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Community acquired pneumonia: 3 vs 5-day course of azithromycin in combination with a beta-lactam

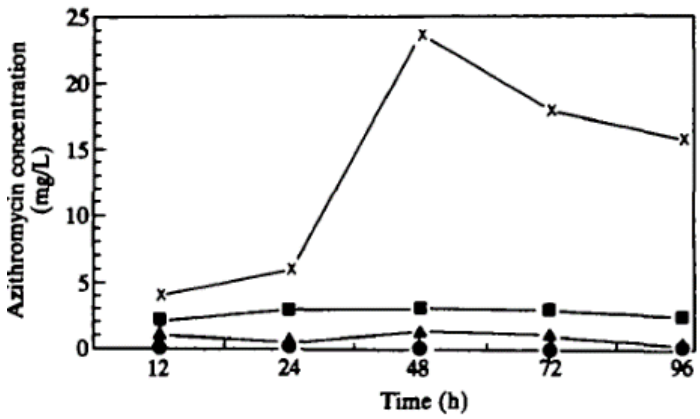
Community-acquired pneumonia (CAP) is a leading cause of hospital admission and mortality, with over 50,000 deaths due to pneumonia in 2016.[1,2] Many ASPs focus on encouraging shorter durations of therapy. Moving from a 5- to a 3-day dosing strategy for azithromycin may avoid an additional two days of antibiotic therapy for patients treated for CAP. In this month's DASON newsletter, we consider the evidence comparing the efficacy and safety of 3- vs 5-day durations of azithromycin therapy in adult patients hospitalized with CAP.

Pharmacokinetics and Pharmacodynamics

Azithromycin is a macrolide antibiotic. Compared to its parent compound, erythromycin, it has a broader spectrum of activity, extensive tissue penetration and a relatively long half-life.[3] Azithromycin has good activity against most respiratory Gram-positive pathogens, some respiratory Gram-negative pathogens (including *Haemophilus influenzae* and *Moraxella catarrhalis*) and other respiratory pathogens (particularly *Legionella pneumophilae*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*).[3] Additionally, macrolides possess potent immunomodulatory effects, through the inhibition of inflammatory cytokines and pathways, that may contribute to improved outcomes.[4,5] Emerging drug-resistant *S. pneumoniae* (DRSP), however, has significantly decreased its use as CAP monotherapy, and its main role in therapy of CAP is in combination with a beta-lactam agent.[6]

Azithromycin achieves excellent peak concentrations within lung tissue- up to 100-fold greater than serum levels.[3,7] Azithromycin also penetrates well into inflammatory cells, such as neutrophils and macrophages. Unlike most other antibiotics, high tissue levels of azithromycin persist within the lung for extended periods of time following short treatment courses.[3,8] Once-daily dosing of azithromycin for 3-5 days yields antimicrobial coverage for up to 7-14 days- a treatment strategy that is likely to improve patient adherence and treatment completion rates.[7] Common dosing strategies for azithromycin are 500mg IV or PO for 3 days or the "Z-pack" dosing of 500mg on day 1 followed by 4 more days of 250mg daily.

Figure: Pulmonary tissue levels of azithromycin. From Baldwin et al, Eur Resp J 1990.[9]
Legend: x alveolar macrophages, ▪ bronchial mucosa, ▲ sputum, • serum.



3 vs 5-day Therapy

First-line therapy of high-risk outpatients (i.e. patients with risk factors for drug-resistant *S. pneumoniae*) and adults hospitalized with CAP includes two options: 1) combination beta-lactam/macrolide therapy or 2) a single agent respiratory fluoroquinolone.[6] Many ASPs promote option #1 in order to avoid the multiple known risks associated with fluoroquinolone agents.

