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PHARMACOKINETICS OF NEWER MACROLIDES*

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Yeni makrolidlerin farmakokinetiği.

Macrolides have been in clinical use since the 1950-ies; erythromycin has so far to some extent withstood the challenge from subsequent developments of e.g. josamycin, megalomycin, oleandomycin, rokitamycin, and roxithromycin.

Modifications of the erythromycin 14-membered nucleus has rendered derivatives like clarithromycin,dirithromycin, flurithromycin, lankamycin, megalomycin, and oleandomycin. The first 15-membered nucleus has appeared, azithromycin. Because of its additional methylated nitrogen atom at position 9a within the lactone ring, this is referred to as an azalide. C-16 membered ring structures apply to spiramycin and its subsequent modifications, i.e. josamycin, miocamycin, rokitamycin, rosaramycin, turimycin, and tylosin.

Improvements of the biopharmaceutical formulations of erythromycin have eclipsed as a microencapsulated formulation in which micropellets of the acid susceptible erythromycin base are each enteric coated, to protect the drug from degradation in the stomach acid fitting it inside a capsule. The ensuing microencapsulated formulation is absorbed better than the leading acid stable salt, the stearate (16).

One important dimension among some of the newer macrolides is the improved pharmacokinetic properties, which will be reviewed below (the term macrolide will be used to encompass also azalide and streptogramins).

SERUM PHARMACOKINETICS

Peak concentrations and total areas under the serum concentration curves of the various macrolides differ. The serum concentrations of most macrolides increase gradually upon dose increases, but by more than would correspond to a multiple of the dose size. This implies a higher bioavailability the higher the dose. Peak concentrations and the time of their occurrence appear in table 1.

Table 1. Concentrations and time of occurrence of serum peaks of macrolides.

Antibiotic	Dose (mg)	Time to peak (h)	Peak conc. (mg/l)	AUC (mg.h/l)	Ref.
Azithromycin	500	2-3	0.4	6.7	(10)
Clarithromycin	500	2-3	0.4	18.9	(24)
14-OH clarithro.			0.7	6.0	(24)
Dirithromycin	500	4-4.5	0.1-0.5		(29)
Erythromycin base	500	1-5	1.9-3.8	5.8-11.2	(16, 21)
Flurithromycin	500	1-2	1-2	16.0	(24)
Josamycin				12.0	(31)
Roxithromycin	150	1-3	5.4-7.9	53.0-81.0	(22)
	300	1.6	10.8	81.0	(24)
Spiramycin	1000			54.0	(23)

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Much interest has centered on serum levels. Thus, for instance, roxithromycin causes much higher serum peaks than the microencapsulated form of the erythromycin base which results in higher serum concentrations than the erythromycin stearate (16). A dose of 150 mg roxithromycin renders maximum serum concentrations of 5.4 - 7.9 mg/l compared to peaks of 1.9 - 3.8 mg/l after 500 mg of the microencapsulated erythromycin base (18, 21). Lower serum levels compared to dose are achieved by azithromycin; although a direct comparison of the pharmacokinetics of azithromycin and erythromycin within the same volunteer cohort does not exist, they appear to be achieving comparable serum concentrations - at least far as the least absorbable erythromycin formulations is concerned. Clarithromycin produces serum levels that are intermediate between the higher levels of roxithromycin on the one hand and those of azithromycin and erythromycin on the other hand.

But one point is often forgotten in presentations of macrolide pharmacokinetics. That is the frequent occurrence of double serum peaks after one single dose of the drug. This has been clearly described for both erythromycin and azithromycin (3, 15) but should apply to other macrolides, also. For erythromycin, the second peak may even be considerably larger than the primary serum concentration peak (15, 16). For azithromycin, it has been demonstrated that the second serum peak in serum is accompanied by a second and parallel rise in the concentration in peripheral (human) lymph (3).

The explanation is that the macrolide is concentrated in bile which is stored within the gall bladder during fasting; the bile is discharged quantitatively and suddenly upon consumption of food. The healthy volunteers included in our studies have received the oral dose while in their fasting state and have been allowed to eat only after 2-3 hours. This stimulates bile discharge with high concentrations of macrolide leading to subsequent reabsorption from the gut and, consequently, a second serum peak.

