A single 2 g oral dose of extended-release azithromycin for treatment of gonococcal urethritis

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Objectives: We treated gonococcal urethritis in men with a single 2 g dose of azithromycin extended-release formulation (azithromycin-SR) to determine its microbiological outcomes and tolerability.

Patients and methods: We enrolled 189 Japanese men with gonococcal urethritis between April 2009 and December 2013. The patients were given a single 2 g dose of azithromycin-SR. Microbiological efficacy was evaluated by the results of the post-treatment molecular testing of Neisseria gonorrhoeae. MIC testing was performed only for pretreatment isolates of N. gonorrhoeae collected from the patients.

Results: We evaluated 130 patients for microbiological outcomes. Of these patients, 122 (93.8%) were judged to be microbiologically cured on the basis of negative test results. All isolates for which the azithromycin MICs were ≤0.25 mg/L were eradicated, whereas 5 of 12 isolates for which the MICs were 1 mg/L persisted after the treatment. Forty-six adverse events occurred in 41 patients. However, all adverse events were classified as mild.

Conclusions: The eradication rate of N. gonorrhoeae was 93.8% in men with gonococcal urethritis treated with a single 2 g dose of azithromycin-SR. The breakpoint MIC of a 2 g dose of azithromycin-SR for gonococcal urethritis associated with clinical treatment failures appeared to be 1 mg/L. With regard to side effects of higher doses of azithromycin, the 2 g dose of azithromycin-SR appeared to improve tolerability. However, the widespread use of a high-dose regimen of azithromycin might lead to the development of further resistance to azithromycin.

Keywords: Neisseria gonorrhoeae, male urethritis, azithromycin-SR

Introduction

The introduction of new drugs to treat gonorrhoea has repeatedly brought about the emergence and spread of Neisseria gonorrhoeae with resistance to these drugs. After clinical strains of N. gonorrhoeae became resistant to penicillin, ceftriaxone was recommended as the primary drug for treatment of gonorrhoea in 1989. In addition to ceftriaxone, single doses of fluoroquinolones and a third-generation cephalosporin were recommended as primary treatment regimens in 1993. However, oral regimens of fluoroquinolones or oral third-generation cephalosporin are no longer recommended because of the continuous increase in clinical strains of N. gonorrhoeae with decreased susceptibilities to these agents in Japan. Furthermore, in 2009 the high-level ceftriaxone-resistant strain H041 was isolated from the pharynx of a female commercial sex worker in Japan. Thus, other drugs for gonococcal infections are required.

Some studies suggested good efficacy of a single 1 g dose of azithromycin to treat gonorrhoea. Since the early 1990s, however, clinical strains with decreased susceptibility to azithromycin have emerged in several countries worldwide. Furthermore, high resistance to azithromycin was reported from Argentina. A single 2 g dose of azithromycin immediate-release formulation has been reported to be effective against uncomplicated gonorrhoea. However, a 2 g dose of azithromycin immediate-release formulation could cause an unacceptable rate of side effects, especially gastrointestinal upset. Recently, a novel microsphere-based extended-release formulation of azithromycin (azithromycin-SR) has been developed that allows administration of a higher dose of azithromycin in a single-dose regimen and improves tolerability. With the microsphere-based preparation of azithromycin-SR, fewer upper gastrointestinal tract side effects are expected than with the immediate-release formulation. However, there have been no studies evaluating the usefulness of a single 2 g dose of azithromycin-SR for the treatment of...
gonorrhea. In this study, we treated male gonorrhea with a single 2 g dose of azithromycin-SR to determine its microbiological outcomes and tolerability.

Patients and methods

This prospective study was approved by the Ethics Committee of the Graduate School of Medicine, Gifu University (reference number 20-94) and registered with UMIN-CTR (UMIN ID: UMIN000013774). We enrolled 189 Japanese men with gonococcal urethritis who visited the iClinic, Benzai Clinic and Kidō Clinic between April 2009 and December 2013. All of the men provided their informed consent, and all had symptoms and signs compatible with acute urethritis. Polymorphonuclear leucocytes with intracellular diplococci were observed in the urethral smears of these patients. Specimens for isolation of N. gonorrhoeae were obtained from the urethra and then inoculated onto modified Thayer–Martin medium. N. gonorrhoeae was identified and confirmed using Gonocheck-II Reagent Tubes (EY Laboratories Inc.) and ID test NH-20 Rapid ‘Nissui’ (NISSUI Pharmaceutical Co., Ltd), and isolates were stored frozen using heart infusion broth with 20% glycerol at −70°C for later testing for susceptibility to antimicrobial agents. At the first visit, the patients’ first-voided urine specimens were also tested for N. gonorrhoeae using the APTIMA Combo 2 (Gen-Probe Inc.), AMPLICOR CT/NG Test (Roche Molecular Systems, Inc.) or ProbeTec ET CT/GC (Becton, Dickinson and Company).

No patients had undergone antimicrobial chemotherapy before visiting the clinics. The patients were given a single 2 g dose of azithromycin-SR. They were asked to return for re-examination 7–21 days after taking the drug and told to remain sexually abstinent until the follow-up visit. At this visit, the first-voided urine specimens were again obtained for testing. Microbiological efficacy was evaluated by the results of the post-treatment molecular testing for N. gonorrhoeae. Not all of the subjects were examined for the presence of Chlamydia trachomatis and genital mycoplasmas. Therefore, clinical outcomes of the treatment were not assessed on the basis of symptoms and signs. The patients were also asked both open-ended and directed questions so that possible adverse events of treatment could be identified. Subject side effects were classified according to the Common Terminology Criteria for Adverse Events. 

