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OVERVIEW OF PHARMACOKINETICS OF FLUOROQUINOLONES

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Fluorokinolonların farmakokinetiğine genel bakış.

Abstract

The fluoroquinolones are well absorbed from the gastrointestinal tract, the bioavailabilities are above 75%. The serum half-life (t 1/2) varies from 3-4 hours reported for norfloxacin to 12 hours for fleroxacin. Metabolism varies. Pefloxacin is subject to major biotransformation and one of the products from pefloxacin, in fact, is norfloxacin. Only 5% of ofloxacin is eliminated as metabolites. Accordingly, the main route of elimination is the kidney for ofloxacin for which an marked increase in t 1/2 occurs in reduced renal function. This is different from the situation for some other quinolones like ciprofloxacin, norfloxacin and sparfloxacin for which the t 1/2 increases only moderately in renal failure. For ciprofloxacin it has been shown that transintestinal elimination occurs and this serves as an alternate route used for elimination in renal incapacitation. The quinolones penetrate well to tissues and phagocytic cells.

Introduction

The major breakthrough in antibacterial agents seen during the past decade has been the emergence of fluoroquinolones. Upon the emergence of rosoxacin and norfloxacin to introduce the fluorine atom in position 6 and piperazine ring in position 7 to enhance antibacterial activity, ciprofloxacin with in cyclopropyl structure, to further enhance antimicrobial activity, emerged and has remained the standard reference compound among the fluoroquinolones.

The purpose of this presentation is to review the pharmacokinetics of the fluoroquinolones of clinical significance today.

Absorption

The fluoroquinolones are well absorbed from the gastrointestinal tract with serum peaks occurring after 1-2 hours. Bergan et al.(2) found a bioavailability of 85% for ciprofloxacin when the same doses were given orally and intravenous to the same subjects. Lode et al.(23) by a similar approach found a bioavailability of 96% for ofloxacin. Absorption is virtually complete for lomefloxacin(17) and pefloxacin(13).

Food impact

Because quinolones are given orally and to a large extent used in an outpatient setting, interactions with food is important. No difference in AUC or amount eliminated in urine has been found when given with compared to without food for ciprofloxacin(20), enoxacin(26), norfloxacin(18) or ofloxacin(16), the only consequence was a little lower peak concentrations which appeared somewhat later when given with food.

Pharmacokinetics

Most of the fluoroquinolones show linear pharmacokinetics. This implies a steady rise in the total area under the serum concentration curve (AUC) in direct proportion to the dose given ant a t 1/2 which is virtually the same for low and high doses. This pattern has been demonstrated for ciprofloxacin(2,14,15), lomefloxacin(4), norfloxacin(27), and ofloxacin(23,28).

In contrast to the above, pefloxacin shows dose dependent kinetics(13). The serum half-life rose steadily from 10 h after a 200 mg dose to 14 h after 800 mg. For enoxacin, conflicting results have been published. Chang et al.(6) found increasing t 1/2 and reduced total body clearance upon dose increases (intravenous administration) whereas the opposite pattern of dose-dependence was observed in another study with clearance increases and the t 1/2, accordingly, becomes reduced upon dose increases(32). Fleroxacin shows dose dependent pharmacokinetics with a t 1/2 increasing from 9 h after 100 mg po to 11.8 h after 1.2 g po(29).

The t 1/2 during the latter phase of elimination may be longer for the earlier developed fluoroquinolones than was originally published. Thus, whereas we initially-in accordance with other studies-found that ciprofloxacin had a t 1/2 of 3-4.5h(2), we later found the t 1/2 to be 5.8

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hours(3) because we followed the serum concentrations for a longer period of time after the dose. Thereby we could monitor the phase when ciprofloxacin was released from the tissue depots, a similar pattern would apply to others.

Routes of elimination

Fluoroquinolones are eliminated to different proportions by the renal route and by metabolic transformation (Table 1). The renal elimination occurs by glomerular filtration and by tubular secretion the latter of which is blocked by probenecid(29,30) and thus occurs by the same route as elimination of penicillins. A significant tubular secretion exists at least for ciprofloxacin, enoxacin, fleroxacin and norfloxacin, possibly also for other fluoroquinolones.

Table 1. Pharmacokinetics of major fluoroquinolones(1,28).

Compound	Bio-availability (%)	(C_{max} C/100 mg)	Serum half-life (h) Normal GFR	GFR* <15 ml/min	Bio-transformation (%)	In urine % dose Parent comp.	Meta-bolite
Ciprofloxacin	80-85	0.4	4-6	<10	15-30	60	7
Enoxacin	90	0.6	5	40	50	40-50	NA
Fleroxacin	96	1.5	10-12		30-40	40-70	15
Lomefloxacin		1.3	7-8	45			
Norfloxacin	70-80	0.4	4-5	<10	20-40	30-40	20
Ofloxacin	90-95	1.0	5.5-7.0	40-50	5	75-80	5-10
Pefloxacin	83	0.8	11	11-15	90	10	50-60
Rufloxacin		0.9	36-40			20-25	

* GFR = Glomerular filtration rate

Ciprofloxacin, norfloxacin, and sparfloxacin are eliminated by both renal and to a significant extent by metabolism, pefloxacin predominantly by metabolism, and ofloxacin and lomefloxacin primarily by renal mechanisms.

