New Directions for Macrolide Antibiotics: Pharmacokinetics and Clinical Efficacy

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The worldwide resurgence of interest in macrolide antibiotics has yielded several semisynthetic derivatives of 14- and 16-membered macrolides which have progressed to clinical trials. The structures and in vitro activities of these compounds were summarized in the preceding minireview (19). In this second article, the pharmacokinetics, immune modulatory effects, and early clinical experiences of these newer macrolide antibiotics are reviewed.

PHARMACOLOGY OF NEWER MACROLIDES

Animal pharmacokinetics. Although some improvements in in vitro antimicrobial activity have been obtained with the newer macrolides, greater oral bioavailability and higher and more persistent levels in serum and tissue also offer opportunities to achieve clinical advantages over erythromycin (Table 1). Since clinical data are becoming available, only a few illustrative examples of the advantageous pharmacokinetics observed in animal models are mentioned.

The oral bioavailability of roxithromycin was increased to 72% in mice and 85% in rats, compared with less than 10% for erythromycin; levels of roxithromycin in serum and tissue were substantially higher, its elimination half-life was longer, and it was more efficacious against experimental infections in rodents than was erythromycin (10).

Levels of dirithromycin in serum were lower but more persistent than those of erythromycin in mice, rats, dogs, and rhesus monkeys; and high tissue/plasma concentration ratios were obtained (U. Busch, G. Heinzl, U. Lechner, and F. W. Koss, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 922, 1988). These features were probably responsible for the observations of greater efficacy and prophylaxis against experimental infections (U. Lechner, K. R. Appel, E. Woitun, and R. Maier, 28th ICAAC, abstr. no. 918, 1988; F. T. Counter, A. M. Feltly-Duckworth, H. A. Kirst, and J. W. Paschal, 28th ICAAC, abstr. no. 920, 1988).

Oral administration of azithromycin to mice, rats, beagle dogs, and cynomolgus monkeys resulted in greater bioavailability, higher levels in serum, greater tissue-serum concentration ratios, and longer half-lives than obtained with erythromycin (9, 15); the combination of the in vitro and pharmacokinetic improvements of azithromycin was demonstrated by its efficacy against several experimental infections which erythromycin failed to cure (15).

Better absorption with oral administration and chemical stability of clarithromycin resulted in higher concentrations in serum and lung tissue, a longer serum half-life, and greater efficacy than that of erythromycin in rodent models (12). Clarithromycin’s greater in vitro activity against Legionella species and higher concentrations in serum and lung tissue resulted in better efficacy than that of erythromycin against a Legionella infection in guinea pigs (12).

Rokitamycin produced higher and more persistent concentrations in serum than parent macrolides because of the combination of its better absorption with oral administration and the high antimicrobial activity of its primary metabolites (16, 28). Its pharmacokinetic behavior in infant rats and dogs was similar to that in adult animals, suggesting utility in pediatric areas (A. Sakai, T. Suzuki, M. Morishita, K. Mizuno, T. Ishioka, and R. Fujii, 28th ICAAC, abstr. no. 913, 1988).

Miokamycin had an analogous pattern of metabolism, resulting in production in vivo of metabolites which possessed antimicrobial activity (31). 16-Membered macrolides such as miokamycin did not promote gastrointestinal motility in unanesthetized dogs, in contrast to 14-membered macrolides such as erythromycin (22).

Human pharmacokinetics. Erythromycin and other lipophilic macrolides show excellent tissue penetration with correspondingly high tissue-to-plasma antibiotic concentration ratios. Therefore, greater concentrations of antibiotic are thought to be achieved at a presumed site of infection. Such findings are in agreement with the apparent volumes of distribution for erythromycin and its derivatives, which are generally quite large.

The pharmacokinetics of the newer macrolides are summarized in Table 2.

