

#A019

Aciclovir (nt!)

(MW 225.2; as sodium salt for IV infusion MW 247.2)

Synonyms: Acyclovir, Acycloguanosine.

Usual dosage: Size of dose and dosage interval depend on route of administration, age and disease to be treated.

Pharmacokinetics

GI fate: Following oral administration, absorption is slow, variable and incomplete; bioavailability is about 20% (range 15 – 30%). See also valaciclovir. PPB range 9 – 22% (poorly bound).

Distribution and metabolism: At steady-state, aVD is ~ 0.8 l/kg; distribution to all tissues with highest concentrations in the kidneys (conc. 10 times that in plasma). Only a small amount (15% of a dose) is converted to the inactive 9-carboxymethoxymethylguanine (CMMG), the only significant metabolite in man.

Elimination: Predominantly excreted in the urine via glomerular filtration and tubular secretion; more than 80% of a dose is excreted unchanged, only little (9 – 14%) is found as inactive, oxidized metabolite CMMG; renal clearance is about 75 – 80% of total body clearance and almost 3 times greater than CrCl (250 ml/min). Up to 2% of a dose is excreted in feces. Elimination $t_{1/2}$ is relatively short (2 – 3 hrs). The therapeutic action of aciclovir in infected cells depends on conversion by herpesvirus enzymes via aciclovir monophosphate to activated aciclovir triphosphate.

Nephrotoxicity

Aciclovir is indirectly nephrotoxic; incidence 12 – 79% [707]. Aciclovir is rapidly excreted in the urine (short elimination $t_{1/2}$ of 2 – 3 hrs). Its concentrations in renal tissue can exceed 10 times that in plasma. The concentration of the drug in renal collecting ducts may exceed the drug's solubility leading to crystallization in renal tubules (obstructive crystal nephropathy) causing acute renal failure. At high plasma levels of aciclovir serum creatinine may rise, typically within 24 – 48 hrs after onset of treatment. Major risk factors for tran-

sient renal impairment besides high drug plasma levels (usually following rapid IV bolus) are fluid depletion, decreased urinary flow and pre-existing renal disease. Note: Crystallization occurs exclusively after (rapid) IV administration (renal accumulation of the drug). These features are reversible or preventable with adequate fluid repletion, reduced aciclovir dose and slow infusion rates (at least 1 hr). In rare cases, focal interstitial inflammation without tubular necrosis, consisting of interstitial hemorrhages, congestion of lymphocytes and plasma cells has been observed [1311].

Neurotoxic (neuropsychiatric) symptoms appearing during aciclovir (and valaciclovir) therapy have repeatedly been recognized [294, 412, 830] and are reported in patients with acute or chronic renal failure [31, 345, 643, 733, 741, 827]. These unusual adverse effects should be regarded.

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are recommended!*

In severe renal impairment (CKD Stage 5_{GFR < 15}) the mean elimination $t_{1/2}$ of 20 hrs is 7 times elimination $t_{1/2}$ in normal subjects; aVD was decreased by 20% and total body clearance was only 10%, which represents non-renal clearance in normal subjects. As renal function decreases, a unique situation develops where a greater part of the drug is converted to the metabolite. In ESRD the drug is probably eliminated entirely by hepatic transformation to the metabolite but the elimination of the metabolite in the urine is limited. It would, therefore, be expected to accumulate. However the clinical significance of such accumulation is not known. In all cases of renal impairment, dosage adjustment is necessary. During *parenteral administration*, adjust dosage as follows:

- In CKD Stage 3_{GFR 59–30}, give usual dose every 12 hrs;
- in CKD Stage 4_{GFR 29–15}, give usual dose every 24 hrs;
- in CKD Stage 5_{GFR <15}, give half the usual dose every 24 hrs or usual dose every 48



hrs. Alternative: Keep the dosage interval the same (8 hrs) and reduce the dose per interval; an initial loading dose (usual dose or half of usual dose) may be useful. The advantage of this schedule is that it minimizes potential toxic peaks whilst maintaining similar mean plasma concentrations.

Oral doses (against varicella-zoster infections) may be reduced to the following:

- In CKD Stage 4_{GFR 29–15}, give 800 mg 3 times daily;
- in CKD Stage 5_{GFR <15}, give 800 mg every 12 hrs, and for herpes simplex 200 mg every 12 hrs.

Hemodialysis: Aciclovir is readily removed by HD. Mean plasma $t_{1/2}$ was approximately 6 hrs, dialysis clearance 820 – 113 ml/min (with conventional membranes), and reduction of plasma levels during one HD was about 60%. Dosage in HD patients [31]:

- ▶ Between dialyses, half the usual dose every 24 hrs and replacement of 60 – 100% of the loading dose after each HD. In the event of severe neurotoxicity and nephrotoxicity due to overdose, removal by one or several HD may be indicated [270].

CAPD: The clearance by PD and CAPD is low, CAPD clearances of 3 – 8 ml/min and elimination $t_{1/2}$ of 15 – 17 hrs have been observed [710, 1271, 1352]. Following IV infusion, the peritoneal dialysate recovery was 6 – 11% of a dose depending on the concentration of glucose in the dialysate.

- Dosage in CAPD patients as in patients with serum creatinine > 7 mg/dl (CrCl 15 ml/min): no substitution necessary [1433]. In view of the possible efficient transfer of aciclovir from peritoneum to plasma, peritoneal administration has been proposed [169, 233].
- For prevention of cytomegalovirus disease (prophylactic treatment) aciclovir and valacyclovir have been used successfully [90, 912]. These drugs should however be given with great caution and have to be withdrawn at the first sign of renal toxicity.

#B067

Buprenorphine

(MW 467.7)

Usual dosage: Differs, according to the route of administration

Pharmacokinetics

Gl fate: Readily absorbed; following sublingual administration, absorption is relatively slow, plasma levels peak within 3 – 4 hrs; substantial first-pass metabolism already in the gut wall and later in the liver, therefore bio-availability 16% of the dose after oral and 55% of the dose after sublingual intake; PPB 95 – 98% (very high); very short plasma $t_{1/2}$, a few minutes only.

Metabolism: Partly metabolized via CYP3A4 to form norbuprenorphin (less active than the parent drug) and by conjugation with glucuronic acid (parent drug and metabolites). Buprenorphine is highly lipophilic. In anesthetized patients, lower plasma levels and a lower clearance by ~30% have therefore been reported, implying lower initial volume of distribution [601].

