Single-dose azithromycin microsphere formulation: a novel delivery system for antibiotics

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Abstract: Azithromycin extended release (Zmax®, Pfizer Inc) is a novel single-dose administration formulation of azithromycin which won FDA approval in June 2005 and is currently approved for the treatment of community acquired pneumonia and acute bacterial sinusitis. Azitromycin is incorporated into sustained-release microspheres which release the drug slowly through 200 μm pores. Because of this sustained release mechanism, most of the drug is released into the lower gastrointestinal tract, reducing gastrointestinal side-effects, and allowing for a higher dose to be administered. The unique pharmacological properties and extremely long half-life of azithromycin make this drug well suited to single-dose administration but gastrointestinal side effects have previously hampered single-dose therapy.

Keywords: azithromycin, microspheres, acute bacterial sinusitis, community acquired pneumonia

Introduction

Azithromycin extended release (Zmax®, Pfizer Inc) is a novel single-dose administration formulation of azithromycin which won FDA approval in June 2005. It is currently approved for the treatment of community acquired pneumonia and acute bacterial sinusitis (Zmax package insert). The immediate-release formulation azithromycin has been available in the United States since 1992 under the trade name Zithromax®, and is approved and widely used for community-acquired pneumonia, acute bacterial sinusitis, otitis media, acute bacterial exacerbations of chronic obstructive pulmonary disease, pharyngitis/tonsillitis, uncomplicated skin and skin structure infections, urethritis and cervicitis, and genital ulcer disease in men (Zithromax package insert). Azithromycin revolutionized antibiotic care as it shortened treatment time for infections from 7–14 days to 1–5 days with comparable efficacy. New technology has enabled a higher dose to be administered as microspheres thus limiting gastrointestinal side-effects and allowing a full course of antibiotics to be given in a single dose.

Pharmacology

Azithromycin is an azolide antibiotic which is similar in structure and function to macrolides, but has important differences. It exhibits time-dependent killing, but because of its unique pharmacological properties and extremely long half-life (~60 hours) the pharmacodynamic parameter for these agents that correlates with efficacy is the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio rather than T > MIC (Odenholt-Tornqvist et al 1995). The AUC to MIC ratio that yields maximal efficacy with drugs from the macrolide and azolide class in animal models is approximately 25 (Craig et al 2002). Whereas penicillin tissue and serum levels are roughly equivalent, very little azithromycin remains in the serum and the majority concentrates inside cells, notably macrophages and neutrophils. These cells

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then migrate to areas of inflammation, providing extremely high concentrations at sites of infection. Azithromycin has demonstrated a 500 to 1 concentration difference between intracellular and extra cellular sites after 1 hour of incubation (Gordan and Blumer 2004).

As more pharmacodynamic information was gained on azithromycin it became apparent that shorter courses of therapy and at least equivalent efficacy can be achieved by frontloading the drug and delivering more drug early in infection. Animal studies have shown that the 50% effective dose can be decreased by giving a larger dose in 1 day compared with the same dose divided over 3 days. This translated into more rapid eradication of bacteria in a gerbil model of otitis media (Girard et al 2002).

Azithromycin extended release is incorporated into sustained-release microspheres. These microspheres are approximately 200 μm in diameter and release the drug through pores. The pore size is in the nanometer range and is ideally suited for the slow release of the active medication once the microsphere has passed through the stomach. Because of this sustained release mechanism, most of the drug is released into the lower gastrointestinal tract, reducing gastrointestinal side-effects, and allowing for a higher dose to be administered (Breen et al 2005). Azithromycin extended release delivers 2 g of azithromycin in one dose while the immediate release 3- and 5-day courses deliver 1.5 g over their entire dosing period.

This 2 g extended-release dose results in higher peak serum concentrations and pharmacokinetic parameters of azithromycin compared with conventional preparations. The peak serum concentrations 24 hour AUC (0–24) on day 1 are 3-fold higher for azithromycin extended release 2 g vs the traditional 1.5 g azithromycin given over either 3 or 5 days: 0.85 μg/mL vs 0.39 μg/mL and 0.85 μg/h/mL vs 0.39 μg/h/mL, respectively (Pfizer Inc, data on file).

Drug levels are also higher at sites of infection, namely lung tissue and white blood cells. Sixty-four adults undergoing lung resection were randomly given 2 g azithromycin extended release or 500 mg azithromycin. Healthy lung tissue was analyzed for AUC (0–24) and was found to have 3-fold higher levels in those individuals who had received azithromycin extended release; 505 μg/h/mL for azithromycin extended release and 130 μg/h/mL for 500 mg. Lung tissue drug concentrations after 24 and 72 hours were 25 and 33 μg/mL, respectively. In another study using azithromycin 500 mg daily for 3 days concentrations at 24 and 72 hours were 9 μg/mL (Pfizer Inc, data on file; Di Paolo et al 2002). In another study 24 healthy adults were randomly given 2 g azithromycin extended release or 500 mg azithromycin daily for 3 days and white blood cell pharmacokinetics in polymorphonuclear leukocytes were analyzed daily for 7 days. The front loaded dose resulted in significantly higher white blood cell peak concentrations (Pfizer Inc, data on file).

