

Alexander A. Vinks · Hartmut Derendorf
Johan W. Mouton *Editors*

Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics

 Springer

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Chapter 11

Macrolides and Ketolides

Françoise Van Bambeke

Abstract Macrolides and ketolides are characterized by a very wide tissular distribution, which is related to their capacity to accumulate in the acidic compartments of the cells. This property is considered an advantage, because it concentrates the drug at the site of infection. Yet, the low serum levels consecutive to this tissular distribution may favor the selection of resistance. Macrolides are essentially bacteriostatic and ketolides are slowly bactericidal. The pharmacodynamic indice that best predicts efficacy is the free 24 h-AUC/MIC ratio for both subclasses. Despite their high concentration inside the cells, macrolides and ketolides remain bacteriostatic against intracellular bacteria, with a potency similar to that observed extracellularly. New formulations have been developed to optimize patient's adherence (extended release tablets) or to further increase antibiotic concentration at the site of infection (powders for inhalation).

Keywords Macrolides • Kétolides • AUC/MIC • Tissue distribution

Pharmacokinetic Development of Macrolides and Ketolides and Impact of Chemical Structure on Pharmacokinetic and Pharmacodynamic Properties

Erythromycin, a natural product isolated from *Streptomyces erythreus* (McGuire et al. 1952), was introduced in the clinic in the mid 1950s and remained for long the only large-scale macrolide used. A major limitation of this drug, however, comes

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from its instability in acidic medium, which results in poor and highly variable bio-availability. This instability is due to the simultaneous presence of a keto function (in position 9) and of an hydroxy function (in position 6), which react in acidic medium to generate a spiroketal which is inactive (Fig. 11.1) (Kirst and Sides 1989). A series of macrolides were therefore developed, which showed an improved stability because they are unable to form a spiroketal (Fig. 11.1). These include 14-membered macrolides like erythromyclamine (Massey et al. 1970, 1974), clarithromycin (Fernandes et al. 1986; Morimoto et al. 1984), roxithromycin (Chantot et al. 1986), and the 15-membered azalide azithromycin (Bright et al. 1988; Djokic et al. 1987). 16-membered macrolides [spiramycin (Kellow et al. 1955), josamycin (Nitta et al. 1967), midecamycin (Kanazawa and Kuramata 1976), miocamycin (Kawaharajo et al. 1981; Omoto et al. 1976), and rokitamycin (Sakakibara et al. 1981)] are intrinsically stable because they do not have a keto function in their macrocycle. In ketolides (Bryskier 2000; Van Bambeke et al. 2008), acid stability is obtained by the lack of cladinose, combined with the substitution of the 6-O position as in telithromycin [HMR-3647 (Denis et al. 1999)], cethromycin [ABT-773 (Or et al. 2000)], and solithromycin [CEM-101 (Hwang et al. 2008)], or of the 9-keto function (as in modithromycin [EDP-420 (Wang et al. 2004)]). Beside this pharmacokinetic advantage, the chemical modifications brought to ketolides also improve their antimicrobial activity and favorably modify their pharmacodynamic profile, making them more bactericidal than macrolides at high concentration (Drago et al. 2005; Zhanel et al. 2002). Thus, the heteroalkyl side chain present in all ketolides improves the activity against both macrolide-susceptible and resistant bacteria by allowing for an additional binding to the domain II of the ribosomal subunit, which allows them to keep activity on methylated ribosomes. Moreover, because they lack the cladinose sugar, ketolides do not induce methylase expression and are not recognized by Mef efflux pumps in *S. pneumoniae* (Douthwaite 2001; Douthwaite and Champney 2001; Van Bambeke et al. 2008).

Macrolides and ketolides also share a weak basic character because they all possess an aminated function on their desosamine moiety that is protonable in acid media. This basic character is responsible for their high level of accumulation inside eukaryotic cells. As proposed for cationic amphiphilic drugs (de Duve et al. 1974), macrolides and ketolides can indeed freely diffuse through the membranes in their non-protonated form and are then trapped in the acidic compartments of the cells (lysosomes) in their less diffusible protonated form (Carlier et al. 1987, 1994). Some molecules have an additional aminated function (erythromyclamine, azithromycin). This may contribute to explain the higher cellular accumulation of azithromycin (Carlier et al. 1994).

Pharmacokinetics

General Pharmacokinetic Properties

The main pharmacokinetic properties of macrolides and ketolides are summarized in Table 11.1.

