Clinical pharmacokinetics of clarithromycin

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CLARITHROMYCIN IS A NEW 14-MEMBERED MACROLIDE ANTIMicrobial agent that exhibits a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative aerobes. Susceptible pathogens include staphylococci, streptococci, *Haemophilus influenzae*, *Legionella pneumophila*, *Mycobacterium*, *Chlamydia* and *Mycoplasma* species (1). In addition, the 14-hydroxy metabolite of clarithromycin appears to have antimicrobial activity which may be additive or synergistic to that of the parent compound (2).

Clarithromycin is an acid-stable analogue of erythromycin with a methoxy substitution at C-6 of the erythronolide ring. This structural alteration prevents acid-induced conversion of the molecule to inactive spiroketal forms in the stomach, improves bioavailability and gastrointestinal tolerance after an oral dose, and therefore increases antibacterial activity (3) compared with erythromycin.

ABSORPTION

Clarithromycin exhibits a more predictable pattern of absorption than the prototype. After a single oral dose of a 250 mg tablet, clarithromycin is rapidly absorbed, with a mean time to maximum concentration (T_{max}) of approximately 2 h and mean maximum con-

centration (C_{max}) of 0.76 $\mu\text{g/mL}$ (3). Steady-state peak serum concentrations are 1.0 to 1.5 $\mu\text{g/mL}$ after a 250 mg twice daily dose and 2.0 to 3.0 $\mu\text{g/mL}$ after a 500 mg twice daily dose. In a study looking at the influence of increasing clarithromycin dose, the mean C_{max} increased approximately in proportion to dose from 0.35 $\mu\text{g/mL}$ (100 mg dose) to 3.97 $\mu\text{g/mL}$ (1200 mg dose) (4). Other clarithromycin pharmacokinetic parameters exhibited nonlinearity (see below). When clarithromycin was administered as a suspension (7.5 mg/kg body weight) to 24 infants and children, mean C_{max} values reached 3.59 $\mu\text{g/mL}$ (5).

The presence of food in the stomach causes a slight delay in both the onset of absorption of the parent compound and the formation of the 14-hydroxy metabolite; overall bioavailability is increased in the presence of food (6). Unlike erythromycin, clarithromycin is stable in gastric acid.

In order to assess the absolute bioavailability of clarithromycin, 19 healthy subjects received - in a three-way, randomized, crossover design trial - two oral formulations (250 mg) and intravenous clarithromycin lactobionate (250 mg) (3). The clarithromycin AUC_{0-24} ratio of oral versus intravenous was 0.51, indicative of a 51% bioavailability of parent compound. However,

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when adjusted for potency (oral: 98.4%, iv: 106.6%) the absolute bioavailability of the parent compound was 55%. The AUC for the metabolite was higher with oral dosing, suggesting that a substantial amount of 14-hydroxy clarithromycin is metabolized on first pass through the liver. Oral bioavailability of clarithromycin does not appear to be dose dependent on the basis of urinary excretion data.

DISTRIBUTION AND TISSUE PENETRATION

Macrolide antibiotics are known to bind to plasma proteins, particularly α_1 -acid glycoprotein. These compounds are lipophilic and they penetrate well into tissues (7). Clarithromycin penetrates particularly well throughout the body while maintaining high concomitant serum concentrations.

Penetration into suction-induced blister fluids was determined in healthy volunteers following three days of clarithromycin 250 mg twice a day (8). Clarithromycin and its 14-hydroxy metabolite yielded percentage of penetration (using AUC ratios) of 55 and 75%, respectively. In a preliminary study, clarithromycin (250 mg single dose) attained saliva to plasma and tears to plasma ratios of 1.73 and 1.01, respectively (9).

Scaglione and Frascini (10) evaluated the diffusion of clarithromycin into respiratory tissues, including the nasal mucosa, tonsils and lungs in adult patients undergoing surgery. For the three days preceding their surgical procedures, patients received clarithromycin, 250 mg twice daily (nasal mucosa or tonsillar tissue), or 500 mg twice daily (lung parenchyma). For clarithromycin and its active metabolite, half-lives ($t_{1/2\beta}$) in sputum were 1.3- to 1.6-fold longer than those in serum. In tonsils, mean 4 h post dose parent and metabolite concentrations were 5.3 and 3.1 mg/kg, respectively, and mean 12 h post dose values were 2.1 and 1.2 mg/kg, respectively. Parent and metabolite concentrations in nasal mucosa 4 h post dose were 5.9 and 3.2 mg/kg, respectively, and mean 12 h post dose values were 2.2 and 1.5 mg/kg, respectively. In lung tissue, parent and metabolite concentrations 4 h post dose were 13.5 and 7.2 mg/kg, respectively, and 12 h post dose values were 2.8 and 2.0 mg/kg, respectively.

