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Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Article

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Prevalence of Gastrointestinal Side Effects in Pediatric Azithromycin Users Between 2019 and 2021: a retrospective study

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Submitted:08-11-2022 Resubmitted: 13-03-2023 Accepted: 17-03-2023

Peer review: blind reviewers

Abstract

Objective: To verify the prevalence of gastrointestinal side effects in patients who used azithromycin between 2019 and 2021. Methodology: This study has a quantitative, retrospective character, using data from 200 patient records between 2019 and 2021. Inclusion criteria were patients who were hospitalized or admitted to the emergency department without any gastrointestinal complaints and who during hospitalization used azithromycin both alone and in conjunction with other antibiotics, regardless of gender. Exclusion criteria were: patients who arrived at the emergency room or outpatient clinic reporting gastrointestinal symptoms, but who did not use macrolides; patients with previous gastrointestinal inflammatory diseases, as it can cause a confounding factor in the inferential analysis. **Results:** the prevalence found was 24.5%; the most reported side effects were: diarrhea (39.6%), constipation (29.2%), bloating (12.5%), vomiting (10.4%), abdominal pain (8.3%); the Odds Ratio (OR) of length of stay in days and dosage were 1.23 (95% CI 1.06 to 1.42) and 1.001 (95% CI 1.0008 to 1.002), respectively. **Conclusion:** The high prevalence of side effects and the associations evaluated show the importance of efficient care in order to reduce them.

Keywords: Macrolides, Drug-Related Side Effects and Adverse Reactions, Gastrointestinal tract, Prevalence.

Prevalência de Efeitos Colaterais Gastrointestinais em Usuários Pediátricos de Azitromicina entre 2019 E 2021: um estudo retrospectivo

Resumo

Objetivo: Verificar a prevalência de efeitos colaterais gastrointestinais em pacientes que usaram azitromicina entre 2019 e 2021. **Metodologia**: Este estudo tem caráter quantitativo, retrospectivo, utilizando dados de 200 prontuários entre 2019 e 2021. Os critérios de inclusão foram pacientes que estavam internados ou foram admitidos pelo pronto atendimento sem qualquer queixa gastrointestinal e que durante a internação fizeram uso de azitromicina tanto isoladamente como em conjunto com outros antibióticos, independentemente do sexo. Os critérios de exclusão foram: pacientes que chegaram ao pronto-socorro ou ambulatório relatando sintomas gastrointestinais, mas que não faziam uso de macrolídeos; pacientes com doenças inflamatórias gastrointestinais prévias, pois pode causar um fator de confusão na análise inferencial. **Resultados:** a prevalência encontrada foi de 24,5%; os efeitos colaterais mais relatados foram: diarreia (39,6%), constipação (29,2%), distensão abdominal (12,5%), vômito (10,4%), dor abdominal (8,3%); o Odds Rattio (OR) do tempo de internação em dias e a dosagem foram de 1,23 (IC 95% 1,06 a 1,42) e 1,001 (IC 95% 1,0008 a 1,002), respectivamente. **Conclusão:** A alta prevalência de efeitos colaterais e as associações avaliadas mostram a importância de um cuidado eficiente para reduzi-los.

Palavras-chave: Macrolídeos, Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos**,** Trato gastrointestinal, Prevalência.

Introduction

Azithromycin is a broad-spectrum macrolide antibiotic with long half-life and excellent tissue penetration. It has been generally used in upper airway infections such as acute bacterial sinusitis, pharyngitis and tonsillitis, as well as lower, such as atypical germ pneumonia, either as a first therapeutic or alternative option in patients allergic to penicillins[1]. However, its use can bring risks, and today it is known that broad-spectrum antibiotics cause changes in the intestinal microbiota that may occur with motility disorders, including *Clostridium difficile* infections. [2,3]

In pediatric patients, similar events occur due to the use of erythromycin, an antibiotic that was also widely prescribed in cases of respiratory infections. However, its stability in acidic medium is limited and causes important gastrointestinal effects, of which the frequency and associative variables are not known .[4] Most studies address side effects in adults, showing variations of 15 to 20% in the use of erythromycin and 5% in the other (azithromycin, clarithromycin).[5] Thus, the present study has great relevance due to the scarce number of studies on the subject, even though it is a constant issue in daily practice.