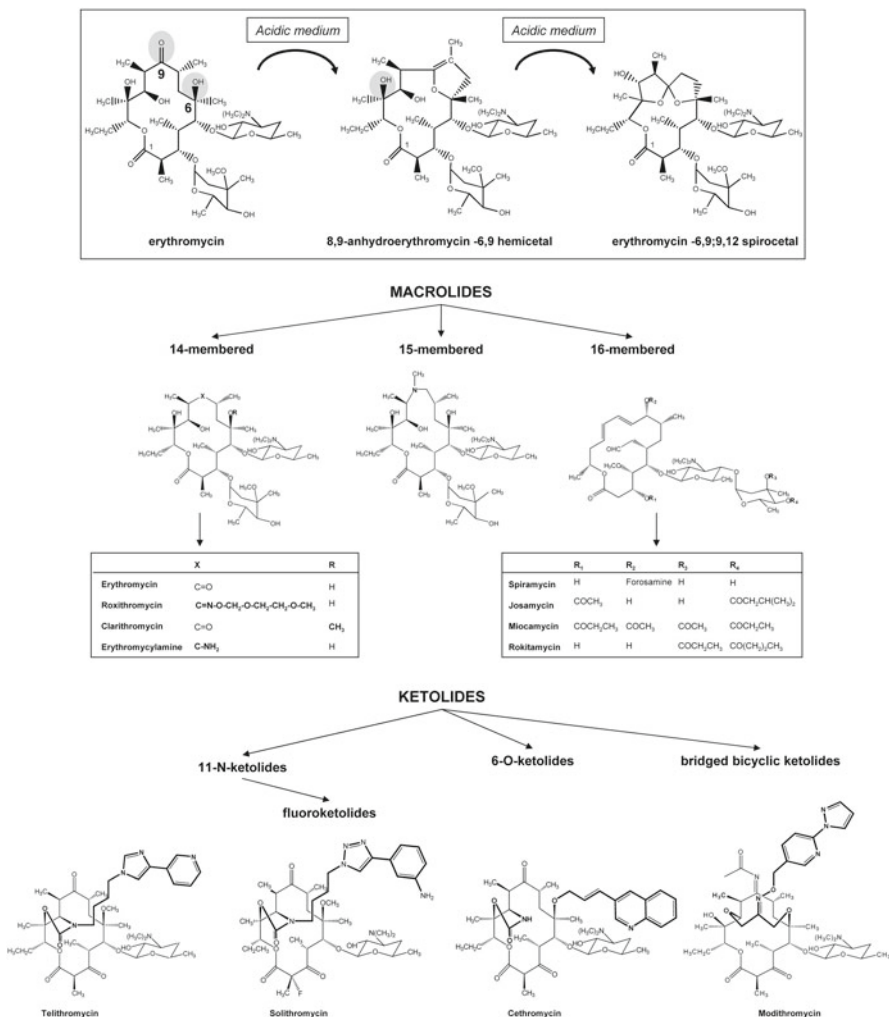


Fig. 11.1 Chemical instability of erythromycin and chemical structure of macrolides and ketolides. Mechanism responsible for the inactivation of erythromycin in acidic medium. The ketone in position 9 reacts with the hydroxyl in position 6 to generate a hemiacetal, which reacts again with the hydroxyl in 12 to produce a ketal. Both the hemiacetal and the ketal are microbologically inactive [Adapted from Kirst and Sides (1989)]. Neomacrolides were made acidostable by either removing the 9-keto function and replacing it with another function (roxithromycin, erythromyclamine, azithromycin) or by substituting the 6-hydroxyl group (clarithromycin). 16-membered derivatives are intrinsically stable because of the absence of a ketone function in the cycle. Likewise, acid stability in ketolides is obtained by removing of cladinose combined with the substitution of the 6-O position (as in telithromycin, cethromycin or solithromycin) or of the 9-keto function (as in modithromycin)

Table 11.1 Main pharmacokinetic properties of macrolides and ketolides

Drug	Erythromycin	Clarithromycin	Roxithromycin	Azithromycin	Telithromycin (HMR-3647)	Cethromycin (ABT-773)	Modithromycin (EDP-420)	Solithromycin (CEM-101)
References	Brogden and Peters (1994)	Fraschini et al. (1993), Peters and Clissold (1992)	Puri and Lassman (1987)	Foulds et al. (1990)	Kuehnel et al. (2005), Lippert et al. (2005), Namour et al. (2001), Shi et al. (2005), Traummüller et al. (2009)	Conte et al. (2004), Lawrence (2001), Pletz et al. (2003)	Jiang et al. (2009)	Still et al. (2011)
Dose for PK studies	500 mg bid po	500 mg po	150 mg bid po	500 mg po	800 mg po	150 mg po	400 mg (1 day followed by 200 mg)	800 mg po (1 day followed by 400 mg)
C_{max} (mg L ⁻¹)	3	3.4	6.8	0.4	1.9	0.32	0.54	1.3
T_{max} (h)	1.9–4.4	2–3	2	2.5	3		3.25	3.5
$T_{1/2}$ (h)	2	5.7	8–13	72	7.16	5.7	15.8	6.65
Vd (L kg ⁻¹)	0.64	3–4			2.9			
Bioavailability (%)	25–60	55	72–85	37	57	60		
Prot. binding (%)	65–90	42–50	73–96	12–40	60–70	85–95		85
Tissue/serum	0.5		1–2	50–1,150	1–5			
AUC (mg h L ⁻¹)	4.4–14	46	70	2–3.4	0.3–0.6			
Conventional dosage in adults	500 mg 4x/day	250–1,000 mg 2x/day	150 mg 2x/day	500 mg 1x/day or 500 mg on day 1 and 250 mg on days 2–5	800 mg 1x/day	300 mg 1x/day ^a	14	800 mg po on day 1 and 400 mg on days 2–5 ^a
Conventional dosage in children	12.5 mg/kg 4x/day	7.5 mg/kg 2x/day	3 mg/kg 2x/day	10 mg kg ⁻¹ on day 1 and 5 mg kg ⁻¹ on days 2–5				

