Azithromycin in acute bacterial upper respiratory tract infections: Observational multicentric study from Bosnia and Herzegovina

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ABSTRACT

Objectives: The primary objective of the study was to examine the effectiveness of azithromycin in the treatment of acute tonsillitis, pharyngitis, tonsillopharyngitis in adults (reduction or withdrawal of clinical symptoms), and the secondary objective of the study was to examine the tolerability of the administered treatment and patient compliance during the study.

Methods: This multi-centric, non-interventional study included 297 subjects with acute tonsillitis, pharyngitis or tonsillopharyngitis. Patients were administered film-coated tablets - azithromycin 500 mg (Azomex®) and followed-up 4 to 5 days. The patients were observed at 2 time points; baseline and one additional assessment. At both time points, we examined physical findings, general condition of the patient to establish severity of the disease. We also measured the tolerability and patient compliance. In the test lists of subjects, the physician, assessed the effectiveness of azithromycin according to the Likert’s scale.

Results: A total of 297 patients were included in the study. The median of symptom improvement was 3 (2.0-4.0) days, with 60 (28.1%) patients who had improvement after 2 days of administration, 135 patients (45.8%) after 3 days of administration, while the 77 patients (26.1%) experienced symptoms improvement within the period of 4 to 6 days after the start of treatment. The treatment outcome was successful in 260 (89.0%) patients, while in 32 (11.0%) the treatment outcome was unsuccessful, which was a significant difference in the successfulness of treatment with azithromycin ($X^2=159.0; p<0.001$). Tolerability of azithromycin was reported to be very good by 235 patients (80.8%), good by 32 (11.0%) and unsatisfactory reported by 8 (2.7%) patients.

Conclusion: The effectiveness and tolerability of the drug azithromycin (Azomex®) film-tablets in the treatment of acute tonsillitis, pharyngitis, tonsillopharyngitis, was found to be good with a small percentage of reported mild side effects.

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INTRODUCTION

Epidemiological data suggest that throat inflammation occurs in both sexes and in all age groups, but the highest incidence is in children aged 5-15 years. In our climate conditions, throat inflammations occur in the late fall and winter, often as an epidemic [1, 2].

The most common tonsillopharyngitis in adulthood is of streptococcal origin. To improve the diagnosis of streptococcal tonsillopharyngitis, four main criteria are helpful, and can also be used in making decisions on treatment, or choice of antibiotic therapy: body temperature >38°C, tonsillar oedema and exudate, enlarged front lymph nodes in the neck and absence of cough. Each of the criteria is scored with one point, and on the basis of their sum we determine the reliability of clinical signs that suggest this is a streptococcal infection. According to the latest guidelines of the Infectious Diseases Society of America (IDSA), the drugs of choice for treatment of streptococcal throat inflammation are penicillin and amoxicillin [3]. In case of allergy to penicillin, the alternatives include the first generation cephalosporins, clindamycin, clarithromycin and azithromycin.

Treatment usually lasts for 10 days for all of them except for azithromycin, for which 3-5 days of treatment is usually recommended [3], which may be the reason for clinicians to introduce azithromycin in case of patients who have no contraindication to penicillin or cephalosporins. Azithromycin has a unique pharmacological profile
that allows long-term storage of the active component at the site of inflammation, short-term dosing, and duration of therapeutic effect for up to 10 days. Azithromycin is recommended in treatment of tonsillopharyngitis in people sensitive to penicillins, as the drug of first choice. In the treatment of tonsillopharyngitis the azithromycin treatment has been shown to achieve clinical success in almost 100% of cases [4]. Our hypothesis was that the administration of azithromycin for 3 to 5 days might cause complete healing in 85% of patients with tonsillitis or tonsillopharyngitis. The primary objective of our study was to examine the effectiveness of azithromycin in the treatment of acute tonsillitis, pharyngitis, tonsillopharyngitis in adults (reduction or withdrawal of clinical symptoms), and the secondary objective of the study was to examine the tolerability of the administered treatment and patient compliance during the study.

**Materials and Methods**

**Patients**

We conducted an observational, non-interventional and multicentre study in 17 medical centres from Bosnia and Herzegovina (Sarajevo, Zenica, Mostar, Tuzla and, Banja Luka). The study included a total of 297 subjects with acute tonsillopharyngitis, who were admitted to a family medicine practice at the primary healthcare level in the period from November 2015 to January 2016. Patients were administered film-coated tablets - azithromycin 500 mg (Azomex®) manufactured by Bosnalijek d.d. Sarajevo and followed-up 4 to 5 days from the date of diagnosis and the start of azithromycin administration.

