Clinical Significance of Pharmacokinetic Evaluation

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Pharmacokinetic(PK) studies are extensively performed in both pre-clinical and clinical phase during drug development. In the pre-clinical PK studies, various experimental animals such as rats, and dogs are used to obtain information that can feedback into the drug design process, and to aid interpretation of efficacy and toxicity studies. In the clinical PK studies, normal volunteers are first enrolled to determine the tolerability and acute toxicity of the drug as a function of plasma concentration, to characterize the PK after single and multiple doses as a function of dose size, and to assess the suitability of the animal models used in toxicology studies with respect to comparability of exposure to the drug and its mebabolites. To determine PK parameters of the drug, compartmental, clearance, and other non-compartmental models are employed. The PK parameters clinically obtained include peak and trough concentrations, half-life, volumes of distribution, area under the concentration-time curve(AUC), and systemic(CLs) and renal clearances(CLr). Each parameter has its own clinical implications. For instance, AUC is often used to compare systemic exposure in toxicology species and humans. AUC values at the mouse LD_{10} and the human MTD are reported to be well correlated for some anticancer drugs. Thus, "pharmacologically guided dose escalation" (PGDE) strategies have been developed to expedite the conduct of early clinical trials. In addition, estimation of the AUC-to-dose ratio provides information on non-linearity of the drug over the therapeutic range. The CLr-to-CLs ratio is also clinically important to assess the major elimination pathway.