Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010

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Citation style for this article:
Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. Euro Surveill. 2011;16(14):pii=19833. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19833

Article published on 7 April 2011

Successful treatment of gonorrhoea is the mainstay of public health control. Cefixime and ceftriaxone, highly active third generation cephalosporins, are today the recommended first-line agents in most countries and azithromycin is a second-line agent. However, there is increasing evidence of decreasing susceptibility and emergence of therapeutic failures. In this report two cases of clinical failure to cefixime are described, one of which additionally shows failure to azithromycin and selection of a less susceptible strain during treatment.

Introduction

Cefixime and ceftriaxone are third generation cephalosporins recommended for first-line therapy for gonorrhoea in the United Kingdom [1]. Cefixime is administered orally in a single dose and is often used in preference to ceftriaxone, which is given intramuscularly (IM). The relationship between dosage given, susceptibility results and treatment failure is still poorly understood but recent reports from Norway [2] and Sweden [3] of treatment failures with cefixime and ceftriaxone, respectively, are beginning to increase our understanding. Azithromycin is an alternative treatment, as a 2-gram dose administered orally, but again the relationship between laboratory findings and treatment failure is unclear. We report here two cases of treatment failure to cefixime, one of which also demonstrated treatment failure to azithromycin, in North East England.

Case 1

In October 2010, a 51 year-old English man, presented at a genitourinary medicine (GUM) clinic in North East England. Prior to this, he had attended his general practitioner (GP) with urethral discharge and dysuria and was treated with amoxicillin and clavulanic acid (co-amoxiclav) for seven days before the tests results were available, which is not first-line treatment for either gonorrhoea or chlamydia, the most common causes of urethral discharge. Tests taken at the visit to the GP returned positive for gonorrhoea and negative for chlamydia and he was referred to the GUM clinic.

At the initial visit (day 1) at the GUM clinic he was symptomatic and reported having had a regular female partner for one year, with whom he last had sex two weeks before. He reported no other sex partners in the last year and no history of sex abroad. On examination, he had a profuse urethral discharge which was diagnosed as presumptive gonorrhoea on microscopy and treated immediately with cefixime 400 mg orally. The laboratory confirmed the diagnosis by isolation of *Neisseria gonorrhoeae* (GC) but reported that the infecting strain of *N. gonorrhoeae* showed decreased susceptibility to cefixime. He was negative for chlamydia, syphilis, and HIV (Table 1).

On recall (day 5), he was still symptomatic and was retreated with azithromycin. The patient returned a further two times, on day 22 and day 30, and remained culture positive for *N. gonorrhoeae* on both occasions (Table 1). He was given a further treatment with azithromycin on day 22 and then on day 40 was treated with ceftriaxone 250 mg IM following the isolation of *N. gonorrhoeae* from urethral sample taken on day 30 (Table 1). His test of cure on day 46 was negative. He reported he had sex with the same contact seven days following his first azithromycin treatment (day 12) but no other sexual contact.

The female sex partner attended another GUM clinic, tested GC culture negative but was treated preventively as a contact of Case 1 with cefixime 400 mg and subsequently azithromycin. She attended GUM Northumberland on day 40 with the index case, declined testing and was treated with ceftriaxone, 250 mg IM. She declared no sex partners other than Case 1.

Case 2

In October 2010, a 23 year-old man attended a different GUM clinic in North East England, as a contact of a chlamydia patient (day 1). He had no symptoms, reported sex with a man two weeks previously, and was treated with azithromycin one gram as a single dose because of his contact with the chlamydia case. He was tested for gonorrhoea (urethra, throat and

rectum) using culture and for gonorrhoea and chlamydia at the same sites using nucleic acid amplification (NAAT) (Aptima Combo 2, Gen-Probe), all of which proved negative. He was also tested for syphilis, HIV, hepatitis B and C markers and was negative (Table 2).

