

PHARMACOTHERAPEUTIC IMPLICATIONS OF KIDNEY FAILURE

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INTRODUCTION

Patients with chronic renal failure (CRF) require prolonged treatments administered daily, most often orally, for specific therapy and treatment of signs of CRF (1), but also for potential concomitant diseases (such as heart failure, osteoarthritis...). The following discussion emphasises particularly the overall pharmacokinetic implications of CRF in dogs. For specific drug recommendations, the reader may refer to reviews (2, 3).

RELEVANT PHARMACOKINETIC CONSIDERATIONS IN RENAL FAILURE

Renal clearance, hepatic clearance, metabolite clearance

Generally, the higher the contribution of the kidney to drug clearance, the greater the effect of CRF on drug elimination. Renal dysfunction may induce an overexposure (i.e. an increase in AUC, with potential first-dose acute adverse effects) to the drug after a single administration and accumulation with repeated administration (in which case adverse effects will occur several days after treatment commences). It should be kept in mind that the contribution of renal clearance to drug elimination shows important interspecies variation and therefore data from humans with CRF cannot be extrapolated to dogs.

CRF may also decrease plasma clearance of drugs cleared or metabolised by the liver. In humans and rats with CRF, alteration in hepatic metabolism was described. In rats with 60% decrease in creatinine clearance, total CYP450 was reduced by 40%. Differences among isoforms were moreover observed: CYP2C11, CYP3A1, and CYP3A2 were the most reduced (45%, 80% and 45%, respectively), while CRF did not change CYP1A2 concentration (4). More unexpectedly, plasma clearance of drugs eliminated by the liver may also be increased by RF. In dogs with a 45% decrease in glomerular filtration rate (GFR), plasma clearance of tolfenamic acid, an NSAID, was increased by 62% (5).

Metabolite disposition may be altered by CRF, and this aspect has been particularly emphasised in dogs over the last few years. For example, area under the curve (AUC) of N-oxide marbofloxacin, an inactive metabolite of marbofloxacin, was increased 2-fold in dogs with a 60%-decrease in GFR, while almost no change was observed for marbofloxacin, normally about 40% cleared by the kidney (6). Under the same conditions, an 80% increase in AUC of enalaprilat, the renally-cleared active metabolite of enalapril, was observed with only a corresponding 30% increase for its prodrug, enalapril (7, 8). In contrast, the apparent clearance of benazeprilat, which undergoes hepatorenal elimination, was increased about 3-fold (8). Pharmacologically active metabolites essentially cleared by the kidney exist for other drugs, such as anti-arrhythmic agents, which should therefore be used with caution.

Effects of CRF on drug-metabolite disposition may be even more complex. Let us consider the example in humans of ketoprofen, whose anti-inflammatory activity resides mainly with the (S)-enantiomer. A low percentage of the dose is excreted in urine, but its clearance is paradoxically decreased in patients with CRF. In fact, CRF decreases the renal elimination of acylglucuronides, and accumulation of these is followed by regeneration of the parent drug by systemic hydrolysis of these conjugates (9).

Plasma protein binding

Distribution may be changed in renal failure by dehydration and by a decrease in plasma protein binding (PPB), as shown for many acidic drugs in human patients. This decrease results from hypoalbuminemia (by urinary loss for example) and/or displacement of drugs by endogenous waste products. In dogs with RF, PPB was not changed for gentamicin (10) and tolfenamic acid (5), but decreased for phenylbutazone (11). However, the clinical relevance of decreased PPB in CRF is limited for most drugs (12). The increase in free concentration induced by drug displacement is immediately buffered by redistribution and increased elimination rate of free drug (assuming the drug has a low extraction ratio). In these circumstances, the total plasma concentration in fact decreases, while the steady-state free concentration will not change (i.e., drug response is not changed either). However, the fall in total plasma drug concentration is relevant for therapeutic drug monitoring (TDM) as the normal response to a decreased plasma concentration would be to increase the dose or decrease the dosing interval, which could lead to overexposure.

