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Azithromycin use in paediatrics: A practical overview

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Azithromycin is an antibiotic that is commonly prescribed for upper and lower respiratory tract infections in children. While it has proven benefits, some concerns regarding azithromycin use have arisen in recent years. This practice point considers azithromycin therapy for acute respiratory infections in otherwise healthy children. Pharmacokinetics, spectrum of activity, the problem of resistant bacteria and clinical aspects are considered, along with recommendations for use and contraindications. Azithromycin should be avoided in patients with a significant risk of bacteremia. It is associated with pneumococcal resistance and, with stated exceptions, is generally not recommended for the treatment of acute pharyngitis, acute otitis media or pneumococcal community-acquired pneumonia in the paediatric population.

Key Words: Antibiotics; Infections; Macrolides; Resistance; Treatment

Azithromycin, the first azalide from the macrolide class of antibiotics, has rapidly become one of the more common antibiotics prescribed by paediatricians, particularly for respiratory infections.(1,2) Azithromycin is easily administered to children as an oral suspension, with once-a-day dosing for a relatively short treatment duration (three to five days) and a favourable side effect profile.

Emerging pneumococcal resistance to penicillin in recent years, the recognition that resistance can lead to more serious complications and the identification of atypical bacteria causing respiratory infections are trends that have prompted some experts to recommend macrolides as first-line therapy for community-acquired pneumonia among ambulatory patients.(3,4) While developed for adults, these recommendations have had an important impact on the prescription of macrolides, in particular azithromycin, in paediatric practice. In the 20 years since the first trials supporting its market registration, however, some concerns have arisen regarding the use of azithromycin in children.

This practice point considers the use of azithromycin for upper and lower respiratory tract acute infections in healthy children in Canada. The use of azithromycin for other conditions (such as cystic fibrosis, HIV-AIDS or other chronic illnesses, in travellers to other countries or in patients with sexually transmitted infections) is beyond the scope of this review.

PHARMACOKINETICS

Compared with other macrolides, the distinctive pharmacokinetic properties of azithromycin have facilitated administration; it is

L'utilisation de l'azithromycine en pédiatrie : un aperçu pratique

L'azithromycine est un antibiotique souvent prescrit chez les enfants en présence d'infections des voies respiratoires supérieures et inférieures. Elle a des avantages démontrés, mais plusieurs préoccupations ont surgi ces dernières années au sujet de son utilisation. Le présent point de pratique permet d'évaluer le traitement d'infections respiratoires aiguës à l'azithromycine chez des enfants autrement en santé. La pharmacocinétique, le spectre d'activités, le problème de bactéries résistantes et les aspects cliniques sont évalués, de même que les recommandations relatives à l'utilisation et les contre-indications. Il faudrait éviter l'azithromycine chez les patients présentant un risque marqué de bactériémie. Ce médicament s'associe à une résistance pneumococcique et, sauf dans des exceptions définies, il n'est généralement pas recommandé pour traiter la pharyngite aiguë, l'otite moyenne aiguë ou la pneumonie pneumococcique d'origine non nosocomiale au sein de la population d'âge pédiatrique.

stable in acidic pH, has a bioavailability >30%, and has a relatively long half-life of up to 96 h.(5) Azithromycin also has a superior pattern of distribution, with significant diffusion to the intracellular compartment and polymorphonuclear neutrophils, and can reach intracellular concentrations up to 100 times higher than the plasma concentration.(6) High drug concentrations within phagocytes partially confer azithromycin with its efficacy for treating intracellular infectious agents. This quality is also the basis for using a five-day treatment for acute pharyngitis and otitis media.(7)

Breakthrough pneumococcal bacteremia in patients undergoing treatment with azithromycin has been described, which is not surprising given that the drug is largely transported within cells rather than in the circulating blood.(8,9) The occurrence of intravascular pneumococcal infections despite treatment suggests that azithromycin should be avoided in patients with significant risk of bacteremia.(4,9)

Spectrum of activity

Similar to other macrolides, azithromycin inhibits bacterial protein synthesis by binding to the 50S subunit of ribosomes and blocking protein translocation. However, unlike macrolides, such as erythromycin, azithromycin has lower in vitro activity against Gram-positive bacteria, including *Streptococcus pneumoniae*, but better in vitro activity against Gram-negative bacteria such as *Haemophilus influenzae* and *Moraxella catarrhalis*.