^aBased on ongoing clinical trials

Absorption

Due to their amphiphilic character, macrolide and ketolide antibiotics are capable of diffusing through membranes, and are therefore in general well absorbed by oral route, with the maximum concentration reached within 2–3 h. The effect of food intake on absorption depends on the formulation, with capsules and powdered suspensions of azithromycin and erythromycin (base or stearate) being best absorbed when taken 1 h before or 2 h after meals (Zhanel et al. 2001). In most cases, digestive tolerance is improved when the drug is taken with food.

Distribution

The most striking pharmacokinetic property of macrolides and ketolides is their large volume of distribution (Bahal and Nahata 1992; Zeitlinger et al. 2009), which is related to their ability to accumulate inside eucaryotic cells.

In humans, macrolides and ketolides distribute largely in most tissues, where they reach concentrations that are well above serum concentrations, in keeping with their capacity to accumulate in cells. However, their penetration in the CNS is limited (Kearney and Aweeka 1999), and only subtherapeutic levels can be reached in this compartment. Penetration in epithelial lining fluid and in alveolar macrophages is best documented (Table 11.2). Additional data on penetration in other tissues are nevertheless available for azithromycin and telithromycin. For azithromycin, sustained and high concentrations are also found in the lung (Di Paolo et al. 2002), tonsils (Foulds et al. 1991), and prostate (Foulds et al. 1990) as well as in inflamed blister fluid (Freeman et al. 1994). Telithromycin achieves high and prolonged concentrations in the lung (Kadota et al. 2002; Khair et al. 2001), nasal mucosa and ethmoid bone (Kuehnel et al. 2005), tonsils (Gehanno et al. 2003), female genital tract (Mikamo et al. 2003), and inflamed blister fluid (Namour et al. 2002). Its free concentration in soft tissues (subcutis and muscle) is close to the free serum concentration (Gattringer et al. 2004; Traunmuller et al. 2009).

The consequence of this large distribution is that serum levels are relatively low (see Table 11.1), so that pharmacodynamic indices may be difficult to reach in the central compartment (see this chapter's section on pharmacodynamics). However, the fact that their tissular and cellular concentrations are high may be an advantage for the treatment of infections localized in these compartments (Schentag and Ballow 1991; Zhanel et al. 2001). The slow release of macrolides out of the cells is indeed suggested to allow for the progressive release of antibiotic at the site of infection (Gladue et al. 1989; Hand and Hand 2001; McDonald and Pruul 1991), with white blood cells playing the role of shuttle for the drug (Amsden et al. 1999). On the other hand, their prolonged retention inside the cells is thought to be a major determinant for their activity against intracellular pathogens (Gladue et al. 1989; McDonald and Pruul 1991; Pascual et al. 2001). This concept, however, will need to be revisited in the light of pharmacodynamics (see section on intracellular pharmacodynamics).

Table 11.2 Distribution of macrolides and ketolides in the respiratory tract

Antibiotic (dose)	AUC (mg h L ⁻¹)			Ratio to serum	Reference
	Alveolar macrophages	Ratio to serum	ELF ^a		
Clarithromycin (200 mg)	4,840	190	390	3.5–15	Kikuchi et al. (2008) and calculated based on the data of Rodvold et al. (1997)
Clarithromycin extended release (1,000 mg)	5,730	205	179	6.4	Gotfried et al. (2003)
Azithromycin (500 mg)	1,674	540	7.7	2.5	Lucchi et al. (2008)
Azithromycin extended release (2,000 mg)	7,028	703	17	1.7	Lucchi et al. (2008)
Telithromycin (800 mg)	5,060	425	184	15	Calculated based on the data of Muller-Serieys et al. (2001)
Cethromycin (300 mg)	636	180	24	6.5	Conte et al. (2004)
Solithromycin (400 mg)	1,500	180	80	10	Rodvold et al. (2012)
Modithromycin (400 mg)	2,560	245	212	21	Furuie et al. (2010)

^aEpithelial lining fluid

Elimination

Macrolides and ketolides are metabolized through the cytochrome P450 (CYP) 3A subfamily, and are also moderate to potent inhibitors of the CYP3A4 pathway, causing numerous drug–drug interactions (Pai et al. 2006; Shakeri-Nejad and Stahlmann 2006). They are thereafter eliminated via the bile with the exception of clarithromycin, which shows significant elimination in the urine (Fraschini et al. 1993). Erythromycin shows the shorter and azithromycin the longer half-life, which is correlated with their differential cell retention. These differences have important consequences in terms of number of daily administrations (Table 11.1) and treatment duration in order to optimize pharmacodynamic indices (see section on intracellular pharmacodynamics).

