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**Tolerance to analgesia dependence liability by topical application of dihydroetorphine to hairless rats**

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The tolerance analgesia and dependence liability of dihydroetorphine following topical application were investigated in hairless rats with and without formalin-induced inflammation. The analgesic effect of dihydroetorphine (s.c.) was 4600-to 7200-fold more potent than that of morphine. In non-inflamed rats, the analgesic effect of 24-h topical application of dihydroetorphine tape (35  $\mu$ g) and 4-day repeated tape applications (20  $\mu$ g/5h/day) decreased with time after the start of application, even though the plasma dihydroetorphine concentrations did not decrease. In formalin-inflamed rats, however, the tolerance to analgesia diminished. Naloxone-precipitated weight loss was observed after 24-h infusion of dihydroetorphine but not after the tape application in non-inflamed rats. A significant rewarding effect was found in the non-inflamed rats conditioned by s.c. injection and tape application but not in the formaline-inflamed rats. These results indicate that topical application of dihydroetorphine has a tolerance and dependence liability when there is no pain, and therefore, it should be used only for pain relief.