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### Estimation of Absorption Rate of $\alpha$ -Human Atrial Natriuretic Peptide from the Plasma Profile and Diuretic Effect after Intranasal Administration to Rats

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The absorption rate of  $\alpha$ -human atrial natriuretic peptide ( $\alpha$ -hANP) after intranasal (i.n.) administration to rats was estimated from the plasma profiles and pharmacological effect (diuretic effect) using a pharmacokinetic (PK) model and a pharmacodynamic (PD) model involving data obtained after intravenous (i.v.) bolus injection. The plasma concentration of  $\alpha$ -hANP after i.v. administration at different doses were fitted to a two-compartment PK model with zero-order excretion and input of endogenous  $\alpha$ -rat atrial natriuretic peptide ( $\alpha$ -rANP) and two elimination processes represented by Michaelis-Menten and first-order kinetics. However, the saturable process was ignored at low doses. The plasma concentrations after low doses via the i.n. route could also be expressed by this model, but with first-order absorption, so that an absorption rate constant was calculated using a deconvolution method. In addition, the diuretic effect plotted against the i.v. dose was represented by the Hill equation and showed an anti-clockwise hysteresis loop versus the plasma concentration. These results suggested that the diuretic effect could be estimated by a PK-PD model having an 'effect' compartment or a homeostatic system. Such a PK-PD model accurately expressed the diuretic effect of  $\alpha$ -hANP at all doses after i.v. and i.n. administrations. The resulting absorption rate constant calculated using the PK-PD model agreed closely with that obtained by the PK model alone. The absorption rate simulated diuretic effect suggested that, for i.n. administration of  $\alpha$ -hANP, a higher absorption rate constant causes a more potent diuretic effect (a dramatic effect over the early period), whereas greater bioavailability is associated with a better hypotensive effect (sustained effect).