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In addition to the side effects, another common problem is the allergic reaction. A study conducted in Ukraine identified betalactamics (48.5%), fluoroquinolones (13.9%) and macrolides (7.9%) as the main causation agents of these reactions, and macrolides are responsible for causing allergic processes, such as urticaria and angioedema in adults.[6]

A Cochrane systematic review study evaluated the chance of side effects in pediatric patients using azithromycin and erythromycin compared to placebo. The study highlighted that macrolides increased the chance of diarrhea, abdominal pain, nausea and vomiting, with odds ratio (OR) of 1.70; 1.66; 1.61 and 1.27 respectively. Therefore, due to the importance of side effects, it is essential that further research evaluate both the prevalence of effects in children and possible association variables.[7]

Methods

This is a study of quantitative and qualitative analysis through the data from the electronic medical records of users of the Júlio Bandeira University Hospital, located in the city of Cajazeiras-PB.

The information was collected through electronic medical records from 2019 to 2021 of patients regardless of age, gender and ethnicity that used macrolides. The transcription of the collected data was performed by the JAMOVI software, as well as descriptive and inferential statistical analysis.

Inclusion criteria were: patients who were hospitalized or admitted to the emergency department without any gastrointestinal complaints and who during hospitalization used azithromycin both alone and in conjunction with other antibiotics, regardless of gender. Exclusion criteria were: patients who arrived in the emergency room or outpatient clinic reporting gastrointestinal symptoms, but who did not use macrolides; patients with previous gastrointestinal inflammatory diseases, as it can cause confounding factor in inferential analysis.

For the sample calculation, a prevalence of 15% of gastric adverse events was estimated in patients who used macrolides, with a confidence interval of 95%, error of 5%, small effect size (0.1), power (1-β: 80%), with a minimum estimated sample of 200 people or medical records. In total, 570 medical records were made available, and the choice was non-random and sequential, following the inclusion and exclusion criteria until reaching the minimum necessary stipulated by the sampla calculation.

The quantitative analysis of prevalence corresponds to the frequency of cases in relation to the total number of cases in the two years. In addition, the chi-square prevalence ratio test was used to verify possible differences in the appearance of adverse events in relation to the qualitative variable from the pre-pandemic period from January 2019 to January 2020 to the pandemic period from February 2020 to February 2021. The result was be considered valid if it respects the level of statistical significance of 5%.

In order to evaluate the association between the variables time, dose, presence or not of gastrointestinal symptom, a Mann-Whitney test and logistic regression were performed. For the formation of the consumption profile will be used the following variables: gender, age, age group (0-11; 12-18 ;19-59; 60 onwards), reason for prescription or consumption and medication used. For the analysis of the prescription ratio, the most prescribed clinical situation was be tabled through absolute and relative frequency. In cases of absence of data, it was decided to discard the chart, therefore moving on to the next one.

Due to the hospital's care profile and internal protocol, patient care is pediatric only, and no macrolide other than azithromycin is used.

The research complies with Resolution 466/2012 of the National Health Council of the Ministry of Health (Brazil), which provides for the Code of Ethics in Research on Human Beings, and was approved by the ethics committee whose opinion: 5081. 873.

Results

The prevalence of gastrointestinal side effects in the sample studied (200 patients) was 24.5%. Of these, 94.5% of the patients were aged 0 to 11 years and 60% of them were male, according to Table 1.

Table 1. Epidemiological and clinical variables.

Variables	Nº	Frequency (%)
Gender		
Male	121	60,5
Female	79	39,5
Age group		
0-11	189	94,5
12-18	11	5,5
Reason for the prescription		
Streptococcus pneumoniae	24	12
Mycoplasma pneumoniae	4	2
Unspecified pneumonia	112	56
Unspecified viral pneumonia	8	4
SARS-CoV-2	5	2,5
Other causes	47	23,5

It is worth noting that the topic "other causes" involves: asthma, lymphadenitis, multiple HIV infections, gingivitis and periodontal diseases.

Regarding the most common side effects, diarrhea stands out as the most common:

Table 2. Prevalence of side effects.

