

## 5 Summary

### **Investigations to modified exogenous creatinine clearance after oral or subcutaneous administration to dogs**

#### Animals and experimental design

29 dogs of different breeds, aged from 2 to 11 years old, were under examination. The glomerular filtration rate was determined using the plasma clearance (P-Cl) of exogenously applied creatinine. The creatinine was administered to the animals as a marker either (1) orally or (2) subcutaneously. At the time of administration, the dogs were either (1) fasting or (2) had just been fed. The study examined intestinal absorption of creatinine based on the absorption of the known indicator xylose.

#### Results:

The results listed occurred after **oral administration** of creatinine:

1. Mono-exponential excretion of the substance creatinine occurred after a time period between 2.5 to 19.5 hours after marker application from unfed dogs and after a time period between 3 to 19.5 hours from fed dogs. During this time frame the median (M) of the  $\beta$  exponents was between -0.0027 and -0.0048 in fasting dogs and -0.0008 and 0.0045 in dogs that had been fed.

The following results occurred after **subcutaneous administration** of creatinine:

2. The mono-exponential excretion of creatinine was observed during a period ranging from 3 to 9 hours (M of  $\beta$  = -0.0040 to -0.0052) when the animals were fasting, and during a period of between 1.5 to 12 hours (M of  $\beta$  -0.0051 to -0.0065) where the animals had just been fed.

The simultaneous administration of creatinine and xylose to the same animals facilitated the comparison of **the intestinal absorption specimen** of both substances. The following results were thereby ascertained:

3. The point of time of maximal serum- [creatinine] ( $t_{\max, \text{creatinine}}$ ) was reached between 0.5 and 3 hours later than the maximal serum- [xylose] ( $t_{\max, \text{Xylose}}$ ) for the same animals, which can be attributed to a different enteric absorption mechanism of both substances.

It is a generally known fact that xylose is absorbed passively in the duodenum and in the upper jejunum in addition to being transported actively by an enteric transport system for sugar molecules. The results of this examination would appear to indicate an absorption of creatinine through the mucosa in a distal segment of the gut. Moreover, it is possible that creatinine in the intestine uses the sodium-dependent transport system for enteric absorp-

tion.

This would appear to indicate that passive and active transport systems exist for both creatinine and xylose. It is worth pointing out at this juncture that creatinine can leave the muscle cells by simple diffusion.

The GFR was calculated as  $P - CL_{\text{creatinine,exogen}}$  using a “non-compartmental model” with the help of the selected timeframes for the mono-exponential excretion of exogenously supplied creatinine. The following findings were thereby ascertained:

4. Following the administration of creatinine to fasting animals, the determined values ranged from  $99.8 \pm 19.53$  to  $113.7 \pm 11.5$  ml/min/m<sup>2</sup> body surface area. These findings are similar to those mentioned in the literature.
5. After feeding, the GFR was found to lie between  $98.3 \pm 12.07$  and  $131.6 \pm 27.78$  ml/min/m<sup>2</sup> body surface area.
6. The choice of application method and the feeding status of the animals exert a discernible influence on the GFR values and the associated exponent  $\beta$  in the mono-exponential section of the excretion curve for creatinine. The GFR values ( $117.5 \pm 14.03$  ml/min/m<sup>2</sup> body surface area) and the associated exponent  $\beta$  were found to differ significantly following subcutaneous and oral administration ( $131.6 \pm 27.78$  ml/min/m<sup>2</sup> body surface area) after feeding. No statistical difference was found for the GFR values ( $113.7 \pm 11.5$  ml/min/m<sup>2</sup> body surface area) and exponents  $\beta$  following the subcutaneous and oral administration ( $99.8 \pm 19.53$  ml/min/m<sup>2</sup> body surface area) of creatinine to fasting animals. The exponents  $\beta$  differ statistically depending on whether creatinine is administered subcutaneously to animals that are fasting or have just been fed. These findings support those in the literature, indicating that renal activity is distinctly higher after feeding.

In practice, the renal function test must be carried out on subjects who are fasting in order to exclude the frequently unknown influence of feeding on the determination of the GFR. According to the findings of this analysis, the administration of exogenous creatinine to fasting animals can be done either orally or subcutaneously. The measurement of serum [creatinine] levels should not be conducted at night, as the GFR can be up to 30 per cent below the daily norm.

It is recommended to take blood samples 3 to 12 hours following the oral administration and 3 to 9 hours following the subcutaneous administration of the marker in order to conclude the renal function test within a day. A third blood sample must be taken within this timeframe to

validate the three measured serum-[creatinine] on the regression line in the semi-logarithmic description. If the coefficient of determination in fasting animals after oral administration of the marker is under  $R^2 < 0.994$  and after subcutaneous administration of creatinine under  $R^2 < 0.997$ , the renal function test must be repeated.

There are at least two advantageous possibilities for applying creatinine to dogs - both the oral administration in the form of tablets as well as the subcutaneous administration of a 5 per cent solution of creatinine result in comparable amounts of GFR in the animals. The classic intravenous administration of exogenous creatinine to determine renal ultra-filtration should also be mentioned here.