MIC testing was performed only for pretreatment isolates of N. gonorrhoeae collected from the patients and surviving storage. The MICs of azithromycin were determined by the agar dilution method.12

Results

Microbiological outcome

A total of 189 men were enrolled in this study. They ranged in age from 16 to 56 years (median, 30 years). All of them were heterosexual, but other demographic and behavioural characteristics, including sexual histories, prior urethritis and sexual partners, were not obtained from most of them. Fifty-nine patients were excluded because of no follow-up visit after treatment; thus, 130 patients were evaluated for microbiological outcomes. Of these patients, 122 (93.8%) were evaluated to be microbiologically cured of N. gonorrhoeae (Table 1).

We attempted the isolation and storage of N. gonorrhoeae from all patients. After storage only 103 isolates grew, and these were the isolates tested to determine the MIC of azithromycin. The MICs of azithromycin determined for these 103 isolates of N. gonorrhoeae ranged from 0.03 to 4 mg/L (Table 1). Of these 103 isolates, all 57 for which the azithromycin MICs were ≤0.25 mg/L were eradicated by treatment with the single 2 g oral dose of azithromycin-SR, whereas one of the 32 isolates for which the MICs of azithromycin-SR were eradicated by treatment with the single 2 g oral dose of azithromycin-SR, whereas one of the 32 isolates for which the MICs were 2 and 4 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 0.5 mg/L persisted after treatment.

Safety and tolerance

Forty-six adverse events (diarrhoea, abdominal pain, nausea and soft stool) occurred in 41 (31.5%) of the 130 patients. Of these 41 patients, 37 (90.2%) had diarrhoea. However, symptoms related to adverse events disappeared in 35 (85.4%) patients by the next day. Furthermore, all adverse events were classified as grade 1.

Discussion

In this study, the eradication rate of N. gonorrhoeae was 93.8% (95% CI, 89.7%–98.0%) in men with gonorrhoea treated with a single 2 g dose of azithromycin-SR. We performed retesting in this study 7–21 days later. The high rate of microbiological efficacy found in this study (93.8%) could be explained by the inclusion of false-positive reactions. However, all patients retested within 2 weeks were truly negative. Thus, the true effective eradication rate was 93.8%. Handsfield et al.13 defined the acceptable clinical efficacy for treatment of gonorrhoea as a cure rate of ≥95% with a lower 95% CI of at least 90%. More stringent criteria required a cure rate of ≥95% with a 95% CI ranging from 95% to 100%. The CDC’s sexually transmitted diseases treatment guidelines1,2 have adopted these more stringent criteria for the primary recommended gonorrhoea treatment regimens but use less stringent criteria of a cure rate of ≥95% with a lower 95% CI of at least 90% for alternative regimens.15,16 The single 2 g dose of azithromycin-SR used in this study for the eradication of N. gonorrhoeae did not achieve a cure rate of 95%.

Clinical treatment failures have been reported for patients with gonorrhoea treated with a single 1 g dose of azithromycin, for which the MICs were 0.125–0.5 mg/L.17 Although the breakpoint of azithromycin for N. gonorrhoeae has not yet been established by the CLSI,12 MICs of ≥2 mg/L are assigned to decreased susceptibility in the GISP protocol.18 In this study, however, the

Table 1. Microbiological outcome of a single 2 g oral dose of azithromycin-SR for treatment of gonococcal urethritis

<table>
<thead>
<tr>
<th>MIC (mg/L) of azithromycin</th>
<th>eradicated</th>
<th>persistent</th>
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</thead>
<tbody>
<tr>
<td>0.03</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>0.06</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>0.125</td>
<td>7</td>
<td>0</td>
</tr>
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<td>43</td>
<td>0</td>
</tr>
<tr>
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<td>31</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>27&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup>The isolates were not cultured.

MICs were 0.5 mg/L persisted after treatment. Similarly, 5 of the 12 isolates for which the MICs were 1 mg/L and all strains for which the MICs were 2 and 4 mg/L persisted after treatment with the single 2 g oral dose of azithromycin-SR (Table 1).
breakpoint of azithromycin MICs associated with clinical treatment failures appeared to be 1 mg/L when a 2 g dose of azithromycin-SR was used to treat male gonorrhoea. However, at present we do not have statistical evidence to support this conclusion, and further experimentation needs to be completed. In Japan, decreased susceptibility to azithromycin has been observed in clinical isolates of N. gonorrhoeae, although no isolates with high-level azithromycin resistance have been reported.19 Recent studies reported that the prevalence of isolates with MICs of ≥1 mg/L exceeds 10%.19 Therefore, a single 2 g dose regimen of azithromycin-SR should not be expected to be as effective as the other recommended regimens, which achieve an eradication rate of 95%. In addition, the widespread use of azithromycin-SR was used to treat male gonorrhoea. However, resistance failures appeared to be 1 mg/L when a 2 g dose of azithromycin-SR for gonococcal pharyngeal infection will be necessary in the future.

With regard to the side effects of higher doses of azithromycin, the 2 g dose of azithromycin-SR improved tolerability in comparison with the result of another study using a 2 g dose of azithromycin-non-SR. This regimen is also expected to eradicate concurrent C. trachomatis and infections by genital mycoplasmas. However, the use of a 2 g dose of azithromycin-SR in monotherapy would not be recommended as the first-line treatment and should be restricted to limited cases of gonorrhoea.

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Transparency declarations
None to declare.

References