Elimination: Following oral administration, mostly excreted in the feces (~ 70% of an oral dose), mainly unchanged; ~ 15% of the dose can be found in the urine, as metabolites. After parenteral administration, 68% of the dose is found unchanged in the feces and about 27% in the urine as metabolites. Elimination $t_{1/2}$ 3 hrs. Because the drug is mostly excreted in feces, an entero-hepatic circulation is likely.

Dosage in renal insufficiency and dialysis patients:

➔ *No dosage adjustments necessary!*

Since the agent is cleared mainly by hepatic extraction (via bile in the feces) and metabolism, elimination is not dependent on renal function, although metabolites are excreted partly in the urine. In a clinical study [601], buprenorphine kinetics were similar in anesthetized healthy patients and those with renal impairment regarding half-lives, aVD and clearances, but plasma levels of the metabolites were elevated in patients with renal im-



pairment (norbuprenorphin 4 times and the main glucuronide 15 times).

- Usual doses may be given in all degrees of renal insufficiency [601, 1452].

No data available regarding removal by HD and PD, but removal is unlikely because of high PPB and high lipophilicity.

No substitution required during and after dialysis.

#C110

Ciprofloxacin (*nt!*)

(MW 331.3)

Usual dosage: 250 – 750 mg twice daily by mouth or 200 – 400 mg IV 2 – 3 times daily, resulting in peak plasma levels in the range of 3 – 5 mg/l (the peak plasma levels required to achieve the target AUC are 2.5 – 3.5 mg/l). In critically ill patients with severe sepsis 400 mg IV 3 times daily has been used [898].

Pharmacokinetics

GI fate: About 75% of an oral dose is absorbed, mainly from the intestine; plasma levels peak within 30 – 90 min; PPB 20 – 40%; most of the absorbed drug can diffuse into the extravascular space; aVD under steady-state condition 2 – 3 l/kg (very high), concentrations in tissues and body fluids higher than in plasma; because of initial first-pass effect in the liver oral bioavailability is ~65% (range 45 – 84%).

Metabolism: 12 – 20% of the dose is converted to a minimum of 4 metabolites, 3 possess lower activity than the parent drug, one is as active as the parent drug.

Elimination: Mostly excreted in the urine, 56% of an oral dose (~45% unchanged and >10% as metabolites) or 75% of an IV dose (63% unchanged and >10% as metabolites), via glomerular filtration and renal tubular secretion; renal excretion greatly exceeds CrCl. A smaller quantity appears in the feces (39% of an oral dose, or 14% of an IV dose); most of the drug is excreted unchanged, only 12 – 20% as metabolites (see above); elimination $t_{1/2}$ 3 – 5 hrs.

Fecal elimination may originate from three sources. Following oral administration, about half of the amount in feces originates from the non-absorbed drug (not following IV administration). Some drug excretion via bile is to be expected. A third and controversial route of elimination is the transluminal excretion of ciprofloxacin across the bowel mucosa into the bowel contents [1660].

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are recommended!*

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partly cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in renal patients. As a consequence, elevated elimination $t_{1/2}$ of up to 12 hrs have only been observed in patients with CKD stage 3 to $4_{GFR\ 59-15}$. It is suggested that in patients with impaired renal function there may be a variable increase in elimination of the drug via the transluminal route (see above: Elimination). This variability in the route of elimination leads to some uncertainty when choosing an appropriate dose of ciprofloxacin in renal patients, especially for those patients with life-threatening infections [1666].

Recommended dosage guidelines

- In patients with CKD stage 2 to $3_{GFR\ 89-30}$ administer usual doses with caution.
- In patients with CKD stage $4_{GFR\ 29-15}$ give half a usual oral dose twice daily or a usual oral dose (500 mg) every 18 hrs or an IV dose up to 400 mg every 18 – 24 hrs.
- In patients with CKD stage $4_{GFR\ 29-15}$ and life-threatening infections administer a

Note: Phosphate binders bind drugs!

usual initial dose, subsequent doses (twice daily) can be reduced.

In patients with CKD stage 5_{GFR <15} (ESRD) under dialysis, elimination by HD and PD is substantial.

Hemodialysis: Even though the HD clearance is ~40 ml/min, normal elimination $t_{1/2}$ has been reported on day of dialysis. Thus,

- administer usual oral dosage on day of dialysis (2 doses, one dose after dialysis) but reduce oral dosage between dialyses to 250 – 500 mg once daily.

CAPD patients: Ciprofloxacin is active against various strains of aerobic gram-positive microorganisms and against most strains of aerobic gram-negative microorganisms. Because the predominant problem in CAPD patients is peritonitis, caused mostly by gram-negative pathogens, the drug has frequently been used in peritonitis. Due to its high efficacy it became a first-line antibiotic against CAPD peritonitis. It is applied orally, by IV injection or IP (in the dialysate of the bags). However, published data are controversial, especially regarding route of administration and penetration characteristics of the peritoneal membrane. Dosage guidelines are not well defined and therefore in this article results from clinical trials are used to evaluate treatment modalities in CAPD peritonitis.

Oral administration

- ▶ Following a single dose of 750 mg, Shalit et al. [1665] found in CAPD patients with peritonitis a prolonged mean terminal $t_{1/2}$ of 16.8 hrs (range 10.7 – 25.2 hrs), even though the peritoneal fluid contained 64% of the plasma concentration of the drug, indicating that a significant amount of the drug was removed continuously via CAPD (mean peak plasma levels 3.6 mg/l, mean peak effluent peritoneal fluid 1.3 mg/l). In a subsequent study [1695], the authors derived trough peritoneal fluid concentrations only after administration of 750 mg 12-hourly for several days. They suggested that, in the treatment of peritonitis and other infections in CAPD patients, administration of oral ciprofloxacin should be lim-

ited to 500 mg daily, preferably in two equally divided doses.