Cellular Pharmacokinetics

The accumulation of macrolides and ketolides has been mainly studied in phagocytic cells [macrophages or polymorphonuclear neutrophils (PMN)]. Variable cellular concentrations (see Table 11.3) have been reported, which can be easily explained by

Table 11.3 Cellular accumulation (cellular to extracellular concentration ratio) ^a of macrolides and ketolides as reported in in vitro studies

Antibiotic	Cell type			References
	Macrophages	PMN	Epithelial cells/ fibroblasts	
Erythromycin	4–38	8	6–12	Bosnar et al. (2005), Carlier et al. (1987), Montenez et al. (1999), Villa et al. (1988)
Clarithromycin	16			Mor et al. (1994)
Roxithromycin	25–60	14	8–23	Carlier et al. (1987), Montenez et al. (1999), Villa et al. (1988)
Azithromycin	40–160	20–517	10–85	Blais et al. (1994), Bosnar et al. (2005), Carlier et al. (1994), Hand and Hand (2001), Lemaire et al. (2009), Mandell and Coleman (2001), Montenez et al. (1999), Pascual et al. (1997)
Telithromycin	5–71	31–300	8	Bosnar et al. (2005), Lemaire et al. (2009), Mandell and Coleman (2001), Pascual et al. (2001), Vazifeh et al. (1998)
Cethromycin	12	207–500	30	Bosnar et al. (2005), Garcia et al. (2003), Labro et al. (2004)
Solithromycin	370			Lemaire et al. (2009)

^aExtreme values when multiple studies have been published

the differences in models and experimental conditions used (concentration range and incubation time). Generally speaking, however, azithromycin and ketolides accumulate to the highest levels, probably related to the dicationic character of azithromycin on the one side and to the greater lipophilicity of ketolides on the other side. These drugs distribute mainly in lysosomes, with a smaller proportion found in the cytosol (Carlier et al. 1987, 1994; Labro et al. 2004; Togami et al. 2010b; Villa et al. 1988). Influx transporters have been suggested to play a role in the uptake of ketolides in white blood cells (Labro et al. 2004; Togami et al. 2010b; Vazifeh et al. 1998), but the kinetics of their accumulation and their subcellular distribution are fully coherent with a passive mechanism of diffusion–segregation. Efflux from the cells is usually slow, but it can be facilitated by the activity of the multidrug transporter P-glycoprotein (Munic et al. 2010; Pachot et al. 2003; Seral et al. 2003b).

Pharmacodynamics

Antibiotics are categorized as either concentration- or time-dependent drugs. Macrolides were for long considered as time-dependent antibiotics, with an efficacy related to the time interval during which their concentration at the infected site remains above the MIC of the offending organism (Carbon 1998; Craig 1998). This was suggested based on the fact that their action on bacteria is essentially bacteriostatic, and that their activity can only be maintained as long as the antibiotic remains bound to the ribosome (this is similar to what is observed with beta-lactams, but is in sharp contrast with aminoglycosides which also impair protein synthesis but also cause translation mistakes [and, therefore, lethal events] in direct correlation to their concentration). Yet, macrolides show post-antibiotic effects (time necessary to observe bacterial regrowth upon drug withdrawal) spanning between one to several hours (Dornbusch et al. 1999; Odenholt et al. 2001), in relation to their particular pharmacokinetic profile, suggesting that time of exposure may not be the only driver for efficacy.

Studies in murine pneumonia models showed indeed that not only time during which clarithromycin concentration remains above the MIC but also the ratio of the area under the concentration–time curve from 0 to 24 h (AUC_{0-24h}) to the MIC and the C_{max}/MIC were significantly correlated to antibacterial efficacy, median survival time, and total percent survival (Tessier et al. 2002). Further animal studies (Ambrose et al. 2007; Craig et al. 2002; Tessier et al. 2005) confirmed that the free AUC to MIC ratio is the major PK/PD determinant for the activity of both macrolides and ketolides.

In Vitro Pharmacodynamic Studies

In Vitro Pharmacodynamic Models

All macrolides are essentially bacteriostatic compounds, causing no or minimal decrease in colony forming units (CFU) (Drago et al. 2005; Furneri and Nicoletti 1991). Ketolides prove slightly more efficient against gram-positive organisms, causing a 1–4 log decrease in CFU of *S. aureus*, *S. pneumoniae*, or *S. pyogenes* over 24 h (Barcia-Macay et al. 2006; Drago et al. 2005; Kays et al. 2007; Woosley et al. 2010). Their killing activity develops over time but is also concentration dependent; it is influenced by the bacterial inoculum (Boswell et al. 1998). Both macrolides and ketolides display post-antibiotic effects that vary between 1 and 8 h (Boswell et al. 1998; Odenholt-Tornqvist et al. 1995); which is suggested to allow long dosing interval despite low serum concentrations. Yet, these low concentrations still leave open the question of the risk of facilitating the selection of resistant organisms.