Although intraphagocytic bioactivity is not a common property of antimicrobial agents (11), the newer macrolide antibiotics achieve high intracellular concentrations. Clarithromycin has been shown to penetrate macrophages and leukocytes, which makes it particularly effective against intracellular pathogens such as *L. pneumophila* and *Chlamydia* species (1). In contrast, penicillin and cephalosporin antibiotics are not actively concentrated by phagocytes, and they possess only modest, if any, intracellular activity (11).

Anderson and colleagues (11) observed that erythromycin was rapidly concentrated by neutrophils, with an intracellular to extracellular (I/E) ratio of 7:3. The I/E ratio for clarithromycin was found to be 9:1. These

investigators concluded that the superior pharmacokinetic properties of clarithromycin will lead to increased intraphagocytic accumulation and bioactivity *in vivo*.

Therapeutic concentrations of clarithromycin have also been found to stimulate protein kinase C activity in polymorphonuclear leukocytes. Thus, in addition to its antimicrobial activity, the drug stimulates cellular host defence mechanisms involving the activation of protein kinase C (12).

METABOLISM AND ELIMINATION

Although the metabolism of the macrolide antibiotics has not been extensively studied, it is known that a portion of the dose is metabolized in the liver. Macrolide antibiotics are demethylated by the cytochrome P-450-III microsomal enzyme system. Clarithromycin is metabolized to eight metabolites, but only one – the 14-hydroxy metabolite – has been shown to have antibacterial activity. Minor metabolic pathways are N-demethylation and hydrolysis of the cladinose sugar to produce inactive metabolites (13). The pharmacologically active 14-hydroxy metabolite appears to undergo further metabolism (N-demethylation or hydrolysis of the cladinose sugar) to inactive secondary metabolites.

The pharmacokinetics of clarithromycin appear to be nonlinear, apparently as a result of capacity-limited saturation of metabolic pathways. However, such nonlinearity is slight at the recommended doses. Disproportionate increases in total clearance, terminal disposition half-life and dose-normalized area under the plasma concentration-versus-time curve have been reported in patients receiving a single high dose (1.2 g) or multiple doses. Similar dose dependency has been observed with the 14-hydroxy metabolite (4). With increasing dose, a significant decline in the metabolite/parent compound plasma concentration ratio and a significant decline in urinary recovery of the metabolite were observed; this is consistent with a capacity-limited metabolism of the parent compound to the 14-hydroxy metabolite. Similar nonlinear pharmacokinetics have been noted with erythromycin (14).

Thirty to 40% of an oral dose of clarithromycin is excreted unchanged or as an active metabolite via the kidneys, and the remainder is excreted via the bile (15). In individuals with normal renal function, the half-lives of clarithromycin and its 14-hydroxy metabolite after a 500 mg dose are 5 and 7 h, respectively (16). As renal function declines, the serum half-lives of these compounds increase to 7.7 and 14 h, respectively. At a creatinine clearance of 30 to 80 mL/min, clarithromycin's half-life is 12 h; this interval increases to 32 h when the creatinine clearance falls below 30 mL/min. For 14-hydroxy clarithromycin at the lower creatinine clearance the half-life is 47 h. Clearly, an alteration in the dose regimen would be advisable in patients with severely impaired renal function.

Severe hepatic impairment could theoretically alter

the pharmacokinetics of clarithromycin and its metabolite so that less metabolite would be formed, and renal clearance of the parent compound would increase. Steady-state levels of unchanged clarithromycin in hepatically impaired patients are similar to those in normal subjects, so if renal function is normal, the drug can be administered without dose adjustment (17).

DOSAGE REGIMENS

The usual adult dosage of clarithromycin for infections of the respiratory tract, skin and soft tissues is 250 to 500 mg every 12 h for seven to 14 days. In patients with both hepatic and renal impairment, or in the presence of severe renal impairment, a decreased dose or prolonged dosing intervals may be appropriate (17). In infants and children, 7.5 mg/kg body weight bid seems appropriate (5). (In Canada, clarithromycin is currently indicated for adults and children above 12 years of age.)

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