Bioavailability

Oral administration is most appropriate for long-term therapy, but enteric absorption and bioavailability may be altered in patients with gastrointestinal disturbances. In humans, results are conflicting. In dogs with a 65-70% decrease in GFR but no concomitant gastrointestinal disturbances, we observed that gastric emptying rate and small bowel transit time, at least for liquids, were not modified. The bioavailability of several test substances (acetaminophen, sulfapyridine and xylose) was also unaffected. Any effect of mild CRF on oral bioavailability seems therefore limited in dogs. In more advanced CRF, oral bioavailability may become more erratic, i.e. decreased (for example in vomiting) or increased (enhanced permeability of intestinal wall).

RULES FOR ADJUSTING THE DOSAGE REGIMEN FOR DRUGS MAINLY CLEARED BY THE KIDNEY

Adjust only when required.

Dosage regimen adjustment should be considered in the following cases: i) the drug is mainly (at least 70% of the dose) excreted by the kidney either unchanged or as an active metabolite, ii) the therapeutic window of the drug or metabolite is narrow, or iii) the kidney is the major organ for metabolism (for hormones like insulin, for example). Practically speaking, only the first two points are currently considered in veterinary clinical pharmacology.

Estimate glomerular filtration rate

Dosage adjustment is generally based upon the assumption that only renal clearance is changed (absorption, distribution, protein binding and pharmacodynamics being taken as unaltered). The key factor for dosage regimen adjustment is the dose fraction (Kf) (2, 3, 13), defined as:

$$Kf = GFR_r / GFR_n$$

where GFR_r and GFR_n are GFR values under renal-impaired and healthy conditions, as the change in GFR is considered the best overall indicator of renal dysfunction and also of reduced renal drug clearance.

GFR assessment remains probably the major critical issue for dosage adjustment in renal failure, because most of the current recommended techniques are not practicable. Estimation of Kf based on the observed plasma creatinine concentration is clearly contraindicated because the relationship between plasma creatinine concentration and GFR is not linear (14). However, rapid assessment of GFR may be possible using plasma clearance (=Dose/AUC) of creatinine (single i.v. bolus at 80 mg/kg; blood sampling at 10 min, 1, 2, 6 and 10 h; the "normal" GFR value is about 3.0-3.5 mL/kg/min (15)).

Choose an adequate strategy

The main considerations for dosage regimen adjustment involve i) reduction of the dose level, ii) extension of the dosing interval, iii) administration of a loading dose, and iv) therapeutic drug monitoring (TDM) (2, 3, 13).

Decrease the dose level - the dosing interval is unchanged and the dose is multiplied by Kf. This approach should be used when the dosing interval is less than the elimination half-life, and with drugs with low therapeutic index.

Increase the dosing interval - the dose is unchanged and the dosing interval is increased by dividing it by Kf. This strategy is appropriate for fixed-dosage forms but the dosing interval may be too long and lead to owner-noncompliance. The decision to reduce the dose or to increase the interval depends also on the drug's action mechanism. For antibacterials (fluoroquinolones, aminoglycosides) with concentration-dependent kill rate, peak concentration should be high to maximize efficacy. Increasing the dosing interval is recommended for such agents. For those (beta-lactams, macrolides...) with time-dependent activity, the "constant-interval, dose-reduction" method seems more appropriate to maintain plasma concentrations above MIC.

Administer a loading dose at the beginning of the treatment - because the time required to reach steady state (about $5 \times t_{1/2}$) is increased (due to increase in half-life), a loading dose can be needed to obtain rapidly therapeutic concentration when drug administration is repeated. The loading dose is the same as in healthy conditions (steady-state volume of distribution and bioavailability are presumed to be unchanged).

Monitor concentrations of drugs with a narrow therapeutic index - TDM should be performed for drugs with a narrow therapeutic index at regular intervals during treatment if renal dysfunction progresses or adverse reactions or therapeutic failure occur. This approach considerably increases the cost of therapy and may require hospitalisation, at least until steady-state concentrations have been reached. The dose may be adjusted by the following equation (16):

$$D_2 = D_1 \times (E_{cn} / O_{cn})$$

where D₂ is the new dose, D₁ the old dose, E_{cn} the effective plasma concentration (fixed), and O_{cn}, the plasma concentration (observed). Peak and trough concentrations are generally assessed over a single dosing interval. Trough concentrations are more easily comparable from one administration to another, but peak concentration are more relevant in terms of toxicity. The observed concentration should be carefully interpreted, according to clinical status of the patient, dosing history, sampling time, concomitant drugs, metabolites and assay. Monitoring free concentrations is highly recommended (see before).