Clinical trials

Three industry-sponsored clinical trials have been performed comparing 2 g azithromycin extended release with other FDA-approved antibiotics for community-acquired pneumonia and acute bacterial sinusitis. Two trials were published in 2005 for the treatment of community-acquired pneumonia (CAP). D'Ignazio et al (2005) randomized 427 patients to receive a single 2 g dose of azithromycin microspheres or levofloxacin 500 mg daily for 7 days in a double-blinded fashion in a multi-center international trial. The primary endpoint was clinical response at test of cure which occurred 14–21 days after initiation of therapy. Patients were all older than 18 years of age and had a clinical diagnosis of mild to moderate CAP (a Fine mortality risk class of I, II, or III) including a chest radiograph with radiographic pneumonia. Patients with immune deficiency, renal, hepatic, or underlying pulmonary disease that could affect treatment/diagnosis, recent antibiotic use or hospitalization, or pregnancy were excluded. One hundred and eighty of the 211 azithromycin-treated patients and 190 of the 212 levofloxacin-treated patients completed the study. All azithromycin patients were compliant with treatment while 10 of the 212 levofloxacin-treated patients did not complete all seven days of therapy. 50.7% of the azithromycin group and 52.8% of the levofloxacin group had identifiable organisms. *Chlamydophila pneumoniae* was most common, followed by *Staphylococcus aureus, Haemophilus parainfluenzae, Mycoplasma pneumoniae, Staphylococcus pneumoniae,* and *Haemophilus influenzae.* None of the *S. pneumoniae* was resistant to levofloxacin while seven were resistant to azithromycin (MIC > 0.5). Five of these seven patients received azithromycin.

At the test of cure the clinical cure rate was statistically equivalent with a cure rate of 89.7% for azithromycin and 93.7% for levofloxacin (95% CI, –9.1% to 1.7%). The bacteriological cure rate was also equivalent with a cure rate of 90.7% for azithromycin and 92.3% for levofloxacin. Two of the subjects with azithromycin-resistant pneumococcus were clinical failures but one of these had clearance of organisms in the sputum. 12.3% of the azithromycin-treated group experienced diarrhea vs 4.7% of the levofloxacin-treated

group. This largely occurred on days one and two of treatment. There were no serious treatment-related adverse effects in either group (D'Ignazio et al 2005).

The second study with CAP, by Drehobl et al (2005), compared a single dose of azithromycin microspheres with clarithromycin extended release 1 g daily for 7 days. The study design was identical to the previous study and randomized 501 patients, of which 499 were treated and 411 met all inclusion criteria. The primary endpoint, again the clinical response at test of cure which occurred 14–21 days after initiation of therapy, was equivalent for the two arms; 92.6% for the azithromycin-treated group and 94.7% for the clarithromycin-treated group (95% CI, –6.9 to 2.6). There were six *S. pneumoniae* isolates resistant to azithromycin and clarithromycin. Two were collected from the azithromycin-treated group and one of these was a clinical failure. This patient also had two other co-pathogens. Four were collected from the clarithromycin-treated group and two of these were clinical failures. All patients completed the azithromycin antibiotic course while 15 of 254 subjects did not complete the 7-day clarithromycin course. 12.1% of azithromycin-treated patients had diarrhea or loose stools compared with 7.5% of clarithromycin-treated patients. These episodes were all mild or moderate (Drehobl et al 2005).

The acute bacterial sinusitis study was performed by Murray et al (2005) and again was an international, multi-center, double-blinded, placebo-controlled trial. Five hundred and forty-one patients with clinical signs and symptoms and radiographic evidence of acute bacterial sinusitis were randomized and 507 met all inclusion criteria. Patients were excluded if they had received any systemic antibiotic therapy in the previous week, had recurrent, complicated, or nosocomial rhinosinusitis, or had undergone recent (within 3 months) nasal or sinus surgery.