- ▶ Golper et al. [1689] studied ciprofloxacin behavior in stable CAPD patients (oral dose of 750 mg every 12 hrs for 4 doses. Peak plasma levels ranged from 2.9 – 6.4 mg/l; clearance by CAPD was 2% of the total body (systemic) clearance; simultaneous ratios of the drug in dialysate and plasma was 0.57 within a dwell time of 4 hrs and 0.75 within a dwell time of 8 hrs. Long-dwell exchanges may be necessary to achieve reasonable dialysate concentrations of oral ciprofloxacin.
- ▶ Zacherle [1707] reported the successful use of oral ciprofloxacin for the first-line treatment of CAPD peritonitis. Fifteen infectious episodes improved within the first 48 hrs and a cure rate of 70% was recorded by day 14.
- ▶ Yeung et al. [1704] studied pharmacokinetics of oral ciprofloxacin (750 mg twice within 12 hrs) in CCPD patients with peritonitis. Mean terminal $t_{1/2}$ was 10 hrs, mean peak plasma levels were 2.7 mg/l, and mean peritoneal clearance was ~1.2% of the mean calculated total body clearance. Two doses of 750 mg within 12 hrs seems to be useful for empirical gram-negative coverage of CCPD peritonitis (sensitive *E. coli* or *Klebsiella* species).
- ▶ In a recent study [1702], 95 episodes of peritonitis in 54 patients on CAPD or CCPD were treated with a combination of oral ciprofloxacin and IP cefazolin. The cure rate was almost 90% of positive cultures.
- ▶ In a multicenter study by Goffin et al. [1706], the efficiency of a simultaneous administration of IV vancomycin 15 mg/kg, and oral ciprofloxacin 250 mg twice daily (500 mg twice daily if residual CrCl was above 3 ml/min) was evaluated in PD patients suffering from peritonitis. In general, vancomycin was repeated during 3 weeks and ciprofloxacin during 10 days or weeks. The aim of the study was to determine whether the systemic route of administration of the antibiotics was an alternative to the usual and inconvenient IP drug application. According to the authors, systemic

vancomycin and oral ciprofloxacin administration is a simple and efficient first-line protocol antibiotic therapy for peritonitis, and oral ciprofloxacin provides satisfactory results in gram-negative infections, compared to IP antibiotics.

- ▶ Leblanc [1667] described 3 cases of peritonitis in CAPD patients who were successfully treated with oral ciprofloxacin.

Intraperitoneal administration

- ▶ One group [1697,1698,1699], used IP administration (25 or 50 mg/l in each bag over several days) in CAPD patients with peritonitis; mean plasma concentration 0.3 and 1.1 mg/l, mean concentration in the effluent dialysate 6.1 and 10.0 mg/l, respectively. The 25-mg/l therapy was successful in 79% of the episodes, and the 50-mg/l therapy was successful in 83% of the episodes.
- ▶ In one report [1700], an IP loading dose of ciprofloxacin was given for 24 hrs, simultaneously the drug was given orally and thereafter only orally; mean dialysate concentrations were initially ~6 mg/l which decreased substantially during the course of the treatment.
- ▶ Pharmacokinetics of IP ciprofloxacin were investigated in 6 non-infected CCPD patients [1661]. A loading dose of 25 mg/l in the dialysate of 4 short-dwell exchanges resulted in dialysate levels of 21 – 13 mg/l during these exchanges (dwell time 1.5 hrs). In the subsequent last bag, devoid of the drug, a peak level of ~1.4 mg/l was observed at 30 min. Instillation of 100 mg/l in the last bag yielded peak dialysate levels of 99 mg/l, falling with a $t_{1/2}$ of 3.3 hrs towards levels of 2 mg/l at ~20 hrs. Instillation of 25 mg/l ciprofloxacin in the last bag yielded a peak level in the dialysate of ~22 mg/l, falling with a $t_{1/2}$ of 3.9 hrs towards dialysate levels of <2 mg/l at 15 hrs. The rapid absorption of the drug from the dialysate into the tissues means that ciprofloxacin has to be added to all CCPD bags to ensure bactericidal dialysate levels; on the other hand, such high antibiotic concentrations, even though they are of short duration, at the in-

fectured peritoneal membrane should produce an optimal therapeutic effect.

- ▶ In a multicenter study in the Netherlands [1701], 98 out of 367 CAPD patients developed peritonitis, 44 of whom were treated with IP ciprofloxacin plus rifampicin (each 50 mg/l per bag) and 54 of whom were treated with IP cephradine (250 mg/l per bag). Initial and late clinical successes were 50% and 37% in the cephradine group and in 75% and 64% in the ciprofloxacin/rifampicin group. Bacteriological success in the group treated empirically occurred in 30% of the cephradine group and in 59% in the combination group.
- ▶ One study [1703] compared oral versus IP ciprofloxacin as primary treatment of bacterial peritonitis in CAPD patients (48 episodes in 46 patients); primary care rate was ~42% in the oral group and ~67% in the IP group. The authors favour IP treatment and recommend 50 mg/l per bag instead of 25 mg/l.
- ▶ In a prospective, randomized, controlled trial with 40 CAPD patients, IP ciprofloxacin was shown to be as effective as the currently recommended regimen of IP vancomycin and gentamicin for treatment of peritonitis, and has advantages over the oral route [1705].
- ▶ Pérez-Fontán et al. [1668] analyzed 682 episodes of bacterial peritonitis treated with IP ciprofloxacin monotherapy in 641 PD patients over a period of nearly 20 years (1988 – 2007). Following satisfactory early results, the effectiveness of ciprofloxacin as a monotherapy in PD-related peritonitis has declined markedly in the long-term for not well explained reasons.

Although frequently and often successfully used, various investigators state that oral and IP administration of gyrase inhibitors, such as ciprofloxacin, have not been endorsed as a first line treatment of peritonitis complicating CAPD, partly due to failure or relapse because of resistant gram-positive bacteria. Concerning IP application, there are indeed differences in the rate of diffusion through the peritoneum in both directions, from the vascular

system and from the peritoneal cavity, in the case of peritonitis where the diffusion through the injured peritoneum is higher when compared to the non-infected situation. The fraction of the administered dose of the drug removed by CAPD or CCPD is < 2% of the dose. Although the low peritoneal clearance has always been regarded as a disadvantage, it should be noted that the concentrations within or around the infected peritoneum are the key factors in the treatment of peritonitis.

CRRT in ICU: Using modified CVVHDF (Q_D and Q_F 1 – 2 l/hr), based on in-vitro calculations 300 mg IV was injected twice daily, 60 min after initiation of CRRT [628]. The mean AUC reached a level higher than the target AUC, and infections were successfully controlled. Other dosage regimens: Using CVVHD (Q_D 1 – 2 l/hr, Q_{UF} 1 l/hr) or CVVHDF (Q_D 1 l/hr, Q_{UF} 1 – 2 l/hr) 200 mg IV was given 2 – 3 times daily [839]. In another report 10 patients were treated with either CVVHF or CVVHDF. All patients received IV infusions of 400 mg once daily which was sufficient to maintain effective drug concentrations in plasma [1691].