In vitro pharmacodynamic models have evaluated the efficacy of macrolides and ketolides in conditions that mimic exposure in human serum or tissues after

treatment with conventional doses. For clarithromycin, this type of study suggested that a bactericidal effect against *S. pneumoniae* could be achieved as soon as time above the MIC was $\geq 90\%$ or the area under the curve to MIC ≥ 61 h; a static effect, or even a regrowth, was observed when these values fell to 8% and 17.3 h. These pharmacodynamic indices are easily reached in epithelial lining fluid than in serum, which may explain the microbiological success observed in the treatment of pneumonia for isolates with MIC as high as 8 mg L⁻¹ (Noreddin et al. 2002). Roxithromycin was less effective than azithromycin when simulating their respective pharmacokinetics in tonsils. Regrowth was observed after 6 h against *S. pneumoniae* and 26 h against *S. pyogenes* with roxithromycin, while viable counts reached the limit of detection in 8–10 h with azithromycin, with no regrowth within 48 h (Firsov et al. 2002). Likewise, simulated free azithromycin concentrations in serum, epithelial lining fluid, and middle ear fluid allow to maintain the concentration above the MIC during 100% of the time, and an area under the curve to MIC ratio ≥ 36.7 h against macrolide-susceptible *S. pneumoniae*, resulting in a bactericidal effect (Zhanel et al. 2003). Yet, insufficient coverage was obtained against resistant strains (Zhanel et al. 2003), as well as against gram-negative bacteria like *H. influenzae* or *M. catharralis* (Treyaprasert et al. 2007). For telithromycin, a bactericidal effect was observed when simulated concentrations in serum and epithelial lining allowed to reach a $C_{\max}/\text{MIC} \geq 3.5$ and an area under the curve to MIC ≥ 25 h, but a bacteriostatic effect was observed when these exposures were twice lower. This means that telithromycin at its conventional dosage should be able to eradicate streptococci with an MIC of 0.25 mg L⁻¹ in serum and 1 mg L⁻¹ in epithelial lining fluid (Zhanel et al. 2005). This type of approach also led to the conclusion that at human-simulated exposure, telithromycin can achieve higher AUC/MIC ratios than clarithromycin against *S. pneumoniae*, and therefore higher chances of microbiological eradication, while the contrary holds true for *S. aureus* (Alferova et al. 2005). Fewer data are available for the other ketolides. Cethromycin was shown to be bactericidal, even against macrolide-resistant strains (Neuhauser et al. 2003). Modithromycin activity is AUC/MIC dependent, as the other ketolides, with simulated values of approximately 10 and 16–20 h required to reach a maximal effect against *H. influenzae* and *S. pneumoniae*, respectively (Homma et al. 2010). The latter value is thus of the same order of magnitude as what has been reported for telithromycin.

Intracellular Pharmacodynamics

Because of their high level of accumulation inside eucaryotic cells, macrolides are claimed to be active against intracellular pathogens. They are, indeed, active in vitro against numerous bacteria causing intracellular infections, like *Legionella*, *Chlamydia* (Blackman et al. 1977; Horwitz and Silverstein 1983), or *Mycobacteria* (Wildfeuer and Haberreiter 1997). However, in vitro models comparing them with other antibiotic classes suggest that their intracellular activity is rather limited, because of (a) their bacteriostatic character and (b) the defeating effect on

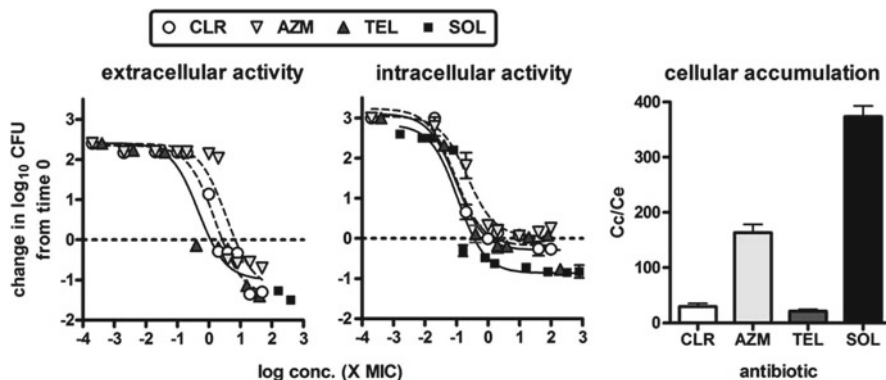
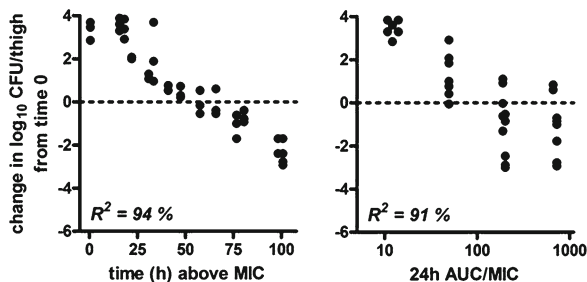