Roxithromycin is characterized by high concentrations in serum. Mean peak concentrations in serum measured 7.90, 10.82, and 12.24 μg/ml after administration of 150, 300, and 450 mg, respectively. The pharmacokinetics of roxithromycin were nonlinear over the dosage range of 150 to 450 mg. Half-life varied with dose, with half-lives of 10.5 h after administration of 150 mg, 11.9 h after 300 mg, and 13.8 h after 450 mg. Time to peak concentration in serum decreased with dose and was in the range of 1.93 to 1.3 h. Renal clearance measured 0.252 to 0.415 liters/h during the 0- to 8-h period after dose administration (29).

Dirithromycin achieved high tissue concentrations despite low concentrations in serum. Dirithromycin had a long, dominant terminal half-life of 20 to 50 h. Tissue concentrations reached a maximum between 5 and 10 h postdose and declined subsequently, with a rate similar to that in serum (terminal half-life in tissue, >20 h). Tissue levels were well in the range of the MICs for susceptible organisms for at least 24 h after a single oral dose of 500 mg. Steady-state concentrations regularly exceeded 1 mg/kg of tissue in tonsil, lung, nasal mucosa, and prostate. Dirithromycin had a total clearance of 250 to 500 ml/min, a volume of distribution at steady state of more than 5 liters/kg of body weight, and a multiphasic disposition. Steady-state concentrations were reached within 4 to 7 days with once-daily dosing (G. Bozler, G. Heinzl, U. Lechner, K. Schumacher, and U. Busch, 28th ICAAC, abstr. no. 924, 1988).

Azithromycin also had an extended half-life and high tissue penetration. When azithromycin was given in a dose of 500 mg intravenously, the half-life measured 41 h and volume of distribution at steady state measured 23 liters/kg.

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with a clearance of 10 ml/min per kg. Orally, azithromycin demonstrated 40% bioavailability after a single dose. Tissue levels 60 h after a second dose of azithromycin given as 250 mg twice daily measured 3.2 mg/kg in tonsil and 1 mg/kg in prostate. Urinary excretion measured 3 to 5% in the 0- to 24-h period (R. M. Shepard, D. J. Weidler, D. C. Garg, P. O. Madsen, C. E. Cox, K. H. Chan, and C. D. Bluestone, 27th ICAAC, abstr. no. 239, 1987).

Clarithromycin was rapidly absorbed, reaching peak concentrations in serum 2 h after dosing regardless of dose size. It followed a one-compartment open model with somewhat nonlinear kinetics in plasma, as half-life varied with dose. When given orally in single doses of 100 mg to 44 subjects, clarithromycin achieved a peak concentration in serum of 0.5 μg/ml, with a half-life of 2.4 h. When these same subjects were administered single oral doses of 1,200 mg, clarithromycin attained a mean peak concentration in serum of 4.4 μg/ml with a corresponding half-life of 4.9 h (L. T. Sennello, S.-Y. Chu, D. S. Wilson, K. S. Laws, S. T. Bunnell, L. L. Varga, and K. Snyder, 26th ICAAC, abstr. no. 419, 1986). Kobayashi administered an oral dose of 400 mg in a phase I clinical study and demonstrated a half-life of 4.73 h, mean peak concentration in serum of 2.14 μg/ml, time to peak concentration in serum of 1.71 h, and area under the serum concentration-time curve of 17.4 mg-h/liter (H. Kobayashi, 26th ICAAC, abstr. no. 420, 1986). Slightly different results were obtained by Ferrero, who administered a dose of 250 mg and measured a half-life of 3.9 h and a peak concentration in serum of 0.5 μg/ml (J. L. Ferrero, K. C. Marsh, B. A. Bopp, D. J. Anderson, and J. Lamm, Pharmacologist 29:152, 1987). When a dose of 1,200 mg was administered, the half-life measured 11.1 h, with a corresponding peak concentration in serum of 2.6 μg/ml (Ferrero et al., Pharmacologist). Animal studies demonstrated high tissue levels (T. Suwa, H. Yoshida, Y. Kohno, K. Fukushima, and H. Kobayashi, 26th ICAAC, abstr. no. 417, 1986), but data on human tissue levels have not been published.