This serum concentration pattern has important consequences for pharmacokinetic studies. One consequence of erratic serum concentration courses is that the number of individuals that should be included in studies determining the pharmacokinetics of a macrolide, e.g. in healthy, young individuals, should be considerably higher than has been customary. An appropriate number of volunteers would be at least 25, if statistical predictions are to have any meaningful predictive force.

Protein binding of macrolides involves alpha-1-acid-glycoproteins (see table 2). Less of the drug is non-protein bound at higher concentrations in the case of both erythromycin and roxithromycin.

Food does not influence the absorption of microencapsulated form of erythromycin base (15, 16), dirithromycin (29), or roxithromycin (27), but enhances the absorption of erythromycin stearate. Food reduces the absorption of azithromycin and roxithromycin, but has no consequence for clarithromycin (26, 30).

DERIVED PHARMACOKINETIC CHARACTERISTICS

By derived pharmacokinetic properties are, in particular, meant serum half-life (t 1/2) and serum clearance (Table 3).

Table 2. Serum protein binding of macrolides.

Antibiotic	Concentration (mg/l)	Serum protein binding (%)	Ref.
Azithromycin	0.02-0.05	50	(*)
	0.1	23	(*)
	1.0	7	(*)
Clarithromycin	0.45-4.5	70	(**)
	45	20-40	(**)
Dirithromycin		15-30	(29, ***)
Erythromycin	1.0	74	(7)
	8.5	65	(7)
Roxithromycin	3.3	96	(22)
	8.4	92	(22)
Spiramycin		18	(11)

*Azithromycin Clinical Investigator Brochure, 1990.
** Data on file, Abbott, Chicago.
*** Data on file, Eli Lilly, Indianapolis.

Table 3. Derived pharmacokinetic properties of macrolides.

Antibiotic	Dose (mg)	Serum half-life (h)	AUC/ 1 g	Ref.
Azithromycin	1000	44	7.9	(3)
	500	35-40	6.7	(9,10)
	500	54	9.8	(20)
Clarithromycin	500	4.9	19	(24)
14-OH clarithro.		7.2	6	(24)
Dirithromycin	500	44 (16-65)		(29,*)
Erythromycin base	250	2.0	18	(21)
	500	2.5	22	(21)
	1000	3.0	27	(21)
Flurithromycin	500	8.0	16	(24)
Josamycin		1.5-2.5		(31)
Roxithromycin	150	10.5	54	(22)
	300	11.3	44	(22)
	450	13.8	37	(22)
Spiramycin	1000	3.5-7.0	54	(23)

* Data on file, Eli Lilly, Indianapolis.

Considerable interest is appropriately focused on the bioavailability of the macrolides and this is usually low. The term bioavailability is designed to express the amount of drug absorbed. The accepted approach to determining bioavailability is comparing the total area under the serum concentration vs. time curve (AUC) after one and the same dose given to a group of healthy volunteers given intravenously and orally (assuming that oral absorption is in focus). This approach presumes that rapid introduction of the drug intravenously is, indeed, comparable to what occurs when the serum levels increase more gradually, as after e.g. oral doses. Cellular and tissue uptake of some macrolides is rather rapid and high; if a major portion of a dose disappears almost quantitatively from the serum compartment to the tissue compartment, I suspect then the AUC after an oral dose may appear relatively lower than after an intravenous dose. This would ensue simply because of a more gradual

serum appearance after an oral dose enables more of the drug to be transferred to tissues from very beginning of the dosage interval than is the case for an intravenous bolus. This will, undoubtedly, lead to bioavailability underestimates that are proportionate to the degree of macrolide tissue affinity.