Because pharmacological studies have demonstrated equivalent serum and leucocyte concentrations when a total of 1.5g of oral azithromycin was administered in divided doses over 3 vs 5 days, several investigators have compared the efficacy of 3 vs 5-day courses of azithromycin in patients with mild to moderate CAP.[8,10]

A meta-analysis of short-course antibiotic regimens, predominantly azithromycin, for mild to moderate CAP by Li and colleagues noted no difference in clinical failures between short course (≤7 days) and long course (>7 days) regimens.[11] Although primarily designed to study durations of ≤7 days, a subgroup analysis of studies using 3-day regimens of azithromycin also showed no difference in clinical failures compared to long course regimens.[11]

A multi-center, randomized, open-label, non-inferiority study by Paris and colleagues compared a 3-day oral azithromycin course (1g daily) to a 7-day oral amoxicillin-clavulanate course (875/125mg twice daily) amongst adult outpatients with mild CAP.[12] Both arms achieved >90% clinical, radiological and microbiological success with minimal drug-related adverse events, leading authors to conclude that both arms were equally effective.[12] Sopena and colleagues also compared a 3-day azithromycin course (500mg daily) to a 10-14 day clarithromycin (250mg twice daily) course in the treatment of inpatients and outpatients with mild-moderate CAP in a multi-center, randomized, open-label trial and also found equal efficacy with >90% clinical response in both arms.[13] Not surprisingly, treatment compliance was superior and drug-related adverse events were less frequent in patients treated with azithromycin than in patients randomized to treatment with the comparator in this trial.[13] Other older clinical trials studying 3-day courses of azithromycin in mild-moderate CAP found comparable outcomes including clinical response, radiological response, and adverse effects.[14-18]

Although the references above suggest a 3-day azithromycin course is sufficient, the studies were largely performed in patients who did not have severe disease. In addition to severity of illness, another important clinical assessment when considering 3-day therapy is clinical response. Patients with complicated CAP (including empyema, lung abscesses and extra-pulmonary complications), patients with an inadequate response to initial therapy (lack of clinical improvement, hemodynamic instability, inability to take or absorb oral medications) or pneumonia due to high-risk pathogens (including *Legionella spp*) would benefit from close monitoring and longer treatment courses.[5] We recommend guideline-driven management that encourages overall treatment durations for at least 48-72 hours after resolution of clinical symptoms (e.g. fever, WBC, hypoxia). For patients with mild to moderate CAP and a good initial clinical response to combination therapy, we suggest a 3-day course of azithromycin combined with a minimum 5-day course of beta-lactam therapy. Results for azithromycin should not be extrapolated to other antibiotics with different pharmacokinetics, in particular those with shorter half-lives.

Adverse Events

Azithromycin is usually well-tolerated with low rates of adverse events (AE) and therapy discontinuation.[3,19,20] However, higher doses of azithromycin have been associated with higher rates of AEs.[3] The most frequent side effects of azithromycin are mild to moderate gastrointestinal symptoms, such as diarrhea (4-5%), nausea (3%) and abdominal pain (2-3%).[3,20] Other adverse events include insomnia, rash, headache and transient liver function derangement.[3] Macrolides have also been associated with QT interval prolongation.[3] In the macrolide class, animal studies have shown that azithromycin is least likely to induce QTc prolongation.[3] Although the data on cardiovascular safety of azithromycin remains inconclusive, the absolute risk of serious arrythmia in most patients remains extremely small.[3] Monitoring with periodic electrocardiograms can be performed during therapy in higher risk patients requiring azithromycin.[3]

Key Points

1. A 3-day course of therapy with azithromycin was as effective as a 7-day course of therapy in patients with mild to moderate CAP.

2. Azithromycin has favorable pharmacokinetics, resulting in a prolonged antimicrobial effect lasting up to 9-10 days after receipt of the third dose of azithromycin.
3. A 3-day course of therapy of azithromycin was associated with improved adherence and fewer antibiotic-mediated adverse effects compared with a 7-day course.
4. Use of combination beta-lactam/macrolide regimens with a 3-day, 500mg daily dose course of azithromycin plus a minimum 5-day course of beta-lactam is sufficient for treatment of uncomplicated, mild to moderate CAP in high-risk outpatients and inpatients.
5. Patients with severe, complicated pneumonia, patients with an inadequate response to initial therapy, or pneumonia due to high-risk pathogens, especially Legionella, should receive a longer duration of macrolide treatment.

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