The patient came back to the clinic with symptoms over a month later, reporting having had sex with the same male partner one week prior, with whom he had been having a sexual relationship for the previous eight weeks. He reported no other sex partner in the previous six months. It is, therefore, likely that he acquired his gonococcal infection from this partner since his initial visit, as he tested negative for gonorrhoea on day 1, or from another source although he denied any other partners. A presumptive diagnosis of gonorrhoea was made at this visit (day 37) by microscopy and he was treated with cefixime 400 mg and doxycycline 100 mg twice daily for one week. Gonorrhoea was confirmed by isolation of *N. gonorrhoeae* from the urethra and presence of *N. gonorrhoeae* specific DNA in the urine. Susceptibility to cefixime and ceftriaxone was determined using discs and to penicillin and ciprofloxacin using Etests (Table 2) but the isolate was not available for confirmatory testing at the reference laboratory. Samples taken from the rectum and throat were negative for *N. gonorrhoeae* using culture and for *N. gonorrhoeae* and *Chlamydia trachomatis* using NAATs.

The patient came again to the clinic on day 48 and reported persistent, intermittent dysuria. He reported no sexual contact since day 30 but was again presumptively diagnosed with gonorrhoea by microscopy and treated with ceftriaxone 250 mg IM. *N. gonorrhoeae* was isolated from the urethra and exhibited decreased susceptibility to cefixime (MIC 0.25 mg/L). Six days later (day 54) the test of cure showed the patient was successfully treated.

Table 1

Clinical and microbiological findings and treatment given for gonorrhoea, Case 1, England, 2010

Case 1	Symptoms	Test results	Susceptibility results	Treatment
Day 1	Dysuria Urethral discharge	Gonorrhoea: culture and NAAT Urethra-positive Throat-negative Chlamydia: NAAT Urethra-negative Throat-negative Syphilis serology and HIV - negative	Cefixime: 0.19mg/L Ceftriaxone: 0.064mg/L Azithromycin: 0.25mg/L Ciprofloxacin: 6mg/L Penicillin: 1.5mg/L Spectinomycin: 12mg/L	Cefixime 400 mg orally
Day 5	Recalled for treatment Remained symptomatic	None	NA	Azithromycin 2 grams orally
Day 22	Urethral discharge	Gonorrhoea: urethra Microscopy intracellular GNDC Culture and NAAT- positive	Cefixime: 0.19mg/L Ceftriaxone: 0.047mg/L Azithromycin: 0.25mg/L Ciprofloxacin: 8mg/L Penicillin: 2.0mg/L Spectinomycin: 12mg/L	Azithromycin 2 grams orally
Day 30	Returned for review Asymptomatic	Gonorrhoea: urethra Culture positive	Cefixime: 0.19mg/L Ceftriaxone: 0.047mg/L Azithromycin: 1.0mg//L Ciprofloxacin: 8mg/L Penicillin: 2.0mg/L Spectinomycin: 12mg/L	None given
Day 40	Discharge returned	None	NA	Ceftriaxone 250 mg intramuscularly
Day 46	Returned for test of cure	Gonorrhoea: urethra Culture negative	NA	None given

GNDC: Gram-negative **intracellular** diplococcic; HIV: human immunodeficiency virus; NA: not available; NAAT: nucleic acid amplification tests.

The male sex partner first came to the GUM clinic mentioned above in September 2010 for a check-up, as a chlamydia contact of a female patient and was given azithromycin one gram. He considers himself gay but has some female contacts. No link to this patient was made until eight weeks later when Case 2 was diagnosed with gonorrhoea. When he was recalled, he refused to provide any additional samples although accepted treatment with cefixime.

Microbiology

The three gonococcal isolates from Case 1 and one of the two isolates from Case 2 were available for extended susceptibility tests using Etests. In addition to decreased susceptibility to cefixime, all were sensitive to ceftriaxone and spectinomycin and were resistant to ciprofloxacin and penicillin (Tables 1 and 2). The isolates from Case 1 showed an increase in the minimal inhibitory concentration (MIC) to azithromycin from 0.25 mg/L (day 1 and 22) to 1.0 mg/L (day 30) and Case 2 showed a MIC of 0.5 mg/L. The three isolates from Case 1 were indistinguishable by *Neisseria gonorrhoeae* multi-antigen sequence typing (NG-MAST) [4],

Table 2

Clinical and microbiological findings and treatment given for gonorrhoea, Case 2, England 2010