Another problem that reduces the precision level of bioavailability assessments of oral doses of macrolides is their erratically occurring bimodal serum concentration peaks profiles. The double peaks are not consistent; they do not appear after every dose and differ in size even in the same individual. Since a second peak increases the total area under the serum concentration curve and the recognized method of bioavailability determination consists of computing the ratio of the total areas under serum-vs.-time concentration curves of oral and intravenous doses (in the same subject after doses of the same sizes), it follows that the outcome involves uncertainties and constraints. Consequently, the published figures for bioavailabilities, which are usually relatively low for macrolides, appear to be rather imprecise estimates.

Bioavailability figures must be viewed in this context. The published value of 37% (10) for azithromycin may very well be a gross underestimate, although the figure was perfectly generated by the method that is currently accepted as appropriate. The algorithm accepted internationally for the determination of bioavailability is more appropriate for drug that are primarily lodged extracellularly and entail sources of error when a major proportion of the dose is transferred rapidly to cells and tissues, and when an irreproducible and unpredictable double peak occurs in serum as is the case for drugs with a sizable enterohepatic circulation like the macrolides.

A bioavailability figure of 54 % for roxithromycin (21) may reflect the lesser tissue affinity of roxithromycin compared to the very much higher tissue and cell concentrations of azithromycin. The bioavailability of clarithromycin is 55 % and for erythromycin 50-70 %; these figures correlate well with the intermediate serum levels afforded by those drugs. Published values for spiramycin are rather disparate and, consequently, difficult to assess.

Notably though, the bioavailability of many macrolides is dose dependent. Such a pattern has been described for erythromycin (15, 16, 21) and roxithromycin (21, 26) (Table 3). In the case of erythromycin, higher doses are afforded by relatively higher bioavailabilities (AUC/dose unit) (Table 3). Roxithromycin exhibits the opposite pattern, relatively lower serum levels-and bioavailabilities-for higher doses (Table 3). The pattern points to non-linear pharmacokinetics for the macrolides.

The non-linearity is underscored by relatively longer serum half-life values for higher doses of erythromycin and roxithromycin. Why e.g. erythromycin and roxithromycin show completely opposite patterns is difficult to say. We may be dealing with saturated mechanisms of absorption, inhibition of enzymes involved in metabolic transformation, but also of transfer to cells and cellular/tissue accumulation. A concentration dependent serum protein binding may also play a role. The lower the non-protein bound moiety, the greater the impact of changes in the serum protein binding is going to be; for roxithromycin, the binding is above 90 % and the free portion increased by a factor of three as the serum level is hiked from 3.3 to 8.4 mg/l.

Upon multiple dosing, increases in both serum half-life and, consequently, AUC have been described for azithromycin (10, 32) and roxithromycin (26).

PHARMACOKINETICS IN CHILDREN

The pharmacokinetics of roxithromycin in children resembles the properties described in adults (1, 17).

PHARMACOKINETICS IN ELDERLY

Roxithromycin exhibits much longer serum-half life and higher serum concentrations in elderly patients than in young subjects. In the former, the values are 2-3 times longer than in young subjects (22, 26). Whereas steady state serum concentrations of roxithromycin in the elderly are higher than after the first dose, the serum half-life remains the same (22). This pattern has been explained by the rather high serum protein binding of roxithromycin where increased serum levels (in case of the steady state) is accompanied by a several times higher free drug concentrations- and, consequently, result in a higher renal elimination by simple glomerular filtration (21).

MODES OF ELIMINATION

Macrolides are metabolized in the liver to a series of biotransformation products (Table 4). These are eliminated in the bile and thus discharged into the gut. Metabolites also appear in the urine. Renal elimination of the unchanged parent compound accounts for but a minor portion, 5- 10 % of the dose (Table 4).

Table 4. Metabolites of macrolides (26 and data from producers).

