Patients with chronic kidney disease (CKD) require prolonged treatments administered daily, most often orally, for specific and symptomatic therapy of CKD. They may be treated also for other potential concomitant diseases (e.g., heart failure, systemic hypertension, and osteoarthritis). Such prescriptions require specific knowledge to optimize the benefit/risk ratio (Riviere and Vaden, 1995; Lefebvre et al, 1996).

1- Pharmacokinetic and pharmacodynamic alterations in renal failure

Drug elimination - Generally, the higher the contribution of the kidney to the elimination of the drug, the greater the effect of renal failure on drug elimination. Renal dysfunction may have two consequences: an overexposure (i.e., an increase in AUC, with potential first-dose acute adverse effects) to the drug after a single administration and, when repeated administrations are performed, an accumulation (adverse effects will occur several days after the start of the treatment). It should be kept in mind first that data from humans with CKD cannot be extrapolated to dogs, and secondly that absence of renal excretion does not mean that pharmacokinetics will be unaltered. Plasma clearance of drugs eliminated by the liver may also be modified by CKD. In dogs with subclinical CKD, plasma clearance of tolfenamic acid, a NSAID, is increased by 62% (Lefebvre et al, 1997). Metabolites disposition may be altered by CKD, as demonstrated for N-oxyde marbofloxacin, an inactive metabolite of marbofloxacin (Lefebvre et al, 1998), or the active metabolite of enalapril, enalaprilat, which is renally cleared (Lefebvre et al, 1999; Toutain et al, 2000). On contrary, no overexposure was observed with ACE inhibitors eliminated by hepatorenal routes, such as benazepril (Lefebvre et al, 1999) and ramiprilat (Lefebvre et al, 2006).

Plasma protein binding - Dehydration and decrease in plasma protein binding (PPB) observed in CKD may affect the volume of distribution. This decrease results from hypoalbuminemia (by urinary loss for example) and/or displacement of drugs by endogenous waste products. The clinical relevance of decreased PPB in CKD is however for most drugs clinically irrelevant (Rolan, 1994). The increase in free concentration is indeed buffered by redistribution and increase in the elimination rate of free drug (assuming that the drug has a low extraction ratio). Consequently, the response to the drug is not changed.

Bioavailability - Oral bioavailability may be altered in renal patients with gastrointestinal disturbances. Effect of compensated CKD on oral bioavailability seems limited in dogs. In dogs with a 65-70% decrease in GFR, but no concomitant gastrointestinal disturbances, gastric emptying rate and small bowel transit time, at least of liquids, were not modified. The bioavailability of different test-articles (acetaminophen, sulfapyridine and xylose) was moreover unaffected (Lefebvre et al, 2001). In more advanced stages of CKD, oral bioavailability may be decreased (for example in vomiting) or increased (increased permeability of intestinal wall).
Drug pharmacodynamics - Very few studies are available about effect on renal failure on drug pharmacodynamics. It was generally assumed that effect is potentialized when drug accumulates. Pharmacodynamics may be modified by renal failure, independently of pharmacokinetics, as shown in humans and rats. In dogs with subclinical renal failure, the free plasma enalaprilat concentration required to produce 50% of total inhibition of the converting enzyme was increased by 2.5-fold (Toutain et al, 2000).

2-Rules for adjustment of the dosage regimen for drugs mainly cleared by the kidney

Adjustment of dosage regimen is difficult, needs an accurate assessment of renal function and requires a good knowledge in drug pharmacokinetics.

Adjust only when required - Dosage regimen adjustment should be considered when: i) the drug (or its active metabolite) is mainly (at least 70% of the dose) excreted by the kidney, and ii) the therapeutic window of the drug or the metabolite is narrow. Unjustified dosage regimen adjustment may lead to therapeutic failure. It is always better, when possible, to select another drug cleared for example by an extrarenal route than to try empirically to adjust the dosage regimen.

Estimate renal function - Dosage adjustment is based upon the assumption that only renal clearance is changed. The key parameter for dosage regimen adjustment is the dose fraction (Kf), defined as :

\[ Kf = \frac{GFRr}{GFRn} \]

with GFRr and GFRn the glomerular filtration rate (GFR) value under renal-impaired and healthy conditions.

Change in GFR is considered the best overall indicator of renal dysfunction and also of change in drug renal clearance. The “normal” GFR value in dogs is about 3.0-3.5 mL/kg/min. GFR assessment remains probably the major limit for dosage regimen adjustment in renal failure, because most of the current recommended techniques are not practicable. Estimation of Kf based from the observed plasma creatinine value is clearly contraindicated because there is no single linear relationship between plasma creatinine concentration and GFR (Finco et al, 1995), at least for advanced stages of CKD.

Choose an adequate strategy - Main approaches for dosage regimen adjustment involve i) reduction of the dose level, and ii) extension of the dosing interval.

Decrease the dose level - the dosing interval is unchanged and the dose is multiplied by Kf. This approach should be used when the dosage interval is lower 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 form, but the dosage interval may be too long and therefore less compliant for the owner. Decision to reduce the dose or to increase the interval depends also on drug action mechanism (eg antibiotics with concentration-dependent activity).
Because the time required to reach steady state (about five half-lives) is increased (due to increase in half-life), a loading dose (similar to that used in healthy conditions) is generally needed to obtain rapidly therapeutic concentration when drug administration is repeated.

3- Other specific therapeutic considerations

Monitor the patient regularly - CKD is a progressive disease and the rate of progression cannot be predicted. Consequently, serial clinical examination and laboratory routine investigations (basal plasma creatinine, USG and proteinuria) should be regularly performed so that therapy may be modified accordingly.

Be aware of potential risk of drug interactions - The number of drugs which can be used for the medical management of CKD is high, especially in end-stage patients: angiotensin converting enzyme inhibitors, other anti-hypertensive agents (eg amiodipine), phosphate binders, calcitriol, alkalinizing agents (eg sodium bicarbonate), erythropoietin, antiemetics (eg metoclopramide), histamine receptor blocking drugs (eg cimetidine), etc. Risk of drug interactions is increasing with the number of drugs prescribed.

Drugs may affect routine markers of renal function – ACE inhibitors which are useful drugs in the medical management of CKD may increase basal plasma creatinine when starting treatment because these agents lower glomerular hyperfiltration. It should not be considered as a potential adverse effect of the treatment and therapy should not be discontinued.

Select appropriate formulation - Oral formulations may be difficult to administer in patients with advanced CKD showing partial or total anorexia. Palatable formulations would be an interesting alternative in such clinical settings to increase the owner’s compliance. In end-stage CKD, parenteral formulations should be preferred.

Avoid nephrotoxic agents – The kidney sensitivity to nephrotoxic agents is higher in the canine patient with CKD. Nephrotoxic drugs (eg aminoglycosides, non steroidal anti-inflammatory drugs, cisplatin) are contraindicated in such patients.

Conclusions

Rational drug prescription in patients with CKD is a difficult challenge for the practitioner. The essential and basic rules are probably to monitor routinely the response to therapy, the changes in renal function and the owner’s compliance. Dosage regimen adjustment should be performed only in specific cases and never empirically.

References