Flurithromycin is characterized by a mean peak concentration in serum of 1.2 to 2 μg/ml after a 500-mg single dose orally. Time to peak concentration in serum was 1 to 2 h, with an area under the serum concentration-time curve of 16.2 mg-h/liter. Half-life was 8 h, with a volume of distribution of 5.5 liters/kg. Flurithromycin achieved tissue concentrations of 5.3 mg/kg in lung, 1.4 mg/kg in bone, 1.1 mg/kg in soft tissue, and 3.0 μg/ml in pericardial fluid (7).

Rokitamycin pharmacokinetics as determined in a crossover study with healthy adults between rokitamycin tablets and rokitamycin dry syrup indicated that the dry syrup achieved values 85% of those obtained with the tablet formulation. Rokitamycin dry syrup (300 mg orally) attained a mean peak concentration in serum of 0.54 μg/ml and an area under the serum concentration-versus-time curve of 0.96 mg-h/liter. When rokitamycin dry syrup was administered to 49 pediatric patients at doses of 5, 10, and 15 mg/kg, mean peak concentrations in serum of 0.26, 0.554, and 0.79 μg/ml, respectively, were achieved. Areas under the serum concentration-versus-time curve measured 0.69, 1.18, and 1.52 mg-h/liter (A. Sakai et al., 28th ICAAC). In neonates and infants given a dose of 10 mg/kg, peak concentrations in serum measured 0.59 μg/ml 30 min after oral administration (K. Sunakawa, H. Akita and R. Fujii, 28th ICAAC, abstr. no. 914, 1988).

### TABLE 1. Salient features of newer macrolides

<table>
<thead>
<tr>
<th>Macrolide</th>
<th>Chemical alteration</th>
<th>In vitro activity (compared with that of erythromycin)</th>
<th>Human pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roxithromycin</td>
<td>14-Membered ring; C-9 oxime derivative</td>
<td>Comparable</td>
<td>High peak concentrations in serum; half-life of 12 h</td>
</tr>
<tr>
<td>Dirithromycin</td>
<td>14-Membered ring; C-9, C-11 oxazine</td>
<td>Comparable</td>
<td>Once-daily administration; high tissue concentrations</td>
</tr>
<tr>
<td></td>
<td>derivative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>15-Membered ring; C-9a tertiary amino</td>
<td>Improved against gram-negative bacteria</td>
<td>Improved peak levels in plasma compared with erythromycin</td>
</tr>
<tr>
<td></td>
<td>derivative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>14-Membered ring; 6-O-methyl derivative</td>
<td>Improved against gram-positive bacteria and Legionella spp.</td>
<td></td>
</tr>
<tr>
<td>Flurithromycin</td>
<td>14-Membered ring; 8-flouro derivative</td>
<td>Comparable</td>
<td>Half-life of 8 h; high tissue concentrations</td>
</tr>
<tr>
<td>Rokitamycin</td>
<td>16-Membered ring; 3'-ester derivative</td>
<td>Improved against Legionella and Mycoplasma spp.</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Miokamycin</td>
<td>16-Membered ring; 3'-ester derivative</td>
<td>Improved against Legionella and Mycoplasma spp.</td>
<td>Data not available</td>
</tr>
</tbody>
</table>

*mg and measured a half-life of 3.9 h and a peak concentration in serum of 0.5 μg/ml (J. L. Ferrero, K. C. Marsh, B. A. Bopp, D. J. Anderson, and J. Lamm, Pharmacologist 29:152, 1987). When a dose of 1,200 mg was administered, the half-life measured 11.1 h, with a corresponding peak concentration in serum of 2.6 μg/ml (Ferrero et al., Pharmacologist). Animal studies demonstrated high tissue levels (T. Suwa, H. Yoshida, Y. Kohno, K. Fukushima, and H. Kobayashi, 26th ICAAC, abstr. no. 417, 1986), but data on human tissue levels have not been published.*