AZITHROMYCIN
3′ -N-Demethylazithromycin
9a-N-Demethylazithromycin
3″-o-Demethylazithromycin
Desdadinosylazithromycin
CLARITHROMYCIN
N-Demethylclarithromycin
14- (R)- Hydroxyclarithromycin
14- (S)- Hydroxyclarithromycin
Descladinosylclarithromycin
DIRITHROMYCIN
This is a prodrug of erythromycylamine (the active compound)
ERYTHROMYCIN
Anhyroerythromycin-6, 9, 9, 12-spiroketal
Erythalosamine
Erythromycylamine
FLURITHROMYCIN
N-Dimethylflurithromycin
JOSAMYCIN
N-Demethyljosamycin
Deacyljosamycin
4″-Deisovaleryljosamycin
ROXITHROMYCIN
Descladinosylroxithromycin
N-Monodemethylroxithromycin
N-Di-demethylroxithromycin
Erythromycin-9-oximine

A reduced renal function has a minor impact on the serum half-life of macrolides, like erythromycin (8) and azithromycin (14). Roxithromycin elimination, in contrast, is significantly slower in patients with severely reduced renal function. Thus one study reported a serum half-life in healthy subjects of 10.5 hours and in patients with renal failure of 17.9 hours and respective AUCs of 81 mg.h/l and 211 mg.h/l (25).

Renal clearances of azithromycin, clarithromycin and spiramycin have been described as respectively 150, 180, and 144 ml/min (30); based on these observations that the total renal clearance exceeds the glomerular filtration rate, it has been proposed that active tubular secretion of the relevant metabolites may occur, possibly by the proximal tubular base transport system (30).

If that is the case, then the considerably lower renal clearances of 35 ml/min for erythromycin and 6 ml/min for roxithromycin (30) may at least in part be due to renal tubular reabsorption. For roxithromycin, the very high serum protein binding, indeed, limits glomerular filtration to but a trincle.

Alcoholic liver cirrhosis increases the serum half life of erythromycin (13). Roxithromycin serum half-life is increased neither in subjects with severely reduced renal function or an impaired hepatic capacity (19). Azithromycin elimination half-life is unaffected by hepatic cirrhosis (20). The same has been described for dirithromycin (19).

TISSUE PENETRATION

One of the distinctive properties of the macrolides generally is that they tend to accumulate in granulocytes, macrophages and tissue cells. Levels in tissues and leukocytes including macrophages exceed those in serum or the extracellular concentrations. High concentrations in phagocytizing cells is an advantage because this enhance the ability of the cells to eliminate the infecting organisms.

High cellular levels apply to both the newer and the older macrolides, e.g. erythromycin. The phenomenon gave impetus to successful relaunching of spiramycin. The ability to reach high tissue levels would differ for different compounds, but for lack of broad encompassing comparative studies, it is deemed impossible to describe in detail how the different compounds compare.

Still, it appears that azithromycin is the compound which reaches the highest tissue levels compared to serum concentrations and niveaus outside the cells (lymph in the case of tissues and extracellular levels for in vitro studies of leukocytes and macrophages) (3).

Azithromycin renders low serum concentrations and higher tissue levels than other macrolides. Roxithromycin shows the inverse pattern, lies at the other end of the spectrum, i.e. the highest serum levels of any macrolide but also relatively low tissue and cellular levels. The extremely high serum protein binding will account for some of this constellation.

The tonsillar tissue levels of clarithromycin, erythromycin and roxithromycin are higher than in serum (4, 5, 30), but only by a factor of ca. 10 %. These macrolides thus exhibit only a minor organotropy compared to azithromycin (12, 30).

Comparisons in other tissues are confusing. Although it is generally accepted as an axiom that tissue penetration is a function of the lipid solubility of the drug, correlation with tissue penetration and lipophilicity is at present difficult to make because valid comparisons of the various macrolides is missing. A further reason for reserved judgement is that evaluable studies have mostly presented tissue

homogenate data; e.g. for azithromycin (9, 10, 12, 28), erythromycin and dirithromycin (5), roxithromycin (4). Sampling of extracellular fluid such as peripheral human lymph or skin blister fluid would render more appropriate and conclusive data.

Levels of macrolides are very low to undetectable in cerebrospinal fluid as has been published for roxithromycin (26).

Concentrations in human milk are extremely low for roxithromycin (26) and probably for other macrolides as well. Concentrations in sputum and tear fluid are comparable to serum concentrations (30).

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