Side effects	Nº	Frequency (%)
Diarrhea	19	39,6
Abdominal distension	6	12,5
Vomit	5	10,4
Constipation	14	29,2
Abdominal pain	4	8,3

The Mann-Whitney test showed that the dosage and longer hospitalization time have an effect on the appearance of side effects, as shown in Table 3.0.

Regression prediction ruled out the null hypothesis (X^2=33; p<0.001; R^2 McFadden: 0.148) and showed the dose (Z=3.98; p<0.01) and days of hospitalization (Z=2.79; p=0.005), are capable of predicting side effects. The odds ratio for dose was 1.001 (95% CI 1.0008 to 1.002) and days of hospitalization was 1.23 (95% CI 1.06 to 1.42). The model had specificity of 94%, sensitivity of 22% and area under the curve (AUC) of 0.76. The chi-square test did not rule out the null hypothesis for differences between both periods (X^2=0.15; p=0.69).

Table 3. Inferential analysis.

	Gastrointestinal symptoms	N	Mean	Median	Standard deviation	P value
Dose	No	151	436.01	320	386.10	
	Yes	49	832.82	800	549.58	P<0.001
days of hospitalization	No	151	4.25	4	2.03	
	Yes	49	5.76	5	2.82	P<0.001

Discussion

The evaluation of drugs in pediatrics is essential due to the pharmacological particularities that characterize the child throughout its development and make it illusory to extrapolate to children data acquired in the adult population.[8] Extrapolation can bring unknown risks and harm the doctor-patient relationship because there is no transparency and precise stipulation of side effects, as is the case with the use of macrolides, which presented a higher prevalence of side effects than presented in the adult literature (5%).[5]

Because it is widely used in airway infections, both higher and lower, seasonality influences consumption, being increased in winter periods. Studies estimate that its consumption increases more than three-fold among adults in the winter period.[4] In pediatrics, the use of azithromycin for *Streptococcus pneumoniae*, a common etiological agent in community-acquired pneumonia (CAP), as well as *Mycoplasma pneumoniae*, stands out. The world estimate of the incidence of CAP among children under 5 years of age in developing countries is about 0.29 episodes/year, which is equivalent to the annual incidence of 150,7 million new cases and is the leading cause of death among acute respiratory infections (AKI) in childhood.[9]

The reported symptoms are in confluence with the literature, with the exception of constipation, which has not been reported so far.[10] Similarly, there was no case of liver failure or sensorineural loss, frequent findings in the bibliography.[11]

The literature does not address the variables dose and time in the appearance of side effects, but it works with the hypothesis of the route of administration, which, until then, did not move away the null hypothesis[7]. Although the present analysis move away out the null hypothesis for both variables, it should be noted that the dose is not clinically relevant. In addition, the same can happen with the length of stay, since the confidence interval comprised values close to 1. Therefore, based on the analysis carried out and the literature, strategies can be developed with the aim of reducing side effects, namely: reduce the length of hospital stay, avoid excessive prescription of azithromycin, adjust the diet with the use of probiotics.

In this context, the limitations of the study involve medical records that present information bias, since the reporting of symptoms by pediatric patients is not specific; the analysis did not take into account the adjustment of the dose in relation to weight, but the total dose administered to the patient; there was concomitant use of other antimicrobials that were not included in the study analysis and that may or may not interfere with the outcome; due to the study design, it is not possible to assess the real risk of side effects and due to the lack of possibility to monitor patients and control external variables that can influence, such as: environmental factors, stress, diet.

As the study site is a public hospital for pediatric patients, the findings can assist healthcare professionals in assessing the risk of side effects, as the higher the risk of onset, the less the need for treatment. It also contributes to improving transparency and communication of possible effects on the patient's family, contributing to humanitarian care.

Funding sources

The study was carried out with its own funding.

Collaborators

Project conception or analysis and interpretation of data

Santos-neto JR

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Article writing or critical review relevant to the intelectual contente

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Acknowledgments

The team of researchers appreciates the commitment of all employees of the research and teaching sector of the Júlio Bandeira University Hospital located in the City of Cajazeiras-PB.

Conflit of interests statement

The authors declare that there are no conflicts of interest regarding this article.

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