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONSHIP [consider using abbreviations PK, PD after here]

Very few studies are available about effects of CRF on drug pharmacodynamics. It was generally assumed that effects only occurred when drug accumulates, but nowadays, this assumption is no longer acceptable. Pharmacodynamics

may be modified by CRF, independently of pharmacokinetics. In rats with RF, thiopental EC_{50} is decreased by about 30%, and clearance and volume of distribution of the unbound fraction are not affected (17). In humans, individual lymphocyte response to glucocorticoids may be more helpful than any pharmacokinetic approach for selection and dosage adjustment of glucocorticoids to prevent allograft rejection in renal transplantation: the response to prednisolone is decreased in patients with CRF, compared to healthy subjects (18). In dogs with RF, the free plasma enalaprilat concentration required to produce 50% of total inhibition of the converting enzyme was increased by 2.5-fold (8).

Pharmacodynamics may remain unchanged, while pharmacokinetics is altered. For example, no difference in ranitidine-induced gastric pH response was observed between patients (creatinine clearance <10mL/min) and healthy subjects (creatinine clearance >80 mL/min), even though plasma drug clearance was decreased 5-fold in CRF patients (19).

CONCLUSION AND FUTURE DIRECTIONS

The practical consequence of complex PK/PD relationships under CRF-conditions is that there is currently no simple way to adjust dosage regimens when information about the effects of CRF on drug pharmacokinetics and pharmacodynamics is lacking. Such information should be provided from experimental models and population kinetics, as recently proposed for gentamicin in horses (20) and digoxin in dogs (21).

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Key words

Bioavailability, dosage regimen adjustment, glomerular filtration rate, pharmacokinetics, pharmacodynamics, dogs