Nephrotoxicity

Fluoroquinolones are generally well tolerated. Adverse effects most often involve the GI tract, CNS, and skin. Ciprofloxacin and a few other quinolones are potentially nephrotoxic which has to be taken into consideration when the drug is given to patients with impaired renal function. It should be noted that the potential nephrotoxicity of the drug may worsen existing renal function and impair any residual renal function.

Two reviews of case reports of renal toxicity associated with ciprofloxacin indicated that such toxicity, although potentially serious, was rare [1688, 1693]. Indeed, all publications contain case reports only whereas series of patients with renal damage have not been published. In most cases, nephrotoxicity induces immune-mediated interstitial nephritis or rarely acute tubular necrosis, without or with (reversible) acute renal failure [236, 1670, 1677, 1671, 1672, 1673, 1674, 1676, 1678, 1682, 1683, 1693], and hematological abnormali-

ties, including autoimmune hemolytic anemia [1677, 1679]. Nearly all patients developing acute renal failure were over 50 years of age. Other risk factors were high doses of the drug (overdose) [1687], inadequate hydration, as well as the use of other nephrotoxic drugs and the presence of other processes likely to contribute to renal damage such as diabetes.

A very few cases of crystal nephropathy have been reported [1680, 1681, 1684, 1686, 1688]. Although experimental studies indicated that crystalluria may be associated with ciprofloxacin [1684, 1687], the likelihood in humans was believed to be very low because previous data showed that crystalluria depended on a urine pH >6.8. In the meantime, cases of crystalluria in humans have occurred with a urine pH <6.6 and <6.0. In the case of decreasing renal function during quinolone treatment a urinary sediment analysis is mandatory [1685].

In order to evaluate the prevalence and incidence of ciprofloxacin nephrotoxicity, Burke et al. [236] asked 4,253 students to take one oral dose of 500 mg ciprofloxacin and about 3,200 students accepted. Three cases of anaphylactoid reactions occurred, all 3 patients recovered.

Drug binding by phosphate binders

A widely unrecognized and even ignored problem regarding drug treatment in renal patients is that all phosphate binders also bind orally administered drugs (Problem 1). In this context, a second serious problem is that data on absorption exists only for a few drugs (Problem 2). A minor problem is that pharmaceutical companies are not able to or are not asked by the authorities to show absorption rates for drugs using their phosphate binders (Problem 3). A further problem is that drugs cannot display their desired effectivity once partly or completely chemically bound already in the GI tract (Problem 4).

A potential problem with the increasing use of quinolone-type antibiotics is the chelation and inactivation of these compounds by several cations in concomitantly administered medication. Insoluble chelate complexes are formed

between the cations and the drug, resulting in dramatically reduced bioavailability of the agent. One of the best investigated drugs in this respect is ciprofloxacin. About ~50% of an oral dose (range 22 – 76%) [1690] is bound when given together with currently used phosphate binders, such as calcium-, magnesium-, and aluminum-containing salts as well as the cationic polymer sevelamer hydrochloride (most likely also sevelamer carbonate), and lanthanum [673, 1694, 1663, 1690, 1662, 1664, 1689]. This logistic problem was described for ciprofloxacin shortly after its introduction [1689, 1696]. Following oral administration, the peak concentrations of ciprofloxacin in the dialysate achieved in CAPD patients on phosphate binders were 8 – 33% of those observed in subjects not receiving phosphate binders [1689].

The most feasible and safe solution to overcome this complex series of problems is to alter the dosage regimen in the patients. It is becoming common practice to take phosphate binders together with the meals (for actual and continuous phosphate binding) and to ingest other prescribed drugs 2 hrs before or after meals. Phosphate binders should be withheld in renal patients when oral antibiotic therapy is conducted.

#C117

Clarithromycin

(MW 748.0)

Usual dosage: By mouth or IV 250 – 500 mg/12 – 24 hrs

Pharmacokinetics

GI fate: Rapidly absorbed; undergoes first-pass metabolism; PPB >70%; bioavailability ~55% of the dose.

Metabolism: Converted in the liver by hepatic P450 isoenzyme to its principal active metabolite; both are widely distributed, and tissue concentrations exceed those in plasma, in part because of intracellular uptake.

Elimination: At steady-state up to 55% of the dose is excreted in the urine, 40% unchanged

and 10 – 15% as active or inactive metabolites; elimination $t_{1/2}$ 4 – 7 hrs.

Dosage in renal insufficiency and dialysis patients:

→ *Limited data available, but dosage adjustments advisable!*

Elimination $t_{1/2}$ is prolonged in renal impairment (>20 hrs in ESRD).

- Usual doses can be given in CKD Stage 2 to $3_{GFR\ 89-30}$.
- reduce dosage by 25% in CKD Stage $4_{GFR\ 29-15}$.
- give 50% of the usual dosage in ESRD (CKD Stage $5_{GFR\ <15}$).

No data available regarding removal by HD and CAPD; thus, application of the drug should be avoided in all dialysis patients, although some sources recommend dose adjustment in HD and no dose adjustment in CAPD.

#E040

Esomeprazole (nt!)

(MW 345.4; for oral application used as magnesium salt MW 767.2, for IV injection used as sodium salt MW 368.4)

Esomeprazole is the effective s-enantiomeric isomer of the racemic mixture of omeprazole (S-omeprazole) (see Omeprazole).

Usual dosage: 20 – 40 mg once daily by mouth.

Pharmacokinetics

GI fate: Because esomeprazole is acid-labile, medications are provided in an enteric-coated granule formulation. Absorption is rapid, plasma levels peak within 1 – 2 hrs. Following a single dose, absolute bioavailability (compared to IV administration) is ~ 65%, following maintenance treatment (20 – 40 mg daily), absolute bioavailability is ~ 90%, much higher because of a saturable first-pass effect. PPB is approximately 97%; plasma $t_{1/2}$ in healthy subjects 1.3 hr; aVD 0.25 l/kg (small).

Metabolism: Esomeprazole is almost completely metabolized in the liver, primarily by CYP2C19 and to a lesser extent by CYP3A4.