All patients had maxillary sinus aspiration with recovery of organisms in 42% of patients. The primary outcome was clinical cure (resolution of signs and symptoms or improvement with no need for further antibiotics) at 17–24 days after the first antibiotic dose. Azithromycin and levofloxacin were equally effective in providing a clinical cure: 94.5% vs 92.8, respectively (95% CI, –2.5% to 5.9%). *S. pneumoniae* was the most common pathogen identified followed by *H. influenzae* and *Moraxella catarrhalis.* Of 81 *S. pneumoniae* isolated 57% were penicillin susceptible, 27% intermediate, and 16% resistant. 85% were azithromycin susceptible while 15% were azithromycin resistant (MIC > 2). All strains were susceptible to levofloxacin. One patient in the azithromycin group had a clinical failure with a *S. pneumoniae*-resistant organism, but the repeat sinus aspiration was clear of *S. pneumoniae* and grew *Escherichia coli* in its place. The incidence of diarrhea was 11.1% in the azithromycin group and 1.9% in the levofloxacin group (Murray et al 2005).

Some authors express concern that this FDA-required study design for acute bacterial sinusitis is not a good measure of antibiotic efficacy for acute bacterial sinusitis. Acute bacterial sinusitis is largely a self-limited disease with clinical resolution seen even in the majority of untreated patients, and no study to date has proved clinical superiority over another agent. With this established test of cure, patients were evaluated for clinical cure 24–52 days after their symptoms began. By this point up to 72% of patients on placebo therapy will have resolution of symptoms. The true value of antibiotics in acute bacterial sinusitis is more likely faster resolution of symptoms enabling patients to return to work or school more quickly. In an editorial following Murray et al's article, Marple suggested a more clinically useful primary outcome would be difference in time to improvement of symptoms with a secondary outcome being quality of life at various intervals after initiation of therapy (Marple 2005).

Pneumococcal macrolide resistance

There is a growing number of *S. pneumoniae* isolates that are resistant to macrolides and azolides, but this is not usually manifested as clinical failures. These drugs exhibit their action by inhibiting ribosome function and hence protein synthesis. Macrolides interact with bacterial 23S rRNA in the 50S subunit. Most resistance has been described via one of two mechanisms: a ribosomal methylase coded for by the *erm* gene, and a macrolide-specific cell membrane-based efflux mechanism, coded for by the *mef* gene. The altered ribosomal binding conferred by the *erm* mutation confers high level resistance while the efflux pump seen with the *mef* mutation is more easily overcome with higher intracellular concentrations of the drug. Current NCCLS standards define macrolide resistance as >1 mg/L for macrolides and >2 mg/L for azithromycin. Because of the high intracellular concentrations in both respiratory tissue and white cells, these levels are easily overcome with azithromycin; however, and few clinical failures are seen with azithromycin even with resistant pneumococcus. Some authors feel an MIC of >32 mg/L is more indicative of true azithromycin resistance (Amsden 1999).

Drug–drug interactions and adverse effects

Azithromycin has few drug interactions and does not interact with CYP3A unlike other macrolides. A single dose of

azithromycin does not increase prothrombin times in patients on warfarin therapy. The major side-effects are gastrointestinal. The overall incidence of gastrointestinal complaints is 17.2%, with the above studies all having an incidence of diarrhea of 11%–12%. With the immediate-release azithromycin preparation there have been rare reports of hearing loss, photosensitivity, angioedema, and cholestatic jaundice (*The Medical Letter* 2005).

Administration

Extended-release azithromycin is a 2 g formulation with a cherry-banana taste that is mixed with 60 mL of water by the pharmacist. It should be used within 12 hours of mixing and taken 1 hour before or 2 hours after a meal. Taking it on an empty stomach helps minimize gastrointestinal side-effects. If the patient vomits within 1 hour of consumption an alternative antibiotic should be considered.

Conclusion

Extended-release azithromycin is the only FDA-approved single-dose antibiotic for the treatment of community acquired pneumonia and acute bacterial sinusitis. This is an example of the potential of nanotechnology to improve on existing therapies. The active agent, azithromycin, was not changed, but the new delivery system has maximized pharmacodynamic parameters while allowing for more convenient dosing of the drug. Due to the novel microsphere formulation gastrointestinal symptoms are reduced compared with the 2 g sachet immediate-release azithromycin, but there is still a 12% incidence of diarrhea. This drug is especially attractive where compliance is an issue because it is ideally suited to observed therapy. It also ensures completion of the antibiotic course. This, coupled with high first-day intracellular concentrations when bacterial load is greatest, have the theoretical chance of reducing bacterial resistance. However, these advantages must be weighed against the increase in gastrointestinal side-effects and added cost of extended-release azithromycin because the immediate-release formulation is now generic. Despite improved pharmacodynamic parameters, there is no evidence supporting its clinical efficacy over immediate-release azithromycin. In future we look forward to the evolving role of nanotechnology in the pharmaceutical field as it both improves on previous therapy, such as with extended-release azithromycin, and also contributes to the development of novel treatments.

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