Fig. 11.2 Comparison of the extracellular and intracellular activity of macrolides and ketolides against *S. aureus* ATCC25923 and of their cellular accumulation in a model of THP-1 human monocytic cells. Activity was evaluated after 24 h of incubation in broth (*left panel*) or in infected cells (*middle panel*) with each antibiotic, using a wide range of extracellular concentrations spanning from 0.0001 \times and 1,000 \times its MIC (the *dotted line* corresponds to a bacteriostatic effect). Cellular accumulation was measured after 24 h of incubation of non-infected cells with 10 mg L⁻¹ of each drug (CLR clarithromycin, AZM azithromycin, TEL telithromycin, SOL solithromycin). One can see that despite high levels of cellular accumulation, macrolides and ketolides are less effective against intracellular than against extracellular *S. aureus*, with only solithromycin being able to reach a -1 log intracellular effect. Likewise, potencies (evaluated by the static concentrations, i.e. the concentrations for which there is no change from the initial inoculum) are of the same order of magnitude against extracellular and intracellular bacteria, with no clear correlation with the respective level of accumulation of each drug. Adapted from Lemaire et al. (2009)

their intrinsic activity of the acidic pH prevailing in lysosomes (see Fig. 11.2 for an illustration). In-depth studies following the influence of time or of concentration on intracellular activity show indeed that azithromycin was only able to prevent the intracellular growth of bacteria sojourning in the cytosol like *L. monocytogenes* or in vacuoles like *S. aureus* and to cause a minor (<1 log) reduction in the intracellular counts of *L. pneumophila* (Barcia-Macay et al. 2006; Carryn et al. 2002; Lemaire et al. 2009). The importance of cellular concentration for activity is further illustrated by the fact that inhibitors P-glycoprotein allow to reach this maximal effect upon exposure to lower extracellular concentrations, by increasing the antibiotic concentration in the infected compartment (Seral et al. 2003a, b). A ketolide like solithromycin systematically showed an increased maximal efficacy (1–1.5 log decrease), but this was not the case for telithromycin, at least against *S. aureus* (Lemaire et al. 2009). It therefore appears that other parameters than accumulation and distribution need to be taken into account in the intracellular activity of antibiotics, among which the expression of activity in the intracellular environment, the bacterial responsiveness, and the cooperation with cell defense mechanisms probably play a central role (Carryn et al. 2003; Van Bambeke et al. 2006).

clarithromycin



telithromycin

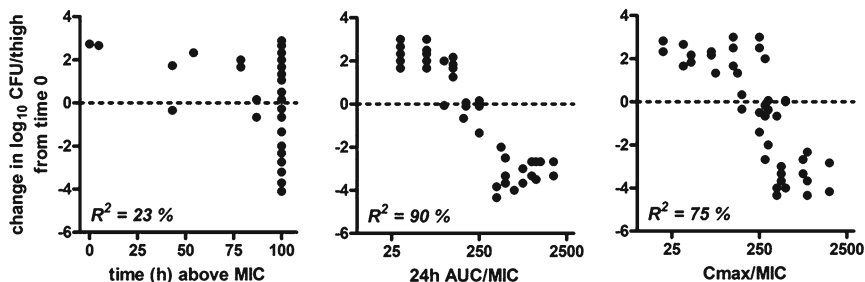


Fig. 11.3 Correlation between efficacy of clarithromycin (*upper panel*) or telithromycin (*lower panel*) against *S. pneumoniae* ATCC10813 and PK/PD parameters in the neutropenic mouse model. The *graphs* show that the efficacy of clarithromycin correlates with AUC/MIC and time above MIC, while that of telithromycin correlates with AUC/MIC and to a lower extent C_{\max}/MIC . Adapted from Craig et al. (2002) and Vesga et al. (1997)

Animal Models

Early studies suggested that macrolides were time-dependent antibiotics (Carbon 1998; Craig 1998). This concept has been revised over the last 10 years, so that it is now accepted that the parameter determining efficacy *in vivo* is AUC/MIC for both macrolides and ketolides (See Fig. 11.3).

Tessier and coworkers were the first to suggest an interdependency between time above the MIC, AUC/MIC, and C_{\max}/MIC ratio when studying the activity of clarithromycin in a model of murine pneumonia (Tessier et al. 2002) and came thus to the conclusion that AUC/MIC ratio is the best predictor of efficacy. Almost at the same time, Craig and coworkers refined this concept by correlating efficacy to the free AUC/MIC ratio, with a value of 20–35 h being needed to reach a static effect for both macrolides and ketolides in a model of pneumonia in neutropenic mice (Craig et al. 2002). Under these conditions, static effects can still be observed with strains showing low level of resistance (efflux-mediated resistance mainly) (Hoffman et al. 2003; Noreddin et al. 2002). Tissular penetration was also

recognized as a major determinant in efficacy, since drugs with longer tissular half-life appeared more effective in a model of pneumonia in leucopenic mice (Veber et al. 1993). Infiltration of inflamed tissues by phagocytes could further help increase local concentration of macrolides (Girard et al. 1990; Schentag and Ballow 1991), but the acidic pH of most abscesses is deleterious to their activity.

Tessier and coworkers demonstrated later that free AUC/MIC ratio was predictive of telithromycin efficacy in the same pneumonia model, with stasis observed for values ranging between 20 and 100 h and maximal effect for values >200 h. In similar experiments, the free AUC/MIC ratio was confirmed to be the main determinant of efficacy for cethromycin, with static effect reached at a value of 50 h (Kim et al. 2002). For solithromycin, stasis was obtained with an AUC/MIC ratio of about 1.4 h for the free fraction in the serum or the total drug in the ELF (Andes et al. 2010).