Note: As with many other drugs, there are 3 problems with esomeprazole in renal impairment. Some cytochrome P450 isoenzymes, such as CYP2C19 and CYP3A4, exhibit a genetic polymorphism due to their deficiency in some sub-populations (poor metabolizers). In renal impairment, 1. esomeprazole metabolism may not only be delayed because of accumulation of metabolites not yet excreted, but 2. may also be slow in poor metabolizers. If drugs are administered concomitantly which 3. use the same CYP450 isoenzyme for metabolism (potential CYP450 inhibitors), these inhibit conversion of esomeprazole. Thus, avoid such inhibitory drugs in renal patients.

Elimination: Mostly excreted in the urine, ~80% of the dose as inactive metabolites, <1% of the dose unchanged; the remainder is found in the feces, also as inactive metabolites.

Dosage in renal insufficiency and dialysis patients:

→ No, or limited data available, but dosage adjustments advisable!

According to the manufacturer, pharmacokinetics in patients with impaired renal function are not expected to be altered relative to healthy volunteers, as <1% of the dose is excreted unchanged in the urine. Therefore his advise is that usual doses can be given to all renal patients.

This statement, however, is in need of correction. The reason for this is that in severe renal impairment inactive metabolites will accumulate, and there is no information that increased removal by the intestine will compensate for the accumulation. Moreover, accumulation of the metabolites leads to a slowing down of metabolism of the parent drug its accumulation, and the risk of serious adverse or toxic effects. UK licensed product information advises caution in patients with CKD stage 4 to $5_{\text{GFR } 29}$, as experience in these patients is limited. No data available regarding removal

by HD and PD, but removal is unlikely due to high PPB.

- Usual doses may be given in CKD stage 2 to $3_{\text{GFR } 89-30}$;
- it is prudent to avoid administration in CKD stage 4 to $5_{\text{GFR } 29}$;
- in dialysis patients give minimal doses or avoid administration because of lack of experience.

Because of the potential nephrotoxicity of the drug it is advisable to evaluate renal function periodically in patients without renal impairment who are on long-term esomeprazole treatment.

Nephrotoxicity

Various cases of omeprazole-induced acute (toxic) interstitial nephritis have been reported. Since esomeprazole is an isomer of omeprazole, the same has to be anticipated for esomeprazole, but so far only one case has been published [527].

Proton pump inhibitor-related acute interstitial nephritis is rare, idiosyncratic, and difficult to predict. During the period 1970 – 2006, 64 cases were published, 59 cases confirmed by renal biopsy [1372].

#F050

Fluvoxamine maleate

(MW 434.4)

Usual dosage: Initially 50 mg once daily by mouth; patients can be titrated within the dose range of 100 – 300 mg/day in two divided doses; not to exceed 300 mg per day.

Pharmacokinetics

GI fate: Readily absorbed; plasma levels peak within 3 – 8 hrs; plasma $t_{1/2}$ 15 hrs; absolute bioavailability 53% of the dose; PPB 80%; mean $a\text{VD}$ ~25 l/kg (extremely large), suggesting extensive tissue distribution.

Metabolism: Extensively metabolized by the liver; 9 metabolites have been identified, constituting ~85% of the urinary excretion products of fluvoxamine.

Elimination: Almost completely excreted in the urine (94% of the dose), ~2% unchanged, the remainder as metabolites. Elimination $t_{1/2}$ up to 35 hrs.

Dosage in renal insufficiency and dialysis patients:

→ *No, or limited data available, proposed dosage advice is preliminary!*

Following treatment with 50 mg fluvoxamine twice daily for 4 and 6 weeks in patients with different degrees of renal impairment (CKD stage 3 to $5_{\text{GFR } 59}$), minimum plasma concentrations of the parent drug are comparable, suggesting that in renal patients accumulation of the drug is unlikely.

In view of the fact that the drug is eliminated almost completely in the urine, this result seems questionable. Most of the drug is removed as (unmeasured) metabolites in these patients, and only 2% of the dose are removed unchanged from the plasma but any precise measurement of such low concentrations is also questionable. In this context and in contrast to pharmacokinetic observations, accumulation of metabolites in patients with severe renal failure under long-term treatment is likely and must be anticipated. The consequence is a concentration-balanced slow-down of metabolism of parent drug and possible accumulation.

Dosage guidelines:

- Administer the usual dosage in patients with CKD stage $2_{\text{GFR } 89-60}$;
- administer a usual dose of 50 mg once a day initially and reduce the subsequent dose carefully according to clinical response in CKD stage 3 to $4_{\text{GFR } 59-15}$;
- avoid dosage in CKD stage $5_{\text{GFR } <15}$ (ESRD) and in all dialysis patients (not data available regarding dialysances).

Note: Phosphate binders bind drugs!

#G027

Glibenclamide

(MW 494.0)

Synonyms: Glybenzcyclamide, Glyburide

Usual dosage: Initially, 2.5-5 mg daily by mouth; if necessary increased by 2.5 mg daily up to 15 mg.

Pharmacokinetics

Second-generation sulfonylurea with much higher potency and shorter elimination $t_{1/2}$ than chlorpropamide.

GI fate: Almost completely absorbed; plasma levels peak within 4 hrs; PPB >97%; plasma $t_{1/2}$ 2 – 2.5 hrs; aVD 0.1 l/kg (very small).

Metabolism: The drug is almost completely converted by hepatic metabolism to hydroxy glibenclamide and 2 minor metabolites, which do not contribute significantly to the hypoglycemic action since they are almost inactive (<10% of the potency of the parent drug).

Elimination: 50 – 55% of the dose excreted in the urine as metabolites, traces unchanged; about 45 – 50% excreted via bile in the feces, mainly as metabolites, 4 – 6% unchanged. Elimination $t_{1/2}$ 8 – 10 hrs.

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are advisable!*

Because of a compensatory increase in excretion via bile in the feces, no clear correlation was found between parent drug and its metabolites and the degree of renal insufficiency; also hemodialysis did not affect the pharmacokinetics, following single or multiple doses [204, 151]. Therefore,

- no dosage reduction is required in renal insufficiency.

However, in CKD stage $4_{\text{GFR } 29-15}$, some delay in excretion has to be anticipated; therefore

- avoid using the drug in ESRD; prescribe gliquidone instead or use insulin which is more suitable because dosage can be titrated.

#G028

Glibornuride

(MW 366.5)

Usual dosage: 12.5 – 75 mg daily by mouth.

