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Safety of azithromycin in paediatrics: a systematic review protocol

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ABSTRACT

Introduction Azithromycin is widely used in children not only in the treatment of individual children with infectious diseases, but also as mass drug administration (MDA) within a community to eradicate or control specific tropical diseases. MDA has also been reported to have a beneficial effect on child mortality and morbidity. However, concerns have been raised about the safety of azithromycin, especially in young children. The aim of this review is to systematically identify the safety of azithromycin in children of all ages.

Methods and analysis MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, Embase, CINAHL, International Pharmaceutical Abstracts and adverse drug reaction (ADR) monitoring systems will be systematically searched for randomised controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, case series and case reports evaluating the safety of azithromycin in children. The Cochrane risk of bias tool, Newcastle-Ottawa and quality assessment tools, and The Joanna Briggs Institute Critical Appraisal tools will be used for quality assessment. Meta-analyses will be conducted to the incidence of ADRs from RCTs if appropriate. Subgroup analyses will be performed in different age and azithromycin dosage groups.

Ethics and dissemination Formal ethical approval is not required as no primary data are collected. This systematic review will be disseminated through a peer-reviewed publication.

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What is already known on this topic?

- Azithromycin is a widely used antibiotic in children.
- It is used for individual patients and as mass drug administration for controlling a few infectious diseases.
- Diarrhoea, nausea and vomiting are the most common side effects of azithromycin.

What this study hopes to add?

- The most frequent adverse drug reactions of azithromycin in children following mass drug administration.
- The likelihood of significant drug toxicity with azithromycin in children.

INTRODUCTION

Azithromycin is a macrolide antibiotic that has a structure modified from erythromycin. Like other macrolides, azithromycin is active against *Streptococcus pneumoniae* and *Moraxella catarrhalis* and is active against atypical pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*.[1] In 2010, azithromycin was the most prescribed antibiotic for adult outpatients in the USA.[2] It is one of the most commonly prescribed antibiotics in children with a prescription rate of between 4% and 14%, which has been used extensively for the treatment of several paediatric infectious diseases.[3–6] It is effective in respiratory infections, which are common in children.

The WHO recommends 3–5 years of annual mass azithromycin distribution (MDA) to control trachoma in communities with >10% follicular trachoma prevalence among children aged 1–9 years.[7] MDA is also used for other infectious diseases in selected circumstances. Some recent evidence suggests that postneonatal infant and child mortality can be reduced in some contexts, by providing azithromycin periodically to all children aged 1–59 months, through an MDA platform.[8–10] The generalisability of the findings is, however, unclear and there is a concern about increasing antimicrobial resistance and other possible adverse consequences if azithromycin MDA was implemented on a wider scale.[11]

Owing to the lack of safety studies, azithromycin is not recommended for children aged less than 6 months for oral formulations and 16 years for intravenous formulations.[12 13] Abdominal discomforts, such as diarrhoea, nausea and vomiting, are the most commonly reported side effects in paediatrics.[12] Recent studies have yielded conflicting information about the cardiovascular safety of azithromycin.[14–16] But these studies most likely reached different conclusions because they involved patients with different

characteristics. Although azithromycin can influence cardiac conduction, adverse consequences are largely confined to patients with established cardiac disease. So the cardiovascular safety of azithromycin in children and adults is unknown. A recent large retrospective review of data from Korea suggests that the risk of QT prolongation is greatest in elderly adults aged 60–79 years.[17] Meanwhile, increased risk of infantile hypertrophic pyloric stenosis (IHPS) in infants has been reported.[18–21]

There is currently insufficient safety information on azithromycin treatment in children. A systematic review about the use and safety of azithromycin in neonates identified only 11 articles.[22] The systematic review indicated that azithromycin significantly reduces the risk of bronchopulmonary dysplasia(BPD) in preterm neonates. Adverse events (AEs) were mainly respiratory, neurological and gastrointestinal but this was probably related to the patient population of sick neonates. There were four cases of infantile hypertrophic pyloric stenosis(IHPS) and the relationship between azithromycin and IHPS requires further investigation.[21] Therefore, this systematic review aims to evaluate all published data and reports on the safety of the drug in children. The systematic review will aim to answer the following questions:

1. What are the rates and categories of azithromycin adverse drug reactions (ADRs) in children? Are ADRs different in children aged 1–59 months? Are ADRs different following MDA?
2. Do cardiovascular events occur in paediatric patients? If so, is there a subgroup of paediatric patients for whom the incidence of cardiovascular events is higher?
3. Do the rates and categories of ADRsvary with dose in children? If so, are there dose-related ADRs?

METHODS

This review will be carried out as Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-analyses guidelines.[23 24] This protocol has been registered in the international prospective register of systematic reviews.

Search strategy

Selection criteria will use the Population, Intervention, Comparison, Outcome, Study design to determine the eligibility of articles. No limitation on language and year of publication will be set.

Population

We will include all paediatric patients aged from 0 to 18 years. We will analyse paediatric patients aged from 1 to 59 months as a subset. There will be no limitation on medical condition or indication.

