Influence of dose and body temperature on change in pharmacokinetics of model compounds under hypothermia

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Since therapeutic hypothermia is expected to provide neuroprotection for severe brain injury, pharmacokinetic changes under hypothermia should be evaluated for appropriate dosing regimen. As a series of investigation, we examined influence of dose and body temperature on change in pharmacokinetics of drugs under hypothermia, by employing phenolsulfonphthalein (PSP) and indocyanine green (ICG) as models eliminated via active transport. Male Wistar rats were anesthetized with pentobarbital, and their body temperatures were maintained at 28 and 32°C by ice pack and 37°C by heat lamp. PSP (0.5, 1, 2 mg) or ICG (0.2, 1, 2 mg) was injected into the jugular vein, followed by collection of blood, bile and urine. In the moderate hypothermic rats (28°C), elimination of PSP was retarded at all doses, and its metabolic clearance was decreased at the highest dose of 2 mg. Under mild hypothermia (32°C), whereas change in PSP pharmacokinetics was not recognized at a dose of 0.5 mg, each clearance (bile, urine and metabolite) was decreased at doses of 1 and 2 mg. Thus dose-dependent change in PSP pharmacokinetics under hypothermia might be related to alteration in saturation range of energy-dependent process such as metabolism and tubular secretion. On the other hand, the biliary clearance of ICG at a dose of 1 mg was reduced to about 50% and 8% at 32 and 28°C, respectively, compared to 37°C. A similar tendency was observed at another ICG doses. Accordingly, the determinant factor of change in clearance should be blood flow during hypothermia, for a drug such as ICG with a high extraction ratio.