Pharmacokinetics

Second-generation sulfonylurea with much higher potency and shorter elimination $t_{1/2}$ than chlorpropamide.

GI fate: Almost completely absorbed (>90% of the dose); PPB ~95%.

Metabolism: No enzyme induction; extensively converted to at least 6 metabolites with little or no hypoglycemic activity.

Elimination: About 66% excreted in the urine and 33% via bile in the feces as metabolites; elimination $t_{1/2}$ ~8 hrs.

Dosage in renal insufficiency and dialysis patients:

→ *No dosage adjustments necessary!*

Even though the elimination of inactive metabolites is prolonged up to 4 fold, no dosage reduction is necessary in renal insufficiency; however,

- administer glibornuride with caution in CKD stage 3 to $5_{\text{GFR } 59}$ and in dialysis patients because the elimination $t_{1/2}$ of the parent drug may be prolonged.
- In CKD stage $5_{\text{GFR } <15}$ (ESRD) insulin is more suitable because dosage can be titrated.

No data available regarding removal by HD and PD (CAPD).

#G029

Gliclazide

(MW 323.4)

Usual dosage: Initially, 40 – 80 mg daily by mouth, gradually increased, if necessary, up to 120 mg daily.

Pharmacokinetics

Second-generation sulfonylurea with much higher potency and shorter elimination $t_{1/2}$ than chlorpropamide.

GI fate: Almost completely absorbed; plasma levels peak within 4 – 6 hrs; PPB 85 – 97%.

Distribution and metabolism: Steady-state conditions are reached within 3 days; aVD 0.2 – 0.3 l/kg (moderate); extensively converted in the liver to at least 7 inactive metabolites.

Elimination: 60 – 70% of the dose excreted in the urine and 10 – 20% in the feces, all as metabolites; elimination $t_{1/2}$ 10 – 12 hrs.

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are advisable!*

- In CKD stage 2 to $3_{\text{GFR } 89-30}$, administer cautiously with close monitoring of blood sugar levels.

In CKD stage $4_{\text{GFR } 29-15}$, elimination $t_{1/2}$ of the drug is significantly prolonged (up to 22 hrs), which may cause prolonged release of insulin resulting in hypoglycemia; therefore,

- the use of oral antidiabetics including gliclazide should be discontinued in CKD stage 4 to $5_{\text{GFR } 29}$ and in dialysis patients and replaced by insulin which can be titrated.

No data available regarding removal by HD and PD (CAPD).

#G030

Glimepiride

(MW 366.5)

Usual dosage: Initially, 1 – 2 mg daily by mouth, may be increased if necessary up to 8 mg daily for maintenance.

Pharmacokinetics

Second-generation sulfonylurea with much higher potency and shorter elimination $t_{1/2}$ than chlorpropamide.

GI fate: Completely absorbed (100%); plasma levels peak within 2 – 3 hrs; plasma $t_{1/2}$ after multiple dosing 5 – 9 hrs; PPB 99.5%; aVD very small (0.14 l/kg).

Metabolism: Glimepiride is extensively metabolized by CYP2D9 in the liver to one main metabolite, a hydroxy derivative with low activity. Another pathway involves formation of an inactive carboxyl derivative.

Elimination: About 60% of the dose is excreted in the urine and 40% in the feces. No parent drug is recovered from urine or feces.

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are advisable!*

Glimepiride is well tolerated in mild, moderate and severe renal impairment. Because of compensatory elimination via the GI tract, accumulation of parent drug is unlikely, and a transient increase in serum concentrations of both metabolites does not result in clinical symptoms.

A starting dose of 1 mg glimepiride can be given to diabetic patients with chronic kidney disease, and the dose titrated based on fasting blood glucose levels. But

- because of the possible accumulation of the active metabolite (risk of hypoglycemia) glimepiride should be used with caution in CKD stage $3_{\text{GFR } 59-30}$, and
- the drug should be avoided in CKD stage $5_{\text{GFR } <15}$ (ESRD); prescribe gliquidone instead or insulin which is more suitable because dosage can be titrated.

Removal of parent drug by dialysis not yet shown but is unlikely because of the high PPB and extensive conversion to metabolites.

#K003

Ketamine hydrochloride

(MW 274.2)

Pharmacokinetics

PPB varies from 10 to 47%, and is much lower than with the other parenteral anesthetics.

Distribution: Although more lipophilic than thiopental, ketamine is water-soluble and available as solutions in NaCl plus the preservative benzethonium chloride. Following IV bolus, the drug is rapidly and widely distributed into body tissues (plasma $t_{1/2}$ 10 – 15 min); aVD extremely large (3 l/kg). The phase of anesthetic action lasts for about 45 min and is determined by redistribution from the CNS to peripheral tissues and hepatic metabolism.

Metabolism: Mostly converted to 2 active and 2 inactive metabolites; metabolite 1 (norketamine) has 10% and metabolite 2 (dehydronorketamine) 1% of the narcotic effect of the parent drug.

Elimination: Predominantly excreted in the urine (80 – 95% of the dose), mainly as metabolites, little unchanged (2 – 3%); 2 – 8% eliminated in the feces; estimated elimination $t_{1/2}$ of the parent drug is ~2.5 hrs, that of the metabolites (in animal experiments) 4 – 6 hrs.

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are advisable!*

In the elderly ketamine appears to influence neither urine output nor glomerular filtration rate and effective renal plasma flow (nephrotoxicity therefore unlikely). It has been shown the combining ketamine with diazepam or other benzodiazepines will reduce the incidence of adverse reactions. In HD patients the agent does not influence the clinical condition.

Experience from ICU concerning the long-term sedation is available for critically ill patients with pre-existing acute renal failure who received daily HD. Under steady-state conditions, ketamine plasma levels were about 25% above the levels in volunteers. The desired therapeutic effect was achieved, and no toxic symptoms were observed; however, significant accumulation of metabolite 2 is known. For general anesthesia purposes in patients with chronic renal insufficiency,

- it is advisable to apply usual narcotic doses with caution in CKD stage 2 to $3_{\text{GFR } 89-30}$, and
- to avoid administration in CKD stage 4 to $5_{\text{GFR } 29}$ if patient is not yet dialyzed.

Removal of ketamine by HD is limited (range 4 – 10% of the dose during one 4-hr HD) due to the wide distribution into body tissues and rapid metabolism. Removal by PD not proven but appears also to be insignificant.

