BEHAVIORAL EFFECTS OF FENTANYL DERIVATIVES IN RHESUS MONKEYS

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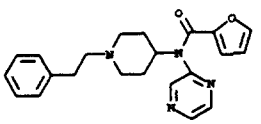
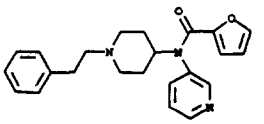
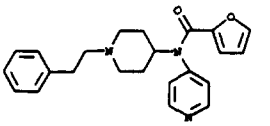
Four fentanyl derivatives (ANQ 3295, ANQ 3296, ANQ 3326 and ANQ 3463), similar in structure to the novel opioid mirfentanil (1,2,3), were examined in rhesus monkeys for their discriminative stimulus, analgesic and positive reinforcing effects. Under some conditions all of the fentanyl derivatives had opioid agonist actions whereas under other conditions some of the compounds had opioid agonist actions while others had opioid antagonist actions. Collectively, data from several assays are consistent with the view that these compounds vary with regard to efficacy at *mu* opioid receptors. Moreover, the compounds that appeared to have low opioid efficacy had analgesic effects that were not attenuated by opioid antagonists and that were not associated with decreases in respiratory function.



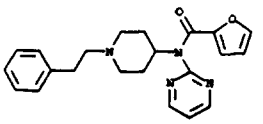
MIRFENTANIL



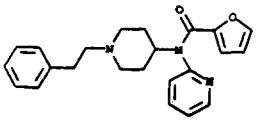
ANQ 3295



ANQ 3295



ANQ 3326



ANQ 3463

The procedures used to assess discriminative stimulus effects, analgesic effects and positive reinforcing effects have been described elsewhere (3,4,5). For studies on positive reinforcing effects, rhesus monkeys were prepared with chronic, indwelling i.v. catheters. During twice daily sessions monkeys could receive injections of various doses of alfentanil, one of the four fentanyl derivatives, or saline. During drug tests, a different dose was available in each of the four, discrete components comprising a session. Each fentanyl derivative was studied alone and in the presence of the opioid antagonist quadazocine. In drug discrimination studies separate groups of monkeys discriminated between saline and either nalbuphine (0.178 mg/kg) or naltrexone (0.032 mg/kg) while responding under a fixed-ratio schedule of stimulus-shock termination. Monkeys that discriminated between naltrexone and saline also received daily injections of 3.2 mg/kg of morphine 3 hours prior to daily sessions. Compounds were assessed for their ability to substitute for nalbuphine or naltrexone and to reverse naltrexone-lever responding in monkeys acutely deprived of morphine. In studies on analgesic effects, the lower 8-10 cm of the shaved tail was immersed in a thermos containing warm (50 or 55° C.) water and the time for monkeys to remove the tail from the thermos was recorded.

Table 1 summarizes some of the results obtained with ANQ 3295, ANQ 3296, ANQ 3326, ANQ 3463 as well as fentanyl and two other fentanyl derivatives [compound 28, ANQ 3568 (4); mirfentanil (1,2,3)]. All of the compounds maintained self administration responding under a fixed-ratio schedule; for three compounds the maximum averaged rate of lever pressing was lower (ANQ 3326 = 1.17±0.09, ANQ 3295 = 1.19±0.26, ANQ 3296 = 1.24±0.12) than rates of lever pressing for ANQ 3463 (1.87±0.74) or alfentanil (2.00±0.22). Positive reinforcing effects of each compound were antagonized by 0.1 mg/kg quadazocine; however, unlike the parallel rightward shift in the alfentanil dose-effect curve observed after pretreatment with quadazocine, lever pressing