### TABLE 2. Pharmacokinetics of newer macrolides

<table>
<thead>
<tr>
<th>Macrolide and dose (mg; route)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>AUC (mg·h/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roxithromycin (300; p.o.)</td>
<td>10.8</td>
<td>1.6</td>
<td>11.9</td>
<td>-</td>
</tr>
<tr>
<td>Dirithromycin (500; p.o.)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Azithromycin (500; p.o.)</td>
<td>0.4</td>
<td>2.0</td>
<td>41 (i.v.)</td>
<td>4.5</td>
</tr>
<tr>
<td>Clarithromycin (400; p.o.)</td>
<td>2.1</td>
<td>1.7</td>
<td>4.7</td>
<td>17</td>
</tr>
<tr>
<td>Flurithromycin (500; p.o.)</td>
<td>1.2-2</td>
<td>1-2</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Rokitamycin (300; p.o.)</td>
<td>0.5</td>
<td>—</td>
<td>—</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* C<sub>max</sub>: Maximum concentration in serum; T<sub>max</sub>: time to maximum concentration in serum; t<sub>1/2</sub>: half-life; AUC: area under the serum concentration-time curve; p.o.: orally; —: data not available in the published literature; i.v.: intravenously.

### MACROLIDES AND THE IMMUNE SYSTEM

The interaction between antimicrobial agents and the various humoral and cellular components of the immune system is an area of active research. Although most studies have used erythromycin, this new feature is applicable to the
newer macrolides as well. Potential cooperation between an antibiotic and the immune system is particularly important in patients with impaired immune function, such as patients with acquired immune deficiency syndrome. Erythromycin and macrolides show excellent penetration of polymorphonuclear leukocytes, macrophages, and lymphocytes (5, 11, 18, 23, 26). This is particularly important in infections with Legionella spp., Mycobacterium spp., Listeria spp., Brucella spp., Staphylococcus aureus, Toxoplasma spp., and Chlamydia spp., which are known to survive intracellularly. Whether or not this class of antibiotics achieves high concentrations in lysosomes of phagocytic cells is unclear. However, intraphagocytic antimicrobial activity was recently reported for erythromycin and clarithromycin (3).

The evidence suggests that erythromycin is not inhibitory and may interact favorably with immune system function. As mentioned above, erythromycin achieves significant intracellular concentrations and remains microbiologically active within the cell (4, 5, 23, 30). Bactericidal oxidative metabolism of the polymorphonuclear leukocyte does not appear to be altered by erythromycin (23, 30). Intracellular penetration of josamycin into alveolar macrophages of patients treated orally with josamycin was recently reported (24).

Mandell and Ebson reported that erythromycin potentiates polymorphonuclear leukocyte phagocytosis (L. A. Mandell and M. Ebson, 12th Int. Congr. Chemother., p. 184–185, 1981); however, Naess and Solberg and van Rensburg et al. showed no effect on phagocytosis (21, 30). Conflicting reports have also been published regarding polymorphonuclear leukocyte chemotaxis. Anderson et al., van Rensburg et al., and Aho and Mannisto published studies which support the enhancement of chemotaxis by erythromycin (2, 4, 30). Nelson et al. reported that chemotaxis was diminished and Naess and Solberg and Forsgren and Schmeling reported no effect (14, 21, 23).

In 1988, Naess and Solberg reported that erythromycin significantly increased the percentage of membrane receptors on polymorphonuclear leukocytes and lymphocytes; however, it did not increase the proportion of lymphocytes rosetting with erythrocyte-antibody cells and erythrocyte-antibody-complement cells (21). Erythromycin did not affect lymphocyte response to mitogen (21). In addition, erythromycin did not alter the levels of serum immunoglobulin G, A, or M or complement (total hemolytic complement, C3, C4) (30).

**CLINICAL EXPERIENCE WITH NEWER MACROLIDES**

Published clinical trial data involving the newer macrolide antibiotics are limited. Several compounds (clarithromycin, azithromycin, dirithromycin) are under development; however, results of the trials have not yet been published. Renewed interest in older macrolides (spiramycin) has surfaced as well, with further exploration of their antimicrobial properties.