With regard to HD patients under long-term sedation, preliminary advice is

- to increase the dosing interval according to clinical response;

- alternatively, to increase the duration of dialysis up to 24 hrs (continuous dialysis/hemofiltration/hemodiafiltration).

Precautions and notes

See under Enflurane

#L065

Lynestrenol

Synonyms: Ethinylestrenol, Linestrenol, Lynenol

Pharmacokinetics

A progesterone (see there). Limited data available.

Dosage in renal insufficiency and dialysis patients:

→ *No, or limited data available, proposed dosage advice is preliminary!*

- The drug may be used as contraceptive in CKD stage 2 to $3_{\text{GFR } 89-30}$. Because of lack of clinical experience it is advisable to avoid the agent in CKD stage 4 to $5_{\text{GFR } 29}$ and in all dialysis patients.

#M002

Mafenide acetate

(MW 246.3, as hydrochloride MW 222.7, and as propionate MW 260.3)

Usual dosage: Applied topically only. The mechanism of action of the drug is not known.

Pharmacokinetics

Well absorbed through damaged skin (wounds). After entering circulation, mafenide is metabolized to an inactive metabolite which retains the ability to inhibit carbonic anhydrase.

Elimination: The absorbed amount is excreted in the urine, probably completely as metabolite.

Dosage in renal insufficiency and dialysis patients:

→ *No, or limited data available, no dosage suggestions possible!*

Due to significant adverse effects, avoid administration to patients with renal insufficiency and those with impaired respiratory function.

#M089

Metronidazole

(MW 171.2, as benzoate MW 275.3, as hydrochloride MW 207.6, as phosphate MW 269.2)

Pharmacokinetics

GI fate: Completely absorbed; plasma levels peak within 1 – 2 hrs; rectal absorption 60 – 80% of the dose, plasma levels peak within ~4 hrs; PPB low (5 – 20%); following oral administration, bioavailability is 90 – 100% of the dose; aVD moderate (0.6 – 0.9 l/kg).

Metabolism: About 40% of the dose (parent drug) is conjugated with glucuronic acid or sulfates, the remainder undergoes oxidative metabolism. About 10% of the dose is converted to an acid derivative which possesses ~5% of the activity of the parent drug and which is only rarely detected in plasma (reason unknown).

Elimination: Up to 75% of the dose excreted in the urine, half of the amount as a hydroxy derivative and a small amount as an acid derivative, the remainder unchanged; up to 15% found in the feces. Elimination $t_{1/2}$ of parent drug 8 hrs (range 6 – 10 hrs), that of hydroxy metabolite 10 hrs (range 8 – 14 hr).

Dosage in renal insufficiency and dialysis patients:

→ *Dosage adjustments are recommended!*

Because of extensive metabolism, plasma $t_{1/2}$ of the parent drug is not altered in impaired renal function. However, plasma $t_{1/2}$ of the hydroxy metabolite is prolonged in ESRD up to 40 hrs, resulting in significant accumulation in plasma.

- Usual doses can be given to patients with CKD stage $2_{\text{GFR } 89-60}$.
- It is advisable to reduce the dosage in CKD stage $3_{\text{GFR } 59-30}$, and to closely monitor for side effects and efficacy of the drug.

Because of the danger of accumulation of the major active metabolite and as long as its toxic effects are still unknown,

- it is prudent to avoid administration in patients with CKD stage 4 to $5_{GFR < 29}$, if they are not being dialyzed.

Removal by HD is substantial; elimination $t_{1/2}$ of the parent drug is <2.5 hrs and that of the hydroxy metabolite <7 hrs during dialysis.

- Between dialyses, either the dose should be reduced or the dosage interval doubled.
- A usual, supplemental dose should be given after each HD.

Peritoneal dialysis and CAPD [238, 253, 579]: Following oral administration, the penetration to the peritoneum during PD is substantial. Concentration in the dialysate may reach up to 65% of the trough plasma concentration.

- A dose of 500 mg every 12 hrs has proved to be effective and does not seem to cause major side effects. Following oral administration in CAPD, plasma and dialysis fluid concentrations are equal. Thus,
- usual dose should be given during CAPD to achieve effective peritoneal concentrations in the treatment of peritonitis.

#M090

Mexiletine hydrochloride

(MW 215.7)

Usual dosage: Initial dose 200 mg every 8 hrs; adjust in 50 or 100 mg increments every 8 to 12 hrs; do not exceed 1200 mg/day.

Pharmacokinetics [851]

GI fate: Rapidly and almost completely absorbed, plasma levels peak within 2 – 3 hrs; PPB ~ 55 %, but reversible.

Metabolism and distribution: Mexiletine is a close structural analogue of lidocaine. Unlike lidocaine, its first-pass metabolism is low, bioavailability is therefore 80 – 90% of the dose. Mexiletine is widely distributed into all tissues, reaching an extremely large aVD (5 – 12 l/kg). The drug easily passes physiological barriers; thus, only 1% of the dose remains in the blood. 58 – 95% of the dose is fi-

nally metabolized by CYP1A2, CYP2D6, and CYP3A4; genetic polymorphism in relation to CYP2D6 has been identified. Several metabolites have minimal antiarrhythmic activity (up to 20% as potent as the parent drug).

Elimination: Excreted entirely in the urine, 10% (range 5 to 20%) unchanged and the remainder as metabolites. Because mexiletine is a weak base, renal clearance depends on pH of the urine. Removal in alkaline urine is extremely slow. Elimination $t_{1/2}$ varies widely (mean 10 hrs, range 5 – 15 hrs).

Dosage in renal insufficiency and dialysis patients:

→ Differentiated dosage adjustments are recommended! [421, 449, 1571]:

Consistent with the limited renal elimination of the parent drug, little change in the elimination $t_{1/2}$ has been detected in patients with reduced renal function. In 8 patients with CKD stage $5_{GFR < 15}$, mean plasma $t_{1/2}$ was 15.7 hrs, and in 7 patients with CKD stage $4_{GFR 29-15}$, mean plasma $t_{1/2}$ was 13.4 hrs. Elevated plasma levels of the drug as a result of accumulation have not been seen in such patients. It has been shown that >90% of the dose is excreted in urine as poorly active or inactive metabolites.