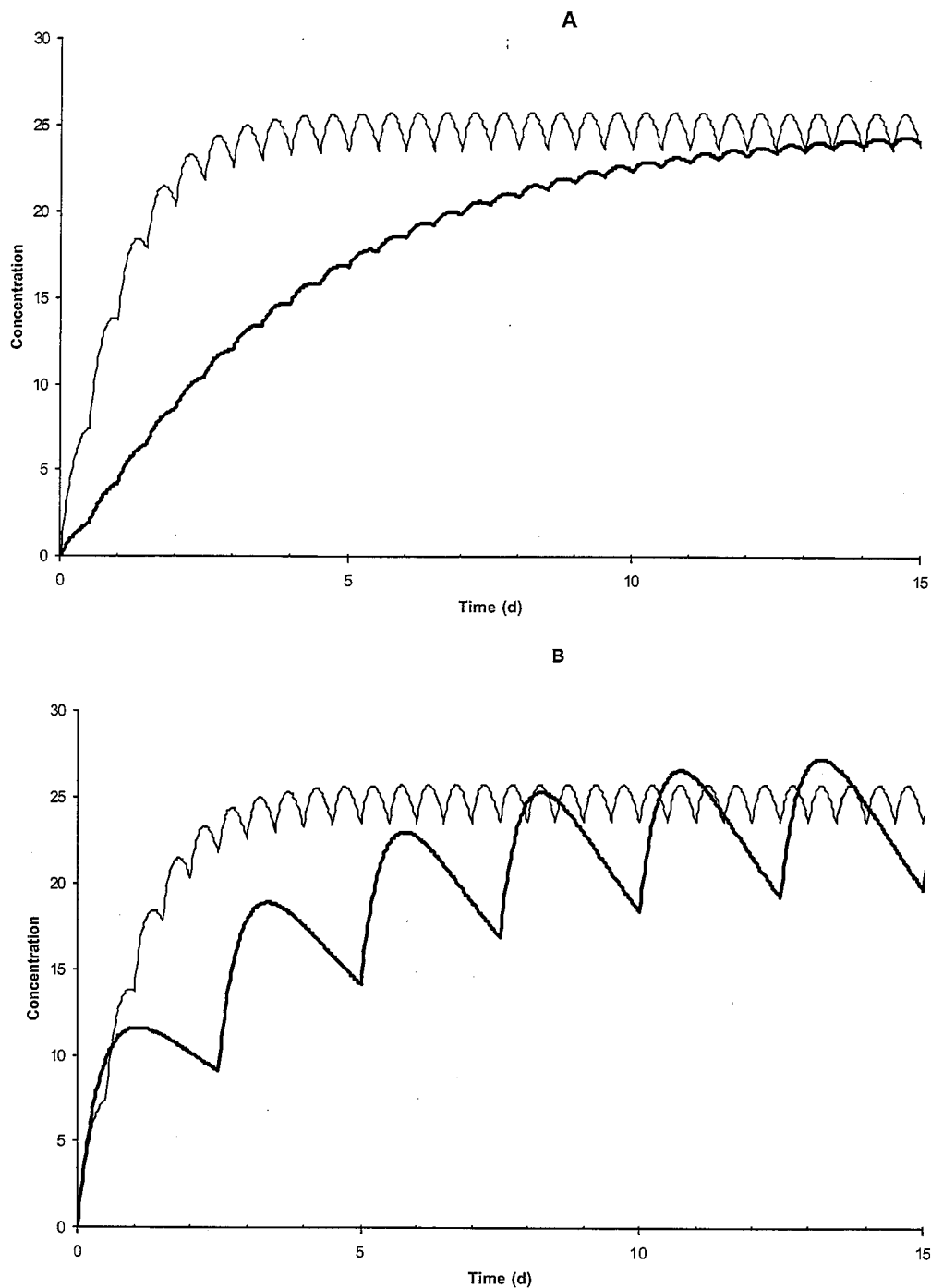


Figure 1 –Simulated plasma kinetics (depicted by an open monocompartmental model) of a hypothetical drug administered twice daily by oral route with a half-life of 12 h and totally cleared by the kidney. The drug plasma concentration-time profile is represented in the healthy dog (thin line) and in the renal-impaired dog (thick line). The GFR (and therefore the clearance of the drug) was decreased by 5-fold. **A.** Dosage adjustment is performed by “constant interval – dose reduction” method. This is the solution generally chosen (especially for drugs with low therapeutic index). With this adjustment, the resulting plasma concentrations peaks in patients will be lower than those obtained in healthy subjects. **B.** Dosage adjustment is performed by “constant dose – interval extension” method. This is appropriate for administration of a fixed-dosage form in patients with moderate renal failure but the dosage interval can be too long, and therefore inconvenient (especially for the owner). The plasma concentration of the drug may remain below the minimal therapeutic concentration for long periods of time. The delay to steady-state is prolonged in both situations because of the increased half-life.

RECOMMENDATIONS

ANTIMICROBIAL AGENTS

Aminoglycosides	Contraindicated because of nephrotoxicity. Risk factors other than renal impairment: ageing, dehydration, dietary sodium restriction, obesity. No concomitant treatment with furosemide. Individualization of dosage regimen is required in renal-impaired dogs. Nomograms are available. TDM highly recommended.
Penicillins	Accumulation, but high therapeutic index. Electrolyte monitoring may be necessary when sodium or potassium salts are used. For dicloxacillin and oxacillin, no change. For others, when GFR<0.5 ml/kg/min, divide the dose by 2 or multiply the dosage interval by 2.
Cephalosporins	Potentially nephrotoxic (especially cephaloridine)
Sulfonamides	Apparently slightly nephrotoxic in the dog. Dosage adjustment recommended: for sulfisoxazole, multiply the dosage interval by 2-3 when GFR<1 mL/kg/min.
Tetracyclines	Severe accumulation, potentially nephrotoxic, exacerbation of azotemia, contraindicated except doxycycline, which has substantial nonrenal elimination.
Fluoroquinolones	Dosage adjustment recommended in humans. Few data available in the dog as yet. No dosage adjustment required for marbofloxacin
Lincosamides and macrolides	No dosage adjustment required for erythromycin and clindamycin. No nephrotoxic effect described.
Metronidazole	No dosage adjustment required

