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Transdermal Delivery of the Potent Analgesic Dihydroetorphine: Kinetic Analysis of Skin Permeation and Analgesic Effect in the Hairless Rat

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Dihydroetorphine is an extraordinarily strong opioid analgesic. To assess its effectiveness after topical application in hairless rats we have examined the kinetic analysis of skin permeation through excised skin and the in-vitro reservoir effect of skin, and have investigated the predictability of plasma concentration and analgesic effect following in-vivo transdermal application.

Dihydroetorphine was moderately permeable from an aqueous suspension through excised hairless rat skin. Dihydroetorphine flux from drug-dispersed pressure-sensitive adhesive tape was threefold that from the applied aqueous suspension. The fluxes through the abdominal and the dorsal skin during tape application fitted the Fickian diffusion equation well after the tape was removed peeling off the outer layer of the stratum corneum. The relationship between the plasma concentration and the analgesic effect was examined for four different rates of infusion of dihydroetorphine. A non-linear pharmacokinetic disposition was observed. Following abdominal (0.28 cm^2, 20 μg) and dorsal (0.50 cm^2, 35 μg) applications of the dihydroetorphine tape, plasma concentration (0.2-0.8 ng mL^{-1}) and analgesic effect were maintained at a suitable level, for more than 8 h, until

removal of the tape. These profiles were predictable using the combined equation for percutaneous absorption, disposition and the analgesic effect, but the analgesic effect was slightly lower than the predicted value.

The results show that it was possible to control the plasma concentration and the analgesic effect of dihydroetorphine by topical application of the analgesic using pressure-sensitive adhesive tape in the hairless rat. It was possible to predict the result using mathematical modeling.