**Methods**

The patients were observed at 2 time points, the first baseline and one additional control assessment. First observation (Day 0) included a medical history and a physical examination of the tonsils and pharynx and assessment whether the inclusion criteria were met. Patients were further divided into two groups, patients with tonsillopharyngitis and patients with pharyngitis. Check-up (2nd observation) was performed on the fourth or fifth day, depending on the severity of the disease and included physical examination of tonsils and pharynx, monitoring the general condition of the patient, the final assessment of the effectiveness of treatment based on the improvement of the patient's general condition. After 5 days, effectiveness, tolerability and patient compliance were recorded.

**Assessment of the drug effectiveness and safety**

The drug effectiveness was assessed on the basis of improvement of the general condition and findings of the pharynx/tonsils, circling the offered answers in the Likert’s scale and rating tolerance, possible side effects and patient compliance. The safety of the product administration was observed by monitoring the incidence of adverse reactions of drugs with the assessment of the relation between drug administration and adverse reaction occurrence (certain, probable, possible, not probable, unclassified relation and non-classifiable).

**Statistical analysis**

Statistical data analysis was performed using the SPSS (Statistical Package for Social Sciences) software, version 16.0. To determine the normal distribution of the tested variables, we used the Kolmogorov-Smirnov test. The study results are presented as the mean value (X) and standard deviation (SD) for variables that followed a normal distribution, or as a median and interquartile range for variables that did not follow a normal distribution, and as absolute and relative numbers. Comparison of mean values between the groups was performed by the Student’s t-test for independent samples if the variables followed a normal distribution, or by the Mann-Whitney test for variables that did not follow a normal distribution. Evaluation of categorical variables was performed by the Chi-Square test or Fisher’s test for independent variables, or by the McNemar’s test for dependent categorical data. The accepted statistical significance was set at the level p<0.05.

**Results**

The study included a total of 297 patients with acute tonsillopharyngitis. The average age of the subjects involved in the study was 40.8±15.2 years. Out of total 297 patients included in the study, 133 (44.4%) were men and 164 (55.2%) women, with no significant difference in gender distribution (X²=3.4; p=0.07). The average age of men in the study was not significantly different (41.0±13.9 years) compared to the mean age of women (40.7±16.2 years; p=0.85). Previous tonsillectomy had 38 (12.8%) subjects. The mean throat inflammations events during last year was 2.0 (1.0 to 3.0). Less than 2 inflammations during the last year was reported by 67.7% patients, 17.2% had 3 inflammations, and 15.2% had 4 or more inflammations during the last year.

The patients were given azithromycin during several days. Azithromycin was administered during 3 days to 180 patients (61.0%), during 4 days to 14 patients (4.7%), and 98 patients (33.2%) received azithromycin for 5 days.

Examining general symptoms in patients with tonsillopharyngitis before and after treatment with azithromycin, we found a significant reduction in the number of
patients with throat inflammation symptoms (Table 1). There was also a significant reduction in number of patients with oedema, exudate and white deposits on tonsils before and after treatment (Table 2).

The median of symptom improvement was 3 (2.0-4.0) days, with 60 (28.1%) patients who had improvement after 2 days of administration, 135 patients (45.8%) after 3 days of administration, while the 77 patients (26.1%) had the improved symptoms within the period of 4 to 6 days after the start of administration.

The physician assessed the effectiveness of azithromycin according to the Likert’s scale, based on the subjective assessment (based on the improvement of the general patient’s condition and the findings of the pharynx/tonsils) (Figure 1). The treatment outcome was successful in 260 (89.0%) patients, while in 32 (11.0%) the treatment outcome was unsuccessful, which was a significant difference in the successfulness of treatment with azithromycin ($X^2=159.0; p<0.001$).

Occurrence of specific side-effects is shown in Table 3 and were usual and expected for azithromycin, with the highest occurrence of nausea (2.4%) and other gastrointestinal (GI) system related side effects (2.0%). Out of a total of 275 patients who reported tolerability of azithromycin, very good tolerability was reported by 235 patients (80.8%), good by 32 (11.0%) patients and unsatisfactory was reported by 8 (2.7%) patients.

**DISCUSSION**

In the study we conducted, empirical administration of azithromycin in patients with a diagnosis of acute tonsillopharyngitis proved to be an effective therapy in 260 (89%) patients, and in 32 (11%) patients the treatment was assessed unsuccessful.