- Initially usual doses may be given to patients with CKD stage $4_{GFR 29-15}$ but dosage should then be reduced according to clinical response;
- in patients with CKD stage $5_{GFR < 15}$ and in all dialysis patients, initial doses should be reduced and maintenance dosage should be tailored according to clinical response. Moreover, it is prudent to avoid administration to these two groups of patients.

Removal by HD and PD is negligible, <3% of the dose is removed by HD, no removal by CAPD. The drug is mostly located outside the intravascular compartment and can, therefore, not be reached by dialysis measures.

Precautions and notes

In addition to the dosage guidelines mentioned above, the dosage of each anti-ar-

rhythmic agent should be adjusted to clinical efficacy and response. The same applies in patients with impaired renal function.

#0001

Obidoxime chloride

(MW 359.2)

Usual dosage: Antidote, used in the treatment of poisonings with organophosphates or related compounds. For its dosage consult toxicological handbooks.

Pharmacokinetics

Similar to pralidoxime (see there); no appreciable PPB.

Dosage in renal insufficiency and dialysis patients:

→ No, or limited data available, but dosage adjustments advisable!

Characteristics of obidoxime did not change significantly in a poisoned patient with a CrCl of 54 ml/min; 80% of the dose was excreted in the urine over 5 hrs [133]. No data available regarding removal by HD or PD (CAPD).

Because of the characteristics of the drug,

- it is advisable to administer usual doses in CKD stage 2_{GFR 89-60};
- to reduce dosage in CKD stage 3_{GFR 59-30}; and
- to avoid administration in CKD stage 4 to 5_{GFR 29} and in dialysis patients.

#P001

Paclitaxel

(MW 853.9)

Synonyms: Taxol, Taxol A

Pharmacokinetics

Following IV dose, paclitaxel exhibits a biphasic decline in plasma concentrations, with mean elimination $t_{1/2}$ ranging from 3 to 50 hrs. PPB 89 – 98%.

Distribution and Metabolism: At steady-state, mean aVD is very large (range 5 – 15 l/kg), indicating extensive extravascular distribution

and/or tissue binding of the drug. Paclitaxel is metabolized in the liver by CYP2C8 primarily to the major metabolite, and by CYP3A4 to 2 minor metabolites.

Elimination: Mostly excreted in the feces (70% of the dose as primary metabolite, 5% unchanged); up to 12% of the dose is excreted in the urine, indicating extensive non-renal clearance; elimination $t_{1/2}$ up to 50 hrs.

Dosage in renal insufficiency and dialysis patients:

→ No data available, no dosage suggestions possible!

Because of (therapeutic) cell toxicity and unclear excretion characteristics, studies in renal patients have not been conducted.

Nephrotoxicity

Among patients Kaposi's sarcoma treated with paclitaxel, 5 patients had renal toxicity of grade III or IV (renal insufficiency with reversible elevations in sCr). These few cases of possible renal disturbance, are insufficient to classify paclitaxel as potentially nephrotoxic.

#P038

Peramivir

(MW 328.4, as carboxylic acid MW 382.5)

Antiviral drug (inhibitor of neuramidase activity of influenza A and B, including H1N1 influenza)

Usual dosage: Adults and adolescents 18 years: 600 mg IV once daily infused for 5 – 10 days; children 6 years and adolescents 17 years: 10 mg/kg IV once daily infused (not to exceed 600 mg/dose) for 5 – 10 days. Dosage in smaller children, see drug insert.

Pharmacokinetics

PPB <30%; not significantly metabolized.

Elimination: Almost completely excreted in the urine (90% of the dose); elimination $t_{1/2}$ varies from 7.7 to 20.8 hrs; no accumulation observed during multiple dosing.

Dosage in renal insufficiency and dialysis patients [1768]:

→ *Dosage adjustment is recommended!*

In renal patients with CKD stage 2_{GFR 89-60}, the mean systemic exposure is 24% higher than in those with normal renal function (an increase not expected to be clinically relevant); with CKD stage 3_{GFR 59-30}, 3.4-fold higher; with CKD stage 4_{GFR 29-15}, 6-fold higher; with CKD stage 5_{GFR <15}, 40-fold higher.

In adults and adolescents 18 years

- with CKD stage 2_{GFR 89-60}, give the usual daily dose;
- with CKD stage 3_{GFR 59-30}, give 150 mg daily;
- with CKD stage 4_{GFR 29-15}, give 100 mg daily;
- with CKD stage 5_{GFR <15} but not yet dialyzed, give 100 mg on day 1, then give 15 mg daily.

In children 6 years and adolescents 17 years

- with CKD stage 2_{GFR 89-60}, give the usual daily dose;
- with CKD stage 3_{GFR 59-30}, give 10 mg/kg daily;
- with CKD stage 4_{GFR 29-15}, give 2.5 mg/kg daily;
- with CKD stage 5_{GFR <15} but not yet dialyzed, give 1.6 mg/kg on day 1, then 0.25 mg/kg daily.

Dosage adjustment for smaller children, see drug insert.

Hemodialysis [1768]: Appreciable removal by HD, thus administration after dialysis.

In adults and adolescents 18 years

- give 100 mg on day 1, then 1.6 mg/kg 2 hrs after each HD, no further dosing between dialyses.

PD and CAPD: No data available.

CRRT in ICU: There is evidence that the drug is eliminated by CVVHF and CVVHD but, at present recommendations cannot be made. Recently, peramivir was administered to two criti-

cally ill patients during SLED treatment (Q_B 200 ml/min, Q_D 300 ml/min) [1769]. With a daily IV dose of 600 mg, mean peak peramivir plasma levels (~27,000 ng/ml) were in the range of those in healthy subjects (45,200 ng/ml). Both patients recovered from the viral infection.

Precautions and notes

Since peramivir is eliminated primarily by the kidney, coadministration with drugs that reduce renal function or compete for active tubular secretion (see under Introduction) will theoretically increase plasma concentrations of peramivir.

Peramivir is not metabolized by the liver; therefore drugs that alter the CYP450 isoenzyme system should not alter the elimination of the drug.

#P063

Pilocarpine

Dosage in renal insufficiency and dialysis patients:

→ *No dosage adjustments necessary!*

#P064

Pimecrolimus

Pharmacokinetics

An immunosuppressive agent for topical use in atopic dermatitis (like tacrolimus); minimal systemic absorption; metabolized in the liver, excreted in feces.

Drug dosage in renal insufficiency and dialysis patients:

→ *No dosage adjustments necessary!*