Upper and lower respiratory tract infections are by far the most common indications for azithromycin prescription in children in Western countries.(10) However, respiratory micro-organism

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susceptibility has changed over the time, and increasing use of macrolides, including azithromycin, is associated with a growing number of pneumococcal strains becoming resistant to macrolides. (4,11-14) Pneumococcal resistance to macrolides has become more common than resistance to penicillin. (4) Furthermore, the strains that are resistant to penicillin are almost always resistant to macrolides as well.

Macrolide resistance is variable in Canada. Since infant vaccination with heptavalent-conjugated pneumococcal vaccine, the prevalence of pneumococcal strains that are not susceptible to erythromycin, isolated in children with invasive pneumococcal diseases, has decreased from 8.8% to 5.8% in Alberta. (15) In Quebec, however, 23% of pneumococcal strains responsible for invasive infections were resistant to erythromycin, (16) suggesting that several factors – including prescribing patterns – play a role in the emergence of antimicrobial resistance.

THE PROBLEM OF RESISTANT BACTERIA

Suboptimal use of antibacterial medications is the most important reason for the emergence and spread of macrolide-resistant pneumococci. Incorrect practices include using antibiotics to treat nonbacterial infections (often viral in origin), under- or overprescribing (eg, administering an antibiotic with a suboptimal spectrum of activity or, conversely, an antibiotic with too broad a spectrum coverage), inappropriate dosing or prescribing for the wrong treatment length. (4,17) Misusing azithromycin has important consequences on the nasopharyngeal carriage of pneumococci. The antibiotic exerts a selection pressure enhanced by its own pharmacokinetic characteristics: the long half-life of azithromycin results in subinhibitory concentrations at carriage sites over a period of several days and promotes the emergence of resistant strains. Many studies have reported a link between the administration of macrolides and nasopharyngeal carriage of resistant pneumococci. (18,19) In Portugal, the use of azithromycin was correlated with the emergence of macrolide-resistant pneumococci. (20)

CLINICAL ASPECTS

Current azithromycin use is based on its pharmacokinetic and pharmacodynamic characteristics as well as its proven efficacy in therapeutic clinical trials. In paediatrics, it is predominantly used to treat both upper respiratory tract infections (eg, acute pharyngitis and acute otitis media) and lower respiratory tract infections (community-acquired pneumonia), (10) illnesses for which *S pneumoniae* is a principal cause of morbidity and mortality.

For acute otitis media, one randomized clinical trial comparing azithromycin with a high dose (90 mg/kg/day/6.4 mg/kg/day) of amoxicillin-clavulanate combination showed that treatment with the beta-lactam antibiotic achieved a higher rate of clinical recovery and bacterial eradication of resistant strains of both pneumococcus and *H influenzae*. (21)

The main problems with using azithromycin to treat acute otitis media are recurrent resistant pneumococcal strains and a suboptimal clinical efficacy against *H influenzae*, determined by bacterial eradication levels in middle-ear fluid. (22,23) Consequently, the American Academy of Pediatrics does not recommend the use of azithromycin for acute otitis media in children unless a child has an anaphylactic allergy to penicillin. (7)

For analogous reasons, similar recommendations should likely apply when treating pneumococcal community-acquired pneumonia. A recent Canadian Paediatric Society practice point on treating pneumonia in healthy Canadian children reserved azithromycin for children with suspected atypical pneumonia and as an adjunct to cefotaxime (or ceftriaxone) in cases of severe

pneumonia. (24) Beyond the risk of resistance, the very low plasma concentrations of azithromycin may increase the risk of serious therapeutic failure.

CONCLUSION

Azithromycin should not be used to treat acute pharyngitis, acute otitis media or community-acquired pneumonia in otherwise healthy children, except in the following cases:

- **Azithromycin should be used as a second-line treatment in cases of life-threatening beta-lactam allergy**, to treat acute pharyngitis caused by macrolide-sensitive group A beta-hemolytic streptococcus.
- **Azithromycin should be considered for treating pneumonia caused by atypical bacteria.** While definitive evidence for this use remains insufficient, azithromycin is recommended for this indication in Canadian and United States guidelines. Azithromycin should be considered for treating nonsevere pneumonia with primary features of atypical bacterial pneumonia: subacute onset, prominent cough, minimal leukocytosis and a nonlobar infiltrate, usually in a school-aged child.

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