Title: STUDIES ON THE EFFECTS OF INTRATHECAL SUFENTANIL, FENTANYL AND ALFENTANIL IN RATS AND CATS

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Introduction. The spinal administration of opiates will produce a powerful modulation of the rostral processing of nociceptive information which occurs in the absence of significant effects on spinal autonomic, or motor systems. The complex pharmacology of intrathecal (IT) drug action suggests that the effects on spinal function are mediated by several of the recognized subpopulations of opioid receptors, notably the mu, delta[1] and kappa receptors. We sought to examine the properties and pharmacology of IT sufentanil and alfentanil in rats and cats, and to determine if these agents produce any pathologic effects on spinal cord tissue.

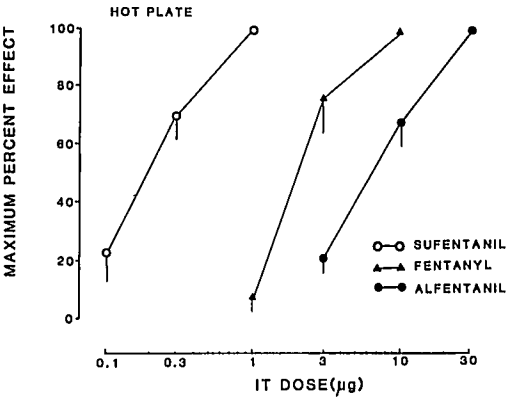
Methods. Rats and cats were implanted with IT catheters and tested 5-7 days following recovery. The nociceptive tests used were the thermally evoked skin twitch in the cat and the hot plate (HP), tail flick (TF) and writhing tests in the rat. Volumes of 10 and 200 µl saline were used as the vehicles for spinal drug injections in the rats and cats respectively. The following experiments were carried out: 1) Time effect curves were established on HP and TF of IT sufentanil, alfentanil and fentanyl in rats. 2) Time effect curves of skin twitch block were established for IT sufentanil and alfentanil in the cat. 3) Dose response curves in the rat were determined on the HP and TF of sufentanil (0.1-1 µg), fentanyl (0.3-3 µg) and alfentanil (3-30 µg) administered intrathecally. 4) Dose responses on the visceral chemical evoked writhing response of IT sufentanil and alfentanil were determined in the rat. 5) To determine sensitivity to naloxone, rats were pretreated with naloxone subcutaneously with doses 0.1, 0.3 or 1 mg/kg in each experiment and then received either the ED_{100} of sufentanil (1 µg) and alfentanil (30 µg) intrathecally. Modified dose ratio plots were determined to estimate the pA_2 values of naloxone to antagonize the antinociceptive effects of both opioid agonists on the HP and TF. 6) To examine the effects on spinal cord tissue, cats were assigned to one of five groups: group I received daily IT injections of the ED_{100} of sufentanil (30 µg) for 5 days, group II received daily IT injections of the ED_{100} of alfentanil (300 µg) for 5 days. Group III received a single bolus IT injection 10 times the ED_{100} of sufentanil (300 µg). Group IV received a single bolus IT injection 10 times the ED_{100} of alfentanil (3000 µg) and group V received daily IT injections of saline for 5 days and served as controls. Response latencies are expressed as the maximum percent effect (MPE) where:

$$MPE = \frac{\text{postdrug latency} - \text{predrug latency}}{\text{cutoff time} - \text{predrug latency}} \times 100$$

where cutoff is 6 and 60 sec on the TF and HP respectively. Two-way ANOVA and Student's t-test were used. $P<0.05$ was considered statistically significant. Dose response curves were analyzed using linear regression. Confidence intervals for the ED_{50} values and slopes are estimated using a least squares analysis.

Results. 1) In the rat IT sufentanil 1 µg and alfentanil 30 µg produced a maximal elevation in the HP and TF latencies at the shortest time examined 3 min; by 30 min the measured response was not statistically different from baseline. Dose response curves on the HP shown in Fig. 1 were not different in parallelity. Similar monotonic dose response curves were also obtained on the TF. 2) In the cat IT sufentanil and alfentanil produced a monotonic dose dependent blockade with the maximum effect achieved with 30 and 300 µg, respectively. At this dose either agent produced a complete block of skin twitch by 3 min and this block lasted for about 10 min. According to these observations sufentanil is 30 times more potent than alfentanil on thermal nociceptive tests. 3) IT sufentanil and alfentanil produced a powerful suppression of the writhing response. Writhing scores during the first 20 min were significantly less in the treated rats than in a comparable saline group, and there was no significant differences in the last 20 min. 4) Systemic naloxone resulted in a monotonic log linear reversal of the antinociceptive intrathecal alfentanil and sufentanil and the apparent pA_2 values on the HP and TF were not different and ranged from 6.44-7.03. 6) Aside from inflammatory reactions seen secondary to catheter placement no other pathology was noted.

Discussion. We have herein provided in vivo evidence for the mu receptor activity of sufentanil and alfentanil (block of the nociceptive responses, monotonic agonist dose response curves and pA_2 values similar to the prototypical mu agonist morphine). In addition, sufentanil and alfentanil exert their effect in the absence of any pathological effect even when administered directly onto spinal tissue. (Supported by funds from Janssen Pharm. and DA0210 to TLY and TW03188 to RN.)



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