Clinical experience with clarithromycin for the treatment of respiratory tract infections

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ERYTHROMYCIN, THE FIRST ANTIBIOTIC OF THE MACROLIDE class, was discovered in 1952 from the metabolic products of a strain of *Streptomyces erythreus* (1). Despite widespread use of this drug, specific problems have limited its usefulness. Poor oral bioavailability secondary to inactivation in an acidic medium necessitates the use of enteric coating or changes in formulation (2). A metabolite has been identified which binds to motilin-like receptors in the gastrointestinal smooth muscle (3). Activation of this receptor leads to an increase in interdigestive gastric motility and side effects. Finally, with a short half-life requiring four daily doses and a perceived lack of efficacy against *Haemophilus influenzae*, erythromycin has been used as a second line drug in the treatment of respiratory tract infections.

Clarithromycin has been introduced recently for use in Canada. This novel macrolide has many properties which would render it effective in a variety of infections. This article will review those properties briefly and the clinical efficacy of clarithromycin for the treatment of respiratory tract infections.

IN VITRO ACTIVITY

Clarithromycin demonstrates excellent activity against many Gram-positive organisms, anaerobic organisms, *Chlamydia* species, *Mycoplasma* species, *Moraxella catarrhalis* and *Legionella* species (4). In general it is about 1 log dilution more potent than erythromycin against most respiratory pathogens. The major metabolite of clarithromycin, a 14-hydroxy derivative, is active especially against *H influenzae* (5). There are in vitro and in vivo data to suggest that the parent compound and the metabolite are active in an additive fashion, thus rendering *Haemophilus* species susceptible to this antimicrobial (6).

PHARMACOKINETIC FEATURES

Clarithromycin is well absorbed from the gastrointestinal tract, is approximately 55% bioavailable and is stable in an acid environment (7). It diffuses well into respiratory tract fluids and tissues. Tonsillar, sinus, bronchial mucosal, alveolar macrophage and lung tissue levels far exceed serum levels both for the parent compound and the 14-hydroxy derivative (8,9). A long half-life of 3.5 h for the 250 mg dose and 4.9 h for the 500 mg dose allows twice daily dosing.

ADVERSE EFFECTS

About 3% of patients receiving the drug have withdrawn from clinical trials because of adverse effects (10). The incidence of these effects has been the same as comparator agents, particularly beta-lactam antibiotics, and significantly less than erythromycin. The

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most commonly reported side effects are nausea (4%), diarrhea (3%), dyspepsia (2%), abdominal pain (2%) and headache (2%).

Given the microbiological spectrum covered, excellent pharmacokinetics and favourable side effect profile, clarithromycin should be an effective agent in the treatment of respiratory tract infections. The rest of this review will cover the clinical experience with this agent in the treatment of upper and lower respiratory tract infections.

UPPER RESPIRATORY TRACT INFECTIONS

Pharyngitis and tonsillitis: Group A streptococcus is still the chief etiological agent responsible for pharyngitis. This organism remains highly susceptible to penicillin and other beta-lactam antibiotics. Erythromycin has been shown to be effective as an alternative agent.

The efficacy of clarithromycin has been examined in two large, multicentre, double-blind, randomized trials (11,12). In the first study patients were randomized to receive clarithromycin 250 mg every 12 h or penicillin VK 250 mg every 6 h (11). In total, 243 patients were enrolled in the study, with 128 patients receiving clarithromycin and 115 patients receiving penicillin VK. In the patients in whom a baseline pathogen could be isolated the clinical success rate with clarithromycin was 100% (clinical cure rate 96% and clinical improvement 4%), a result which was identical to the group that received pencillin VK. The bacteriological response rate was 98% for both the clarithromycin-treated patients and the penicillin VK-treated patients. The side effect profile of the two drugs was similar. In a second study 65 patients received clarithromycin while 63 patients received pencillin VK (12). The post treatment clinical success and bacteriological cure rates for clarithromycin were 95 and 88%, respectively, with both rates 91% for penicillin VK. The conclusions of these studies were that clarithromycin was as safe and effective as penicillin VK in the treatment of streptococcal pharyngitis.

The outcome of these two studies and three other studies were summarized recently (13). In five multicentre trials, 1031 patients with documented streptococcal pharyngitis were randomized to receive a 10 day course of clarithromycin 250 mg ql2h (n=468), a comparator agent, penicillin VK, 250 mg q8h (one study, n=227) or 250 mg q6h (two studies, n=178), or erythromycin stearate 500 mg q12h (two studies, n=158). The clinical success rate and bacteriological eradication rate for clarithromycin was 98 and 95%, respectively. There were no differences compared with the reference agents.

From these studies it appears clear that clarithromycin is effective in the treatment of streptococcal pharyngitis.

Sinusitis: Sinusitis has been shown to be caused by *Streptococcus pneumoniae*, *H influenzae*, primarily nontypeable strains, and *M catarrhalis*. A significant minority of *Haemophilus* strains produce beta-lactamase as do the majority of *Moraxella* strains (14,15). Given the excellent tissue penetration of clarithromycin and the activity against beta-lactamase producing organisms, it seems likely that clarithromycin would be effective in this indication.

Clarithromycin has been compared with amoxicillin in two studies (16,17) and amoxicillin-clavulanate in another (18). In a multicentre, single-blinded study conducted in Finland, 50 patients with clinical and radiological evidence of acute maxillary sinusitis received clarithromycin 500 mg ql2h or amoxicillin 500 mg q8h (16). Both antibiotics achieved a clinical success rate of 91% within 48 h post treatment. Radiological resolution was seen in 91% of clarithromycin-treated patients and 89% of patients receiving amoxicillin. Bacteriological cure was achieved in 88 and 91% of evaluable patients for clarithromycin and amoxicillin, respectively. The response rate for amoxicillin may be higher in this study than in clinical practice since beta-lactamase producing strains were excluded from the study.

