Telithromycin

Elsewhere in this issue, Clay and colleagues (1) describe a serious adverse event related to telithromycin. This report should cause physicians who prescribe telithromycin to pause in order to be sure it is the right antibiotic for the circumstances. Herein we provide information about telithromycin to help clinicians decide when to prescribe it.

Telithromycin (Ketek, Aventis Pharmaceuticals, Bridgewater, New Jersey), the first marketed ketolide antibiotic, is a modification of the macrolide structure. Like macrolides (2), telithromycin blocks protein synthesis (3). However, compared with macrolides, it has increased affinity for the binding sites on domains II and V of the 50S ribosomal subunit (4). This attribute provides increased activity against bacteria that are resistant to macrolides because of both methylation- and efflux pump–mediated mechanisms (*erm*B and *mef*A, respectively) (2). Telithromycin is active in vitro against bacterial pathogens most commonly isolated from patients with mild to moderate community-acquired respiratory tract infections. These include infection with *Streptococcus pneumoniae* (both penicillin- and macrolide-resistant strains) as well as ß-lactamase–producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (5, 6). Telithromycin is also active in vitro against *Mycoplasma pneumoniae* and *Chlamydophilia pneumoniae* (7). While telithromycin demonstrates potent in vitro activity against other respiratory pathogens (such as *Legionella pneumophila* and *Bordetella pertussis*), clinical data about its effectiveness for these infections is limited. It is not active against erythromycin-resistant *Staphylococcus aureus* (2).

Following oral administration, telithromycin is widely distributed in the body, partially metabolized in the liver, and excreted primarily in feces and urine (8). It is present in high concentrations in bronchial mucosa, epithelial lining fluid, alveolar macrophages, and polymorphonuclear cells (9). In randomized, blinded clinical trials, telithromycin was not statistically inferior to the comparator antibiotic for treatment of its U.S. Food and Drug Administration–approved indications: mild to moderate community-acquired pneumonia (10–12), acute bacterial sinusitis (13–15), and acute exacerbations of chronic bronchitis (16, 17). The recommended dosing is 800 mg once daily for 5 days for the latter 2 indications and for 7 to 10 days for community-acquired pneumonia. According to the prescribing information provided by the manufacturer, dose modification is not required for liver disease (3). Dose reduction is indicated in chronic kidney disease; for patients with a creatinine clearance less than 0.50 mL/s (<30 mL/min), the dosage should be 600 mg once daily (3). The most common adverse effects are gastrointestinal (diarrhea and nausea), occurring in 8% to 10% of patients (3). In a safety study of 12 000 patients, the rate of adverse events was similar to the comparator drug, with the exception of visual disturbances (blurred vision, diplopia, and accommodation difficulties), which occurred in 0.6% of exposed patients (18). Physicians should caution their patients that these effects are most common after the first or second dose of medication, may persist for several hours, and often recur with subsequent doses (3). Liver abnormalities in patients taking telithromycin and related antibiotics are discussed in detail in the report by Clay and colleagues (1).

Physicians should proceed with extra caution when prescribing telithromycin in several situations. They should avoid the drug in patients who are hypersensitive to macrolide antibiotics (3) and in patients with myasthenia gravis (3, 19). Similar to clarithromycin, telithromycin acts as an inhibitor of the cytochrome P450-3A4 (CYP-3A4) enzyme system. Therefore, telithromycin is contraindicated in patients receiving cisapride or pimozide (3). If the patient takes a medication metabolized by the CYP-3A4 system, physicians should monitor more closely and be prepared to withdraw the affected drug. For example, because telithromycin substantially increases serum concentrations of simvastatin (3) and related drugs (namely lovastatin or atorvastatin), it is best to stop treatment with these medications while the patient is receiving telithromycin (3). Coadministration of drugs that induce CYP-3A4 (for example, rifampin) or inhibit it (for example, ketoconazole) may significantly alter telithromycin serum concentrations (3). Telithromycin's potential to prolong the corrected QT interval results in a warning against using the drug in patients already at increased risk for this condition, including those receiving class IA and class III antiarrhythmic agents (3).

The recent report of hepatic failure with telithromycin (1) should prompt clinicians to think carefully when considering this drug to treat a specific patient. They should ask themselves 6 questions, which are important to consider when prescribing any antibiotic. First, is antibacterial therapy really necessary for this patient? Second, what are the rates of antibiotic resistance in the community? Physicians should ask their microbiology laboratory to keep them up to date about the current rates of resistance to alternative antibiotics. High rates of resistance to macrolides could be an important consideration favoring telithromycin. Third, does the drug's pharmacokinetic profile offer an advantage? Once-per-day dosing, as with telithromycin, may be an advantage if the patient's adherence is a concern. Fourth, is the patient taking any other drugs? If so, do they interact with any of the antibiotics under consideration? Fifth, is cost an issue for the patient? Sixth, what is the potential for drug toxicity? If substantial toxicity is a possibility, what are the frequency and severity of the adverse event? In the present situation, we know of 3 very serious events (1) among the 11 million patients exposed to telithromycin worldwide (20). How to weigh the answers to these questions is the essence of that mysterious process

we call clinical judgment. While we may not understand how clinicians make complex decisions, the first step in coming to judgment is obvious: Ask the right questions.

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