Title: Applied pharmacokinetics in preclinical research

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Abstract:

This thesis addresses the topic of development and practical utilization of rat models in preclinical pharmacokinetic studies. An analysis dealing with the impact of intra- and inter-individual variability on the results of animal comparative studies showed that cross-over design brings more accurate conclusions in these experiments than the often-used parallel setting. Results obtained on the basis of a parallel design significantly differed in our investigation (AUC_{last} ranged from 9.62 to 44.62 mg/ml.min.g). Furthermore, in 4 cases out of 15 pair comparisons of individual parallel groups, the confidence interval did not include the 100% value. That means that in more than a quarter of studies it would be misjudged that the compared drug formulations have different pharmacokinetic properties, though they are in fact the same product.

The practical use of cross-over design is demonstrated in pharmacokinetic studies comparing the absorption of various formulations with abiraterone and cinacalcet. In a fasted state, a new, innovated formulation with abiraterone was better absorbed than the reference (AUC_{last} of a reference 30.3 mg/ml.min.g, innovated formulation 81.0 mg/ml.min.g). Thiscorresponds to anticipations based on previous *in vitro* data. We also managed to develop a model for testing the influence of concomitantly consumed food on absorption, which has been tried out in these formulations. In accordance with information from literature, the reference product reached twice as high values of AUC_{last} with food than in a fasted state (80.7 mg/ml.min.g with food, 40.0 mg/ml.min.g in a fasted state). The concomitant application of abiraterone and cinacalcet with cycloheximide, an inhibitor of chylomicron secretion, in both cases lead to decreased absorption capacity in contrast to separate administration (AUC_{last} of abiraterone separately 12.3 vs. 5.5 ng.hod/ml with cycloheximide; AUC_{last} of cinacalcet separately 66.6 vs. 46.2 ng.hod/ml with cycloheximide).

Gastric pH of rats was also determined within the research. Rats have slightly higher gastric pH in a fasted state (3,5) compared to humans (1-2). However, the values can be modified either by the administration of pentagastrin, after which the pH in the stomach resembles human conditions, or omeprazole, resulting in the pH growing to values of people suffering from hypochlorhydria. These modulators of pH can be used in observation of the pharmacokinetics

of drugs with pH-dependent absorption, as it is shown in a practical example of a study with dasatinib.

The last part of the thesis concerns toxicokinetics, describing a model for the evaluation of post-mortem redistribution of alprazolam in rats. This is the first study detailing changes in concentrations of alprazolam in blood and selected tissues that can be seen after death. Plasma concentrations of the drug at all time points were higher than before death, whereas overall peaks were reached in adipose and liver tissue. Although the total amount of alprazolam in the lungs had not changed much, a rise in concentration was recorded in the liver, renal and heart tissues in the course of 24 hours. Despite the limits of this experiment, it can be expected that moderate post-mortem redistribution of alprazolam occurs in humans. That can have an impact on the interpretation of toxicological findings in the investigation of deaths related to the use of alprazolam.