Pharmacokinetics of Hippurate in Uremic Rats
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Hippurate (HA) is a harmful uremic toxin, which accumulates to a high degree in uremic plasma. The accumulation of this toxin in serum is the source of a number of pathological effects. The functional failure of the excretion system for uremic toxins causes its accumulation in blood. We recently reported that organic anion transporter 1 mainly accounts for HA uptake in the kidney. To begin developing an understanding of the pharmacologic action of HA, we conducted a pharmacokinetic investigation using uremic rats. The pharmacokinetics of hippurate was examined following a single i.v. administration to normal and 5/6 nephrectomized rats (CRF rats). In control rats, the renal and biliary clearances for HA were determined to be 15.2 and 0.1 ml/min/kg, respectively. The majority of HA was excreted in an unaltered state and the main route was via the urine. The dose dependency of the HA pharmacokinetic parameters after iv. administration was also examined. Plasma clearance decreased with increasing dosage from 0.1 to 5 mg/kg, suggesting that renal tubular secretion is responsible for the elimination of HA. The renal clearance of HA was comparable to that of p-aminohippurate (PAH) in normal rats, suggesting that excretion rate of HA is determined by renal plasma flow rate as well as PAH. The plasma clearance of HA was significantly decreased in CRF rats. The biological half life was more prolonged in CRF rats (61 min) than in control rats (28 min). Furthermore, the renal clearance of HA was more highly correlated with PAH clearance than creatinine clearance in CRF rats. In conclusion, HA is primarily eliminated from the plasma via the kidney by active tubular secretion, and the renal clearance of HA may be relevant factor for renal function in chronic renal failure.