**Table 1. Presence of general symptoms in patients with tonsillopharyngitis before and after administration of Azithromycin**

<table>
<thead>
<tr>
<th>General symptoms</th>
<th>Examination I</th>
<th>Examination II</th>
<th>% change</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt;38.5</td>
<td>271 (91.2%)</td>
<td>16 (5.4%)</td>
<td>-94.1</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>General weakness</td>
<td>254 (85.5%)</td>
<td>51 (17.3%)</td>
<td>-79.9</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>216 (72.7%)</td>
<td>63 (21.4%)</td>
<td>-70.8</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Cough</td>
<td>135 (45.5%)</td>
<td>63 (21.4%)</td>
<td>-53.3</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>94 (31.6%)</td>
<td>44 (15.0%)</td>
<td>-53.2</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Bad breath</td>
<td>164 (55.2%)</td>
<td>23 (7.8%)</td>
<td>-86.0</td>
<td>$p&lt;0.001$</td>
</tr>
<tr>
<td>Sore throat</td>
<td>273 (91.9%)</td>
<td>41 (13.9%)</td>
<td>-85.0</td>
<td>$p&lt;0.001$</td>
</tr>
</tbody>
</table>

**Table 2. Physical examination of tonsils and pharynx in patients before and after administration of azithromycin**

<table>
<thead>
<tr>
<th>Tonsils</th>
<th>Examination I</th>
<th>Examination II</th>
<th>% change</th>
<th>Examination I</th>
<th>Examination II</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema</td>
<td>203 (69.0%)</td>
<td>67 (22.9%)</td>
<td>-67.0</td>
<td>274 (92.3%)</td>
<td>87 (29.4%)</td>
<td>-68.2</td>
</tr>
<tr>
<td>Exudate</td>
<td>152 (51.7%)</td>
<td>22 (7.5%)</td>
<td>-85.5</td>
<td>180 (60.8%)</td>
<td>14 (4.7%)</td>
<td>-92.2</td>
</tr>
<tr>
<td>White deposits</td>
<td>97 (33.0%)</td>
<td>20 (6.8%)</td>
<td>-79.4</td>
<td>53 (18.0%)</td>
<td>6 (2.0%)</td>
<td>-88.7</td>
</tr>
</tbody>
</table>

**Table 3. The most common reported side effects and their incidence**

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2.4</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.3</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1.0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.7</td>
</tr>
<tr>
<td>Other complaints in the GI system</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Figure 1. Effectiveness evaluation of azithromycin in patients with tonsillopharyngitis**

Effectiveness was measured as an improvement in the clinical features and the local condition. Physical examination of tonsils before and after administration of azithromycin showed a statistically significant reduction in the oedema by 67.0%, in exudate by 85.5%, and in whitish deposits by 79.4%. A similar percentage of reduction was found in oedema by 68.2%, in exudate by 92.2%, and in white deposits on pharynx by 88.7% after treatment with azithromycin.

Several studies were performed that examined the ef-
fectiveness and safety of azithromycin in the treatment of acute infections of the upper respiratory system. Thus, in a study from 2014, azithromycin in the treatment of acute infections of the upper respiratory system achieved a high degree of effectiveness: in the treatment of sinusitis, it achieved a degree of effectiveness of almost 96%, in the treatment of tonsillitis it achieved a degree of effectiveness of 99%, and in the treatment of acute otitis media it achieved the degree of effectiveness of 100% [4]. Pharmacokinetic properties of azithromycin are the following: low plasma concentration and high and sustained concentration in tissues, distribution in almost all tissues and body fluids, it concentrates in phagocytes, including polymorphonuclear cells, monocytes, macrophages and fibroblasts. This cellular kinetics of azithromycin in leukocytes with the aforementioned intrinsic tissue distribution contributes to achieving extremely high concentrations at the site of inflammation. The gradual release of azithromycin from phagocytes is accelerated on contact between phagocytes and cause of infection, while fibroblasts serve as a reservoir of azithromycin, which is gradually released and transported by phagocytes to the site of inflammation [5,6]. Thanks to its unique pharmacological properties, it has an excellent safety profile and is suitable for special groups of patients such as children, adults, and people with impaired liver and/or kidney function. Unlike other macrolides, azithromycin does not inhibit or stimulate the cytochrome P-450, which means that it does not interact with drugs metabolized by this enzymatic system. Because of elimination of azithromycin mostly by stool, its negligible biotransformation and a low share of renal elimination, the dose modification is not required either in hepatic or in renal insufficiency [7].

