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Development of a pharmacokinetic model to describe the distribution and excretion kinetics of a renal function marker using transcutaneously obtained data in rats

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Recently, a novel method was introduced that simplifies measurements of kinetics following intravenous injection of exogenous markers by a transcutaneous approach. A measurement device equipped with a LED and a photo diode to excite and detect the emission signal of the marker transcutaneously assesses the kinetics of the intravenously applied marker. From this kinetics the half-clearance time ($t_{1/2}$) is calculated. In a multi-compartment model the late exponential phase of the kinetics is dominated by the excretion of the marker and the half clearance time $t_{1/2}$ can be calculated using the exponential representing this late phase.

In this study a novel pharmacokinetic model was developed describing the distribution and excretion kinetics of a renal marker using transcutaneously obtained data in rats.

Based on the classical two-compartment model (plasma and interstitial space) a three compartment model was introduced that adds the injection volume emptying exclusively and unidirectionally into the blood stream as extra compartment. This model covers the complete experimental course of the measurement including injection of the marker and subsequent mixing in the blood stream. It describes the entire kinetics from time of injection until the marker is almost completely excreted. The model was further improved by introducing a correction term that compensates for drifts of the baseline that may change fluorescence levels by processes unrelated to excretion such as photo-bleaching. A linear corrective term was added to the three-exponential fit function, that significantly reduced variability of $t_{1/2}$ estimates without changing its mean value.

The new model provided $t_{1/2}$ estimates that did not differ from the current standard approach: a comparison in n = 20 healthy awake male SD rats of the $t_{1/2}$ derived from the one-exponential approach ($t_{1/2,1e}$=22.67 ± 3.71 min) and the three-exponential approach ($t_{1/2,3e}$ = 22.60 ± 3.21 min) shows that the results are equal, both in mean values and standard deviation. However, there is an advantage in the use of the 3-e approach especially if the excretion is slow. Indeed, $t_{1/2}$ cannot be calculated from a 1-e model (as a finite value) based on 2 hour measurements when excretion is very slow, a characteristic feature of the late stage renal disease. In contrast, the novel model provides a three-exponential fit with a corrective term for baseline drift to determine $t_{1/2}$ using the complete concentration-time characteristic allowing determination of $t_{1/2}$ even if excretion is extremely slow.

Importantly, standard deviation of $t_{1/2}$ values calculated by the new model is significantly lower than the one obtained with the established methods. An investigation with n = 30 measurements in healthy awake male SD rats shows $t_{1/2}$ values of $t_{1/2,3e\text{-}lb}$ =22.37 ± 2.02 min compared to the one-exponential fit $t_{1/2,1e}$ =21.66 ± 3.38 min, the two-exponential fit $t_{1/2,2e}$ =25.52 ± 3.11 min and the three-exponential fit without baseline correction $t_{1/2,3e}$ =21.53 ± 3.21 min. The increased precision of this method reduces the number of experimental animals required to show a significant change of $t_{1/2}$ of 10% by a factor of more than 2.

In summary, in healthy rats the new three compartment model with a baseline correction term provides estimates of $t_{1/2}$ of increased precision over the standard approach at the same level of accuracy. The increased precision can be directly translated into a reduction of experimental animals required for a successful study of changes in $t_{1/2}$. Moreover, in contrast to the standard approach the new model allows determination of $t_{1/2}$ values even under the conditions of extremely delayed excretion that are of major clinical interest.