In vivo pharmacodynamic studies of macrolide activity against intracellular bacteria confirm their poor efficacy, with azithromycin causing a 0.2 log drop in intracellular counts in a model of *S. aureus* peritonitis (Sandberg et al. 2009). This goes thus against the idea that intracellular breakpoints could be higher because of the high accumulation of these drugs (Amsden 2001).

Human Pharmacodynamics

Pharmacodynamics of macrolides and ketolides have also been examined in humans, with the aim of determining target attainments rates and for rationalizing dosages of currently used molecules or establishing those of molecules in development.

For registered drugs, Noreddin and coworkers showed that, upon treatment with conventional dosages, the probability of attainment of a free AUC/MIC₉₀ target of 30 h in serum or ELF was systematically higher for telithromycin (99 % in serum; 100 % in ELF) than for clarithromycin (91.3 % in serum, 99.9 % in ELF) and even more than for azithromycin (81.3 % in serum, 82.3 % in ELF) against susceptible pneumococci (Noreddin et al. 2009). For telithromycin, Lodise and coworkers proposed that a fAUC/MIC ratio of 3.375 h in serum and of 27 h in ELF can predict microbiological eradication (Lodise et al. 2005). They attribute these low values to the high local concentration of the drug at the site of infection and/or its delivery from PMN migrating to the site of infection. In pharmacodynamic studies examining other ketolides vs *S. pneumoniae*, Conte and coworkers reported that treatment with 150 or 300 mg cethromycin allows to reach an AUC/MIC₉₀ of approximately 110 and 340 h, respectively (Conte et al. 2004), which is well above the proposed target of 50 (Kim et al. 2002). Furuie and coworkers reported an AUC/MIC₉₀ of 84 h in patients having received 400 mg modithromycin (Furuie et al. 2010), but no target value has been proposed for this drug so far. With respect to solithromycin, recent data suggest that at dose of 800 mg at day one followed by a daily dose of 400 mg allows to reach the target of ELF AUC/MIC > 1.3 h for stasis (Andes et al. 2010) with a probability of 99.9 % for MICs as high as 1 mg L⁻¹ (Okusanya et al. 2010).

Table 11.4 PK/PD target for macrolides and ketolides and corresponding breakpoints

Antibiotic	PK/PD target	fAUC (h)	PK/PD bkpt (mg L ⁻¹)	CLSI bkpt (S≤; mg L ⁻¹)	EUCAST bkpt (S≤; mg L ⁻¹)	Reference for PK/PD target
Clarithromycin	fAUC/MIC > 20–30 h	~23	~0.8	0.25	0.25	Tessier et al. (2002)
Roxithromycin	fAUC/MIC > 20–30 h	~7	~0.25		0.5	
Azithromycin	fAUC/MIC > 20–30 h	~2	~0.07	0.5	0.25	Tessier et al. (2002)
Telithromycin	fAUC/MIC > 3.375 h	~2.5	~0.75	1	0.25	Lodise et al. (2005)
Cethromycin	AUC/MIC > 50 h corresponding to a fAUC/MIC of ~5 h	~1.6	~0.03	NA	NA	Kim et al. (2002)
Solithromycin	fAUC/MIC > 1 h	~2	2	NA	NA	Andes et al. (2010)

Table 11.4 shows the proposed PK/PD targets for these compounds and compares the PK/PD breakpoints that can be calculated on this basis with the susceptibility breakpoints from CLSI and EUCAST. One can see that the current susceptibility breakpoints are of the same order of magnitude as the PK/PD breakpoints, suggesting they correctly take into account pharmacodynamic criteria.

New Formulations

Extended Release

In spite of the already long half-life of macrolides, extended release formulations have been developed by pharmaceutical companies in order to obtain appropriate AUCs while at the same time reducing the number of daily administrations. Figure 11.4 and Table 11.2 compare the pharmacokinetic properties of these formulations with those of the corresponding immediate release formulation. The extended release formulation of clarithromycin allows giving the daily dose in a single administration, with almost no change in pharmacokinetic parameters as far as AUC is concerned (Gotfried et al. 2003; Guay et al. 2001). The serum concentration remains longer above the susceptibility breakpoint and sustained levels are obtained in epithelial lining fluid and macrophages.

An extended release form of azithromycin has also been registered. Because of the extended half-life of this drug, this formulation allows for a single dose treatment.

