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PHARMACOKINETICS OF TOLVAPTAN, A POTENT, SELECTIVE, NONPEPTIDE VASOPRESSIN V2 RECEPTOR ANTAGONIST, IN RATS AND DOGS
Ken Umehara, Masayuki Furukawa, Noriuyki Koyama, Tadaaki Ohtani, Minoru Uchida and Eiji Kashiyama
Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., 463-10 Kagasuno, Kawauchi-cho, Tokushima 771-0192, Japan

Tolvaptan is an orally administered nonpeptide vasopressin V2 receptor antagonist under development for the treatment of hyponatremia and congestive heart failure. Pharmacokinetics of tolvaptan was conducted using non-labeled and 14C-labeled tolvaptan (14C-tolvaptan) in Sprague-Dawley rats and beagle dogs. Following the oral administration of tolvaptan to fasted rats and dogs, the drug was rapidly absorbed and the serum concentrations of the compound increased with increasing dose in both animal species. The tissue distribution of radioactivity in rats was high in the liver, digestive tracts, adrenals and kidney. The number of tissues that contained higher concentrations of radioactivity than that in the serum was greater in the female rats than in the male rats. The in vitro plasma protein binding of tolvaptan was 97.2% or more in mouse, rat, rabbit and dog and human, with albumin and α1-acid glycoprotein contributing to the binding profile. The cumulative recovery rates of radioactivity in feces and urine after the single oral administration of 14C-tolvaptan to rats and dogs were essentially 100%. Tolvaptan is eliminated principally by metabolism in rats and dogs, and several metabolites have been structurally identified. Monohydroxylation, oxidation and oxidative cleavage of the benzazepine ring were principal metabolic reactions, and chiral inversion and hydrolysis were also observed. The metabolism of tolvaptan was investigated using rat liver preparations to elucidate various metabolic pathways of tolvaptan to the degraded products.

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EVALUATION OF CHANGE IN DISPOSITION OF PHENOLSULFONPHTHALEIN AND INDOCYANINE GREEN AS MODEL COMPOUNDS AT LOW TEMPERATURES IN RAT LIVER PERFUSION SYSTEM
Hirotaka Miyamoto, Hideaki Miyake, Shintaro Fumoto, Mikiro Nakashima, Hitoshi Sasaki, Junzo Nakamura, and Koyo Nishida
Graduate School of Biomedical Sciences, Nagasaki University; 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

We have obtained basic information concerning the pharmacokinetics of model compounds with different elimination processes during hypothermic conditions (32°C and 28°C) in rats in vivo (Biol. Pharm. Bull. 30, 1763, 2007). In this study, we compared the disposition of phenolsulfonphthalein (PSP) and indocyanine green (ICG) as model compounds among the different temperatures in the rat liver perfusion system, aiming to determine the individual step of change in detail in hepatic clearance pathways during hypothermia therapy. The liver of male Wistar rats was perfused at 37°C, 32°C or 28°C by single-pass mode according to the method of Nishida et al (Pharm. Res. 6, 140, 1989) with slight modification. The outflow and biliary excretion profile were analyzed. After bolus injection, the extraction ratio (E) of PSP was significantly decreased at 32°C and 28°C compared to 37°C, suggesting an influence of hypothermia on the active hepatic uptake process. Different from PSP, ICG was almost extracted by single-pass even in the hypothermic group due to high hepatic clearance of ICG. With respect to biliary excretion, PSP and its metabolite excretion were decreased by low temperature. The decreasing tendency was marked in case of ICG. Moreover, to consider the steady-state condition, we performed the rat liver perfusion with constant infusion mode at a concentration of plasma beta phase. The E of PSP and ICG at steady-state were about 20 and 100 %, respectively, in each perfusion temperature. However, biliary excretion rates of PSP and ICG were considerably decreased. Accordingly, the change in hepatic disposition of a drug in the hypothermic group could differ with the disposition processes.