Intervention

Azithromycin given either as periodic MDA at intervals up to 12 months or as a therapeutic agent.

Comparison

Placebo. Other antibiotics or no comparison.

Outcome

The incidence and category of ADRs (especially cardiovascular safety; eg, cardiac arrhythmia or a prolonged QT-time, or pyloric stenosis) in paediatric patients.

Study design

In the systematic review, we will include all types of studies, including randomised controlled trials (RCTs), cohort studies, case–control studies, cross-sectional studies, case series and case reports. Only peer-reviewed publications will be included. We will exclude editorials, conference abstracts and reviews. Studies that include both the children and adults will be excluded if they do not separate the data. We will also review ADR reports from pharmacovigilance systems.

Search strategy

MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, Embase, CINAHL and International Pharmaceutical Abstracts will be searched. All searches will be from the beginning of the database until February 2019 and all languages will be included. The search strategy will be developed based on the instructions in Cochrane handbook for systematic reviews of interventions and will be specific for each database.[23] The search strategy will include a combination of the medical subject headings and free text terms for azithromycin and neonates, infants and children (online supplementary appendix 1). We will look for additional studies in the reference lists of selected articles and contact authors for unclear information.

We will also search ADR spontaneous reporting systems to include: (1) warnings issued; (2) case reports of ADRs to azithromycin in children reported and (3) signal detection studies performed.

Study records

The studies will initially be independently selected by two reviewers (WYL and XCP, students) on reading of the title and abstract of the articles. Once relevant articles are screened in, a complete analysis of the full-text articles will be performed by the previously defined selection criteria. Any disagreements will be resolved by discussion with a third reviewer (LNZ, a trained pharmacist) if needed.

Risk of bias in individual studies

The RCTs will be assessed using Cochrane risk of bias tool for assessing the risk of bias while case–control and cohort studies using Newcastle-Ottawa Scale.[25 26] The case series and case reports will be assessed using The Joanna Briggs Institute Critical Appraisal tools.[27] No quality assessment will be done for reports from the ADR monitoring system.

Data extraction

Data will be extracted from all included studies using specifically developed data extraction forms. Extracted information will contain: (1) the article metadata, including authors' name, principal author's country, and study setting and purpose; (2) method (study design and information of study quality according to quality assessment criteria of different types of studies); (3) participant and setting (sample size, age, gender composition, inclusion criteria, diagnostic criteria and setting); (4) intervention (medicine, route and dose); (5) outcomes (type and severity of ADRs); (6) conclusion (authors' conclusion on safety evaluation) and (7) confirmation of eligibility for review.

For continuous data, mean, SD and number of participants will be extracted. For categorical data, events and total number of participants will be extracted. Whenever possible, we will use the results from an intention-to-treat analysis. If necessary, the author of the included studies will be contacted to gather relevant information.

WHO—Uppsala Monitoring Centre system will be adopted to evaluate the relevance of suspected ADRs and azithromycin in case reports.[28]

Data analysis and synthesis

Data synthesis

Relative risks (RRs) will be measured in RCTs and cohort studies, odds ratios (ORs) in case–control studies and reporting ORs in ADR spontaneous reporting systems.[29] The RRs of ADRs present in at least two RCTs and cohort studies will be calculated, and only the RR>1 with at least three cases will be included suggesting that more ADRs will be associated with azithromycin. Meta-analysis will be carried out in Revman, if possible. RRs and 95% CIs will be estimated for each RCT. The heterogeneity will be assessed using the χ^2 test, and further quantified using the I^2. The data will be considered homogeneous if $I^2 \leq 50\%$. Fixed effects models will be used to produce summary RRs and 95% CIs where heterogeneity did not exist. If statistical heterogeneity did exist then random effects models will be applied.

Logistic regression models will be used to identify univariable and multivariable risk factors for AEs. We will include all significant variables in univariable logistic regression analysis. The multivariate analysis will be performed with the variables with $p<0.05$ ($p<0.05$ will be considered to be statistically significant) and calculate the OR and 95% CI of the study factors. All significant variables are as follows: (1) age; (2) sex; (3) body weight; (4) administration route; (5) rationality of indication; (6) rationality of dose and (7) rationality of course of treatment.

Subgroup analyses

Subgroup analysis will be performed on different age groups and different dosage of azithromycin.

Setting and participants

Patients and the public were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

The results of this systematic review will be disseminated through the publication of papers in peer-reviewed journals. Our findings should be of benefit to both health professionals, who prescribe azithromycin, and patients, who receive azithromycin.

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Contributors PPX contributed to developing and drafted the protocol. LNZ contributed to developing the protocol. IC contributed to supervised the development of the protocol and revise the protocol. TX, SQ and LNZ contributed to revise the protocol. All the authors have approved the current protocol version.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval There is no need for an ethical assessment because we only search and evaluate the existing literature.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All the data relevant to the study are included in the article or uploaded as supplementary information.

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