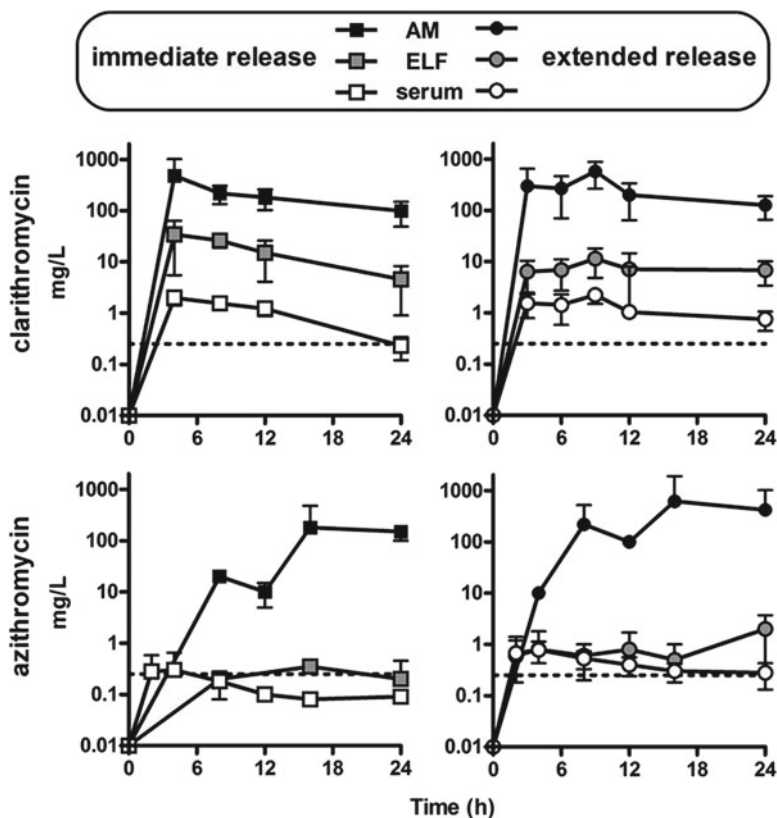


Fig. 11.4 Comparative pharmacokinetics of clarithromycin and azithromycin with immediate release and extended release formulations in serum, epithelial lining fluid (ELF), and alveolar macrophages (AM). For clarithromycin (*upper panel*), volunteers received nine doses of 500 mg immediate release form every 12 h or five doses of 1,000 mg extended release form; pharmacokinetics was evaluated after the last dose [constructed based on data from Gotfried et al. (2003), Rodvold et al. (1997)]. For azithromycin (*lower panel*), volunteers received a single dose of 500 mg immediate release form or of 2,000 mg extended release form [constructed based on data from Lucchi et al. (2008)]. The *dotted horizontal line* corresponds to the EUCAST susceptibility breakpoint of each drug (0.25 mg L^{-1})

The formulation, which has been developed using the microsphere technology, increases the serum AUC from 3.1 mg h L^{-1} to 10 mg h L^{-1} , which is not negligible in view of the low serum concentrations of this drug (Lucchi et al. 2008). It also maintains the serum concentration above the susceptibility breakpoint for 24 h and increases the exposure to the drug in ELF as well as inside macrophages (Lucchi et al. 2008) or in sinuses (Ehnhage et al. 2008; Fang et al. 2009). Of interest also, the overall exposure ($\text{AUC}_{0-120 \text{ h}}$) is similar or even slightly higher in serum or in white blood cells after administration of a single dose of extended release formulation vs. a 3 days treatment with the 500 mg immediate release form; C_{min} at 120 h is similar

with the two dosage regimens as well (Liu et al. 2007). As for the immediate release formulation, efficacy best correlates with the AUC/MIC ratio, with significantly higher success rates observed when this ratio is >5 (Muto et al. 2011). It should be kept in mind, however, that the dose administered is 2 g instead of 500 mg for the immediate release formulation, but no difference in tolerability between the two formulations has been reported so far (Lucchi et al. 2008). This formulation may thus offer an opportunity of optimizing patient adherence (Swainston and Keam 2007).

Aerosols

Beside their indications in respiratory tract infections, macrolides are also widely used in cystic fibrosis or bronchiolitis where they have shown their potential in improving respiratory function through their immuno-modulatory and anti-inflammatory effects (Shinkai et al. 2008). It is therefore not surprising that aerosol formulations of macrolides are now being developed. Azithromycin dry powder inhalers (Zhang et al. 2010) have been evaluated in rats. The best formulation allows to deliver high concentrations in the respiratory tracts with an AUC in the ELF that is 161-fold higher than that obtained with a same dose administered by IV route and a bioavailability of 43 %. Likewise, telithromycin aerosols are also investigated, but rather for the treatment of pulmonary infections (Togami et al. 2010a), with again higher concentrations in lung epithelial lining fluid and alveolar macrophages and lower concentrations in serum than following the administration of an oral formulation.

Conclusion

The pharmacokinetic profile of macrolides and ketolides is essentially characterized by their wide tissular distribution due to their accumulation in the lysosomal compartment of the cells. This however, does not necessarily translate in high efficacy against intracellular bacteria because of the bacteriostatic (or slowly bactericidal for ketolides) character of their activity and of the deleterious effect of acid pH on their activity. Pharmacodynamic studies have shown that the free AUC/MIC ratio is the best predictor of efficacy. Yet, the high volume of distribution of these drugs also translates in low serum concentrations and therefore low AUC in the central compartment. PK/PD breakpoints take however this limitation into account and clearly define the conditions for rationally using these drugs.

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