In a multicentre, single-blinded study conducted in Canada, 70 patients received clarithromycin 500 mg ql2h while 72 patients received amoxicillin 500 mg q8h (17). At 48 h post therapy, clinical success was achieved in 85% of clarithromycin-treated patients and 80% of amoxicillin-treated patients. The radiological resolution rates were similar.

In another multicentre, single-blinded trial conducted in Canada, 87 patients received clarithromycin 500 mg ql2h while 84 patients received amoxicillin-clavulanate 500 mg q8h (18). The clinical success rate and bacteriological eradication rate for clarithromycin were 89 and 91%, respectively, while they were 100 and 96% for amoxicillin-clavulanate. Clarithromycin was better tolerated than amoxicillin-clavulanate in this study, with the clarithromycin-treated patients experiencing half the gastrointestinal side effects compared with the patients receiving amoxicillin-clavulanate.

From these studies it appears that clarithromycin is as effective as beta-lactams in the treatment of acute maxillary sinusitis.

LOWER RESPIRATORY TRACT INFECTIONS

Acute exacerbations of chronic bronchitis: The major pathogens implicated in this clinical entity are the same as those identified in acute sinusitis. Recently, the value of antimicrobial agents for this disorder has been established (19,20).

In a double-blind, randomized, multicentre trial, 111 patients with acute exacerbations of chronic bronchitis received clarithromycin 250 mg q12h while 114 patients received ampicillin 250 mg q6h (21). Both clarithromycin and ampicillin were effective with clinical success rates of 97 and 91%, respectively. Pathogen eradication rates were 86% for clarithromycin and 88%

for ampicillin, but patients who had beta-lactamase producing strains were excluded from the study. Although the incidence of gastrointestinal side effects was the same for both agents, there were a few more dropouts in the clarithromycin-treated group.

In a second, very similar trial involving 125 patients, clarithromycin-treated patients had a 96% clinical cure rate compared with a 91% rate for ampicillin-treated patients (22). The bacteriological cure rate was 96% for clarithromycin and 100% for ampicillin. In this study there were more gastrointestinal side effects with clarithromycin, but the dropouts were the same.

In two randomized, multicentre studies (one double-blind and one single-blind), 96 patients received clarithromycin 500 mg q12h while 92 received ampicillin 500 mg q6h (23). The clinical success rate and bacteriological response rate for clarithromycin were 97 and 95%, respectively, compared with 97 and 91%, respectively, for ampicillin. The side effect profiles for the two drugs were similar.

Two studies have compared clarithromycin to cefuroxime and cefaclor for the same indication (24,25). In these studies the 500 mg dose of clarithromycin was compared with a 500 mg dose of the comparator agent. The clinical response rate was the same for clarithromycin and cefuroxime but better for clarithromycin than cefaclor. The bacteriological response rates were the same. Clarithromycin and cefuroxime axetil had a similar incidence of gastrointestinal side effects, while cefaclor had fewer than clarithromycin in this study.

Several studies have examined patients suffering from a variety of lower respiratory tract infections including acute bronchitis, acute exacerbations of chronic bronchitis and pneumonia (26-29). Clarithromycin has been compared with amoxicillin, cefaclor and cefixime in double-blind, randomized trials. In all instances the clinical success rates and bacteriological eradication rates were similar.

Pneumonia: Pneumonia in the outpatient setting is most often caused by *S pneumoniae* but other atypical organisms, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila* have assumed increasing importance. The clinical presentation of patients infected with atypical organisms is often similar to those infected with the usual bacterial pathogens and it is difficult to separate these entities on clinical grounds alone (30). Beta-lactam antibiotics are not considered the drugs of choice for treatment of atypical pathogens.

Several studies have examined the efficacy of clarithromycin in patients with community-acquired pneumonia (31,32). Anderson and co-workers (31) compared clarithromycin 250 mg q12h with erythromycin stearate 500 mg q6h in a multicentre, double-blind, randomized trial. Clinical success and radiological response were similar in the two groups, but the side effects were less with clarithromycin. Chan and co-workers (32) compared clarithromycin 250 mg ql2h to erythromycin stearate 500 mg q6h in a multinational, multicentre randomized clinical trial. The clinical response rate and radiological resolution rate for clarithromycin-treated patients was 97 and 90%, respectively, while it was 96 and 85% for the erythromycin-treated group. The patients receiving clarithromycin experienced fewer side effects than the erythromycin-treated patients.

Clarithromycin has been shown to be effective in the treatment of patients with pneumonia caused by *Mycoplasma* (33), *Chlamydia* (34) and *Legionella* (35) species.

SUMMARY

Clarithromycin has demonstrated excellent clinical results in the treatment of upper and lower respiratory tract infections. In well designed, well conducted randomized clinical trials, clarithromycin has been shown to be as effective as the usual agents in the management of patients with streptococcal pharyngitis, sinusitis, acute exacerbations of chronic bronchitis, acute lower respiratory tract infections and pneumonia. In many instances the studies masked the potential advantage of clarithromycin compared with standard beta-lactam antibiotics, since beta-lactamase producing strains were excluded from most studies for ethical reasons. The side effect profile appears similar to most beta-lactam antibiotics and better than erythromycin. Given clarithromycin's spectrum of activity, excellent pharmacokinetics, few significant adverse effects and proven efficacy in the management of respiratory infections, it should prove useful in the physician's armamentarium.

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