Newer macrolide derivatives are expected to retain the clinical indications of erythromycin, which include upper and lower respiratory tract infections, skin and skin structure infections, and genital tract infections caused by erythromycin-susceptible organisms.

Roxithromycin is the most extensively studied of the newer macrolides. Roxithromycin is well tolerated at a dose of 150 mg twice daily and may have a lower incidence of side effects than erythromycin. Equivalent clinical and microbiologic responses in the treatment of lower respiratory tract infections were shown in comparative studies (8, 17). Roxithromycin was also efficacious in the treatment of atypical pneumonia caused by *Chlamydia psittaci*, diagnosed via complement fixation (6). Favorable clinical responses were also shown in *Mycoplasma pneumoniae* (13), genital infections caused by *Chlamydia* and *Ureaplasma* spp. (20), and skin and skin structure infections (1).

Dirithromycin is in clinical trials to evaluate safety and efficacy in the treatment of pharyngitis, acute-superimposed-on-chronic bronchitis, pneumonia, and skin and skin structure infections. Preliminary data from German trials have shown efficacy in the treatment of respiratory tract infections (H. Mielenz and K. Bestehorn, 28th ICAAC, abstr. no. 926, 1988).

In vitro data are available for azithromycin; however, no clinical trial data have been published. On the basis of preliminary trial data, rokitamycin appeared to show clinical efficacy in the treatment of *Mycoplasma*, *Chlamydia*, and *Campylobacter* infections. Clinical efficacy was 88% in 306 of 622 cases in which an organism was isolated. Individuals were treated with 20 to 40 mg/kg per day. The incidence of adverse drug events was low at 1.9% (R. Fujii and T. Nishimura, 27th ICAAC, abstr. no. 458, 1987). Rokitamycin also demonstrated preliminary efficacy in the treatment of chlamydial infections of neonates, premature babies, and infants. Clinical effectiveness was observed in 93% of pneumonia cases and 100% of conjunctivitis cases (Sunakawa et al., 28th ICAAC).

There has been one report of clinical experience with miokamycin in the treatment of respiratory tract infections. Clinical response was reported to be good to excellent in 84 of 86 patients. Pathogens were eradicated in all cases in which a bacterial organism was cultured (27).

Clarithromycin has been used in the therapy of acute and chronic upper and lower respiratory tract infections, with a symptomatic response rate of 88.5% observed. Sixty-one patients were treated with 200 to 400 mg/day for 7 to 14 days. Preliminary studies also indicated the effectiveness of clarithromycin in the treatment of nongonococcal urethritis and cervicitis of chlamydial and unknown origin. Response rates measured 80 to 91.7% (Kobayashi, 26th ICAAC). The in vitro activity of clarithromycin, although similar to that of erythromycin, appears to be greater against *Legionella pneumophila*. Whether this difference will be seen clinically has as yet to be determined.

**SUMMARY**

Erythromycin and related macrolide antibiotics have recently enjoyed a resurgence of clinical interest. This is a result of activity against organisms which are becoming more prevalent, particularly in immunocompromised hosts and, in addition, better understanding of the unique tissue penetration properties and potential immunomodulating properties of macrolides. Other features of clinical interest possessed by certain of the newer macrolides include the potential for once-daily dosing, resistance to acid degradation in the stomach without enteric coating, and possibly reduced gastrointestinal side effects.

The new macrolides are expected to retain the clinical indications of erythromycin, which include upper and lower respiratory tract infections, skin and skin structure infections, and genital tract infections caused by erythromycin-resistant organisms. In addition, enhanced activity has been demonstrated in animal models and in vitro against *Toxoplasma, Legionella, Haemophilus*, and *Campylobacter*.
spp. New macrolide derivatives also show promise to expand the antimicrobial spectrum of erythromycin to include *Mycobacterium* and *Borrelia* spp.

ACKNOWLEDGMENTS

We thank M. A. Pozsgai and L. W. Cran dall for assistance in literature searches. We also thank Connie F. Dugan for typing the manuscript.

LITERATURE CITED