1 g and 10 at 200 mg. A further analysis of 1808 patients treated during the GRASP 2003 collection showed 769 treated with cephalosporins, predominantly ceftriaxone (437, 57%),

**Table 1** $MIC_{50}$, $MIC_{90}$, and $MIC_{max}$ values (mg/l) for *Neisseria gonorrhoeae**

| | Cefuroxime | Ceftriaxone† | Cefixime |
|---|---|---|---|
| $MIC_{50}$ | 0.06 | 0.008 | 0.016 |
| $MIC_{90}$ | 0.25 | 0.03 | 0.06 |
| $MIC_{max}$ | 8 | 0.25 | 0.125 |

*From Wiedemann and Grimm,[9] also ($MIC_{max}$) Rice and Knapp.[10]
†Ceftriaxone is the only cephalosporin tested against current English and Welsh isolates in GRASP and $MIC_{50}$, $MIC_{90}$, and $MIC_{max}$ values in 2003[3] were 0.002, 0.008 and 0.125 mg/l respectively, rather below the values in table 1.

**Table 2** Pharmacokinetic assumptions for compounds reviewed

| Parameter | Cefuroxime oral | Cefuroxime intramuscular | Ceftriaxone intramuscular | Cefixime oral |
|---|---|---|---|---|
| V1, volume of distribution (l) | 24.2 | 12.0 | 14.7 | 19.0 |
| k10, elimination rate ($h^{-1}$) | 0.55 | 0.53 | 0.082 | 0.204 |
| Fu, unbound fraction | 0.67 | 0.67 | 0.05 | 0.35 |
| F, bioavailibility | 0.8 | 1.00 | 1.00 | 0.5 |
| ka, absorbtion constant ($h^{-1}$) | 0.82 | 1.00 | 1.00 | 0.55 |
| $t_{½}$, half life (h) | 1.25 | 1.31 | 8.45 | 3.40 |
| References | 11–13 | 11–13 | 14, 15 | 16 |

cefixime (207, 27%), and cefuroxime (80, 10%), but did not indicate dosages.

The $fT>MIC_{50}$, $MIC_{90}$, and $MIC_{max}$ values for the cephalosporin regimens predominantly recorded in the audit are detailed in table 3. The ceftriaxone and cefixime regimens yielded serum levels above the $MIC_{max}$ for more than 15 hours, above the $MIC_{90}$ for at least 22 hours and above the $MIC_{50}$ for at least 29 hours. The performance of cefuroxime was less impressive, with even the higher doses (1 g oral and 1.5 g intramuscular) failing to counterbalance completely the consequences of the shorter half life and higher MICs than for cefixime and ceftriaxone. Thus, the time above $MIC_{90}$ was only 11.2 hours for the 1.5 g intramuscular regimen, 10.0 hours for the 1 g oral regimen, and 6.8 hours for the 200 mg oral regimen. For isolates with $MIC_{max}$, the $fT>MIC$ for cefuroxime values were only 0–4.6 hours.

## DISCUSSION

Despite national guidelines to use cefixime or ceftriaxone, the data from both the North Thames Audit and from GRASP showed a range of cephalosporins to be in use for the treatment of gonorrhoea in 2003, notably including oral and intramuscular cefuroxime. Are all these cephalosporins regimens equally efficacious, and might some be more prone to promote resistance? There is good clinical trial evidence for the efficacy of ceftriaxone 250 mg intramuscular and cefixime 400 mg oral in gonorrhoea, and to show that these regimens are equivalent in efficacy.[17] There are also small, rather old, trials to support the use of cefuroxime 1.5 g intramuscular[18] and cefuroxime axetil 1 g oral.[19] We cannot, however, find formal validation of cefuroxime axetil at 200 mg in gonorrhoea, and one study found cefuroxime 1.0 g oral inferior to ciprofloxacin for gonococcal urethritis in men, though not for cervical infection in women.[20]

We are unaware of any precise determination of the $fT>MIC$ value needed to ensure clinical efficacy with cephalosporins in gonorrhoea but some guide can be gained from the work of Jaffe *et al*[21] on penicillin. These authors found that efficacy correlated with a total drug level above 4 × MIC for 7–10 hours. Allowing for the protein binding of penicillin (70–80%), this condition corresponds to an $fT>MIC$ of 7–10 hours. On this basis, cefixime 400 mg orally and ceftriaxone 250 (or 500) mg intramuscularly seem more than adequate against any gonococcus likely to be encountered, whereas the cefuroxime regimens (and particularly the 200 mg oral schedule) are marginal at best. Notably, de Hoop *et al*[22] associated two treatment failures with a 1.5 g intramuscular cefuroxime regimen with MICs of 0.5–1 mg/l, whereas this regimen was consistently successful against infections caused by more susceptible strains. In addition, it should be realised that the $fT>MIC$ data are population means and that, therefore, a fair number of individuals will have significantly lower values. Monte Carlo simulations would provide insight into the dispersion of these values,[8] but was not undertaken in the present exercise.

Even where pharmacodynamically borderline cefuroxime regimens are clinically effective, there must be concern that they will select for gonococcal variants with stepwise reductions in susceptibility, arising via mutation or PBP gene recombination. Experience with penicillin showed how the ''typical'' MICs for β lactamase negative isolates crept up

**Table 3** Time (h) for which free drug concentrations exceed summary MIC parameters ($fT>MIC$) for the most used cephalosporin regimens in gonorrhoea

| | Cefuroxime | | | Ceftriaxone | | Cefixime |
|---|---|---|---|---|---|---|
| | 200 mg oral | 1 g oral | 1.5 g intramuscular | 250 mg intramuscular | 500 mg intramuscular | 400 mg oral |
| $MIC_{50}$ | 9.6 | 12.6 | 13.9 | 57.9 | 66.4 | 29.2 |
| $MIC_{90}$ | 6.8 | 10.0 | 11.2 | 41.0 | 49.5 | 22.4 |
| $MIC_{max}$ | 0.0 | 0.0 | 4.6 | 15.0 | 23.6 | 18.8 |

from around 0.004 mg/l in the 1940s to around 0.12 or 0.25 mg/l nowadays, and with therapeutic dosages needing to be increased commensurately. This gradual erosion seems less likely if treatment uses regimens with a good ''margin'' of activity. On this basis, we advocate that where cephalosporins replace fluoroquinolones the preferred agents should be ceftriaxone 250 mg intramuscularly or cefixime 400 mg orally, not cefuroxime, and certainly not low dose cefuroxime axetil.

## CONTRIBUTORS

CAI and DML initiated the work and prepared the manuscript; JWM performed the pharmacodynamic analysis; KJ contributed data on behalf of the North Thames Audit Group; KAF contributed data from GRASP 2003; and all authors reviewed the manuscript.


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