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Pharmacokinetic and pharmacodynamic evaluations of a potent analgesic dihydroetorphine in hairless rat

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To evaluate the pharmacokinetic and pharmacodynamic characteristics of a novel opioid analgesic, dihydroetorphine (DHE), concentrations of DHE and itsglucronide (DG) in plasma and central nervous system (by liquid chlomatography-tandem mass spectrometry) and the antinociceptive effect (by tai-immersion test) were measured after intravevous (i.v., 2 μg/kg), intracutaneous (i.c., 2 μg/kg), subcutaneous (s.c., 2 μg/kg), intraperitoneal (i.p., 10 μg/kg), and oral (p.o., 200 μg/kg) administrations in hairless rats. An elimination half-life of plasma DHE concentration was 37.2 min after i.v. injection. Brain DHE concentration reached a maximum within 6 min after i.v. injection, and the concentration ratio in brain to plasma was 5.17. Relative bioavailabilities of DHE to i.v. injention (100%) were 70.8, 79.8, 16.7, and 0.37% after i.c., s.c., i.p., and p.o. administrations, respectively. Area under the plasma concentration-time curve ratios of plasma DG to DHE concentrations after i.v., i.c., s.c., i.p., and p.o. were 1.76, 3.26, 4.74, 14.5, and 290, respectively. Antinociceptive effects appeared rapidly after i.v., i.c., s.c., administrations but were diminished after i.p. and p.o. administrations, and these effects were closely related to the brain DHE concentrations. DHE was excreted mainly as DG in bile (89.5% of the dose) by 240 min after i.v. injection. Serum protein binding of DHE was 83.4%, which was not influenced by DG. Glucronidation of DHE was detected in the liver, intestine, and kidney in vitro but was minimal in the skin and brain. In conclusion, DHE was rapidly distributed to the brain in relation to producing the antinociceptive effect, and then it was rapidly metabolized to the pharmacologically inactive DG.