A new route of elimination has been demonstrated for ciprofloxacin; transintestinal elimination(25). This means that a portion of the dose passes across the intestinal wall; after an intravenous dose, 15% is eliminated thus by direct delivery from blood to the intestinal lumen without going via bile (less than 1% of the dose appears in bile and this is to a major extent removed by absorption from the gut).

A compound like pefloxacin is eliminated mainly by biotransformation-to 5 metabolites one of which is norfloxacin (dehydroxypefloxacin). A saturable, non-renal pathway of elimination has been indicated(13).

Renal impairment

The importance of transintestinal elimination was demonstrated by comparison between normal subjects and patients with renal failure. In the former, 17% appeared in faeces (10% as parent compound and 7% as metabolites) compared to 66% (35% as parent compound and 31% as metabolites) in the faeces in the renal failure patients(25). The figures for urine were 75 % (63% parent compound and 12% metabolites) in normal subjects and 28% (22% parent compound and 6%) in renal failure subjects. Consequently, the data demonstrate that, for ciprofloxacin, the transintestinal route compensates almost completely for the reduced renal capacity. Accordingly, transintestinal elimination serves as a safety valve for the elimination of ciprofloxacin in cases of renal impairment. This explains why ciprofloxacin t 1/2 is raised only a little in total renal failure.

The demonstration of transintestinal elimination in humans has required an intravenous formulation (to avoid interference from unabsorbed drug after oral administration). This mode of elimination has in humans only been demonstrated with certainty for ciprofloxacin, but from the pharmacokinetic behavioral pattern it can be suspected that transintestinal elimination must be

substantial also for norfloxacin and sparfloxacin because these are both subject to trivial increases in t 1/2 in total renal failure and metabolism is too limited to explain why the t 1/2 does not increases more in renal failure.

In opposite position we find ofloxacin of which 90-95% is eliminated in the urine and metabolism contributes but 5-10% of the dose. Ofloxacin, consequently, exhibits a markedly prolonged elimination in reduced renal function. The rise in t 1/2 commences at about 40 ml/min and rises to 40-50 hours in renal failure. No transintestinal elimination is apparently in operation. Fillastre et al.(12) observed a rise in t 1/2 from 7.9±1.8 h to 37.2±23.3 h. This was the consequence of the gradual decrease in renal clearance as a function of gradual reduction in glomerular filtration rate (GFR). A similar pattern has appeared for lomefloxacin(4). Dose adjustment in patients with reduced renal function would seem advisable particularly for enoxacin, lomefloxacin and ofloxacin.

Haemodialysis has little influence on the elimination t 1/2 of most of the fluoroquinolones. Thus a supplementary dose after haemodialysis is not needed for lomefloxacin(4) or pefloxacin(24). On the other hand, extraction of ciprofloxacin has led to at t 1/2 of 3.2 h during haemodialysis as contrasted with 5.8 h between periods of haemodialysis(5).

Liver impairment

Liver failure does not affect pharmacokinetics of pefloxacin according to one study(19), in which was found that no dose adjustment is needed in liver failure, whereas another study reported significantly longer t 1/2 of 35.1 h in 16 subjects with histologically proven liver cirrhosis (normal subjects had t 1/2 = 11 h in the same study)(7). Urinary excretion of unchanged pefloxacin was larger and that of norfloxacin lower in patients with hepatic cirrhosis than in normal subjects. The degree of dose reduction in liver impairment is, consequently, impossible to predict. The reason may be that concomitant reduction of the kidney function varies. If both the liver and the kidney functions are reduced, prolonged t 1/2 must result. Monitoring of serum concentrations is recommended in this patient group.

Norfloxacin disposition has been shown to be uninfluenced by liver failure(11). The same applies to ciprofloxacin(9,10,21). Studies on patients with a combined hepatic and renal impairment would seem to be needed to fully assess the consequences of terminal disease in these key excretory organs.

Tissue penetration (Table 2)

A prerequisite for penetration to tissues is that a moiety is non-protein bound. Protein binding of ofloxacin is low, 25%, and not influenced by concentrations within the therapeutic range(23).

Penetration to CSF in persons with normal meninges is low for ciprofloxacin, but ca. 60% for pefloxacin(8,33).

Table 2. Serum protein binding and transfer to tissues(1,22,31).

Compound	Protein binding (%)	Extravascular penetration (% conc. extravasc. vs. serum conc.) Skin blister
Ciprofloxacin	35	117-120
Enoxacin	50	114-130
Fleroxacin	23	90
Norfloxacin	15	106
Ofloxacin	10	120-125
Pefloxacin	15-25	70

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