The choice of antibiotics in the treatment of infections should be done according to the microbiological isolation of the pathogen and its susceptibility to a particular antibiotic, or based on the findings of an antibiogram. In practice, this is often not the case, so an antibiotic is most often administered empirically. Empirical treatment is based on the fact that some bacteria are more prone to locate themselves and cause an infection in certain places of the body, in certain organs or body fluids. In empirical treatment, care should be taken that the selected antibiotic with its antimicrobial spectrum covers the presumed pathogen, and achieves effective concentrations at the site of infection. According to the recommendations of the American Academy of Family Physicians, azithromycin is the drug of choice in the treatment of bacterial infections of the upper respiratory system. The administration of azithromycin is recommended for patients allergic to beta-lactam antibiotics [8]. The results of our study have not shown such a superior effectiveness which can be a result of increased resistance to macrolides. From the data published worldwide between 2000 and 2011, the resistance to macrolides ranges from 1.1% to 97.9%. In the United States, though the rates of resistance to macrolides generally range from 3% to 15%, some individual studies show high rates of up to 48% [9].

In a similar study conducted in several centres, including Bosnia and Herzegovina, the percentage of cured patients was 85.3%, and the percentage of patients with improved clinical condition was 9.8%. We can conclude that the degree of effectiveness in patients with tonsillitis treated with azithromycin was 95.1%, and the therapy was proclaimed unsuccessful in 4.9% of patients [10]. In our study, we have evaluated the tolerability of azithromycin, and patient compliance. In the study a small percentage of side effects were reported. The most common side effects, occurring in less than 2% of patients were nausea, gastrointestinal related symptoms, diarrhea and vomiting in 2 patients. In similar studies, side effects were reported in 9.1% of patients, and they were usually related to digestive system, similar to our study [10]. Thanks to the short treatment and a high degree of effectiveness, azithromycin therapy, in pharmaco-economic terms, represents a more favourable treatment option compared to other antibiotics. Treatment with azithromycin is effective, lasts shortly for 3-5 days, is taken once a day, ensures good cooperation with patients, all of which results in a high percentage of healing and a shorter duration of symptoms. Antibiotic treatment that lasts for 7 to 10 days or longer, or is dispensed 2 or 3 a day, is often accompanied by poor patient compliance, premature termination of therapy, which can result in low effectiveness, the development of resistance and the need for the use of other antibiotics [11].

In addition to high effectiveness and good tolerability, in the treatment of acute infections of the upper respiratory system, azithromycin shows additional benefits such as an anti-inflammatory activity. Azithromycin has an anti-inflammatory activity: it can reduce inflammatory processes, increase the removal of mucus, prevent and reduce the formation of biofilm and enhance or reduce specific immune reactions, as needed. There is already clear evidence that azithromycin can significantly affect the inflammatory processes by modulating the inflammatory cell chemotaxis, synthesis and production of cytokines and chemokines, expression of adhesion molecules, production of reactive oxygen metabolites and nitric oxide (NO) [7]. Despite the recommendations of doctors, non-com-
pliance with prescribed treatment regimen remains a problem in the treatment of all conditions, including the treatment of bacterial infections of the upper respiratory system. Non-compliance of patients leads to the extension of time of treatment, the exacerbation of underlying disease, an increased need for hospitalization, and an increase in bacterial resistance to antibiotics. A number of clinical studies have confirmed that the patient compliance is reduced if the treatment regimen includes the use of antibiotics several times a day. Also, it was confirmed that patients adhere to the prescribed treatment regimen 100% only in the case of administration of antibiotics once a day [12, 13].

In our study the patient compliance has been measured using subjective assessment by doctors according to the Likert’s scale. Out of a total of 287 questions answered about the patient compliance, it has been noted that in the test lists of subjects the compliance in 256 (86.2%) was very good, in 28 (9.4%) good, while in 3 patients (1.0%) the compliance was unsatisfactory.

In similar clinical trials, the compliance of patients taking azithromycin reached a high 97% [13].

**CONCLUSION**

Based on the results of the conducted multicentre observational study of the effectiveness of the drug azithromycin (Azomex®) film-tablets in the treatment of acute bacterial pharyngitis or tonsillopharyngitis, it has been concluded that the drug had shown good effectiveness and tolerability with a small percentage of reported and mild side effects. Simple dosing (1 time a day) and short-term treatment have shown a very good patient compliance and a high level of response to treatment.

**ACKNOWLEDGMENT**

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**DECLARATION OF INTEREST**

Authors declare no conflict of interest.

**REFERENCES:**