ANTI-INFLAMMATORY DRUGS

NSAIDs	Dosage adjustment recommended for many NSAIDs in renal-impaired human patients. Nephrotoxic risk. Among NSAIDs used in canine medicine, tolfenamic acid does not accumulate.
Corticosteroids	They should be used with caution because they may worsen azotemia

CARDIOVASCULAR DRUGS

Digitalis glycosides	Accumulation of digoxin, but not digitoxin. TDM highly recommended.
ACE inhibitors	Dosage adjustment recommended in humans for those extensively cleared by the kidney. In dogs, enalaprilat and captopril are cleared mainly by the kidneys, and benazeprilat and ramiprilat by the liver and the kidney. In dogs, there is no risk of overexposure with benazeprilat. Potential interaction with NSAIDs.
Antiarrhythmic drugs	Hepatic elimination, but should be used with caution because active metabolites are most often cleared by the kidney and the therapeutic index is low.
Diuretics	Decrease elimination and diuretic response for furosemide in dogs with renal failure. Concomitant treatment with nephrotoxic agents (NSAIDs, aminoglycosides) is contraindicated.

ANESTHETICS

Barbiturates	Contraindicated because of renal hemodynamic effects and potential increase in sensitivity of the central nervous system in renal-impaired subject.
Ketamine	Reduced risk of adverse effects in renal-impaired dogs
Volatile anesthetics	Isoflurane should be preferred to halothane and methoxyflurane.
Muscle relaxants	Contraindicated. In human patients with renal disease, atracurium and vecuronium are preferable because they are eliminated mainly by extrarenal route, and apparent resistance to neuromuscular blocking agents has been described.

See: Riviere JE, Vaden SL (1995), Drug therapy during renal disease and renal failure, in *Canine and Feline Nephrology and Urology*, CA Osborne and DR Finco, ed. Baltimore, MA, Williams and Wilkins, pp. 555-572; Lefebvre HP, Braun JP, Toutain PL (1996), Drug prescription in renal-impaired dogs. *Rev. Med. Vet.*, 147, 11, 757-782.

Appendix 2 - GFR assessment in practice: example of plasma exogenous creatinine clearance test

Chronic renal failure is suspected in an aged dog. The plasma creatinine concentration in fasted conditions is 1.8 mg/dL. A plasma exogenous creatinine clearance test is performed, using creatinine, administered by bolus i.v at 80 mg/kg. Six 1-mL blood samples are collected at 2 and 10 min, and 1, 2, 6 and 10 hours. The following concentrations are observed, and the basal concentration is subtracted from each one:

Time (minutes)	Observed Plasma Creatinine (mg/dL)	Plasma Concentration Minus Basal Concentration (2.2 mg/dL)
2	26.5	24.3
10	22.1	19.9
60	16	13.8
120	12	9.8
360	9	6.8
600	6.8	4.6

The area under the plasma curve (AUC) is calculated by the trapezoidal rule, as follows.

The area of the first trapeze (mg.min/dL) between 2 and 10 min is equal to: $(10-2) \times (19.9 + 24.3)/2 = 176.8$

The second trapeze between 10 and 60 min has area: $(60-10) \times (13.8 + 19.9)/2 = 842.5$

Continue similarly for the third and fourth trapeze.

The last trapeze between 360 and 600 min has area: $(600-360) \times (4.6+6.8)/2=1,368$

The total AUC is equal to the sum of the five trapezes :

$176.8+842.5+708+1,992+1,368= 5,087.3$ mg.min/dL (i.e. 50.87 mg.min/mL)

The plasma creatinine clearance (i.e. GFR estimate, mL/kg/min) is equal to the dose divided by the AUC: $80/50.87 = 1.6$ mL/kg/min (which corresponds to mild renal failure).

Conclusion: For most drugs, no dosage adjustment would be required for this dog.

Practical information :

- The dog should be fasted overnight (at least).
- Creatinine is stable in plasma, so assays can be delayed.
- The cost of the creatinine at 80 mg/kg for a 20-kg dog is less than \$2.

Reference : Watson ADJ, Lefebvre HP, Laroute V, Ferré JP et al (1998), Comparison of clearance tests to assess glomerular filtration rate in dogs. *Proc. 16th ACVIM forum*, San Diego, 711 (abstr.).