Case 2	Symptoms	Test results	Susceptibility results	Treatment
Day 1	Asymptomatic Contact of a chlamydia case	Gonorrhoea: culture Urethra-negative Throat-negative Rectum-negative Gonorrhoea and chlamydia: NAAT Urine-negative Throat-negative Rectum-negative Syphilis serology and HIV- negative Hepatitis B and hepatitis C markers-negative	NA	Azithromycin 1 gram orally
Day 37	Dysuria Urethral discharge	Gonorrhoea: microscopy Urethra –intracellular GNDC Gonorrhoea: culture Urethra- positive Rectal-negative Throat-negative Gonorrhoea and chlamydia-NAAT Urine- GC positive/CT negative Throat-negative Rectum-negative	Cefixime: sensitive[a] Ceftriaxone: sensitive[a] Penicillin 0.25mg/L Ciprofloxacin 8mg/L	Cefixime 400 mg orally Doxycycline 100 mg bd / seven days
Day 48	Dysuria persisting intermittently Purulent discharge on examination	Gonorrhoea: microscopy Urethra –GNDC Gonorrhoea: Culture Urethra- positive	Cefixime: 0.25mg/L Ceftriaxone: 0.064mg/L Azithromycin: 0.5mg/L Ciprofloxacin: 8mg/L Penicillin: 2mg/L Spectinomycin: 8mg/L	Ceftriaxone 250 mg intramuscularly
Day 54	Symptoms subsided No discharge	Gonorrhoea: culture Urethra- negative	NA	None given

bd: twice daily; CT: *Chlamydia trachomatis*; GC: *Neisseria gonorrhoeae*; GNDC: Gram-negative intracellular diplococcic; HIV: human immunodeficiency virus; NA: not available; NAAT: nucleic acid amplification tests.

[a] Disc sensitivity testing only available.

belonging to sequence type (ST) 3779 (*por*, 2147; *tbp*B, 110) but distinct from the isolate from Case 2 which belonged to ST 3431 (*por*, 2078; *tbp*B 110). All isolates contained the *pen*A mosaic allele [5]. Susceptibility to cefixime of both isolates from Case 2 had been determined using discs at the local laboratory and appeared initially sensitive and then exhibiting reduced susceptibility. This could indicate acquisition of a different strain but could also reflect difficulties in testing gonococcal susceptibility and remains unresolved as the initial isolate was unavailable for confirmatory testing at the reference laboratory. In the absence of treatment failures, the relationship of zone size to clinical failure is unknown and the second isolate was referred to Sexually Transmitted Bacteria Reference Laboratory (STBRL) by request of the clinician suspecting treatment failure.

Discussion

We report two cases of treatment failures to cefixime in England, one of which fulfils all the criteria for a verified failure [6]. The second case has limited information on the pre-treatment isolate but otherwise is consistent with a treatment failure and similar to a previous report [7]. The MICs to cefixime of 0.19-0.25 mg/L are consistent with the report from Norway [2] and with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [8] breakpoints of MIC 0.12 mg/L, although these remain putative until the relationship with clinical failure is fully clarified. They are also compatible with Monte Carlo Simulation modeling that suggests peak serum cefixime concentrations are inadequate for successful eradication of infections exhibiting MICs of 0.125 mg/L and above at the current doses used [9].

Case 1 also demonstrated treatment failure to azithromycin on potentially two occasions following treatment, on days 5 and 22. The patient admitted having had sex with the same contact between the two treatments and so he could have been re-infected with the same strain, which subsequently then failed azithromycin treatment again. However, the female contact was never diagnosed with gonorrhoea. The MIC breakpoint that equates with treatment failure for azithromycin is not known and is currently arbitrary, but in this instance the increase in MIC over time suggests selection of resistant strain during therapy, as previously demonstrated in the laboratory [10].

Dissemination of gonococcal isolates with cefixime decreased susceptibility in England and Wales has been largely clonal, belonging to ST 1407 or closely related STs, all sharing the *tbp*B 110 allele, as in these isolates [unpublished data]. Public health control of gonorrhoea is dependent on successful antimicrobial therapy and lessons should be learnt from the extraordinary ability of the gonococcus to be resistant and innovative treatment regimens will need to be used to prevent gonorrhoea becoming an infection difficult to treat. A viable organism is essential to detect emerging resistance as well as for susceptibility testing for individual patient management and therefore maintaining culture will be of paramount importance.

Acknowledgements

The authors would like to thank the staff of the Newcastle HPA Laboratory and the Sexually Transmitted Bacteria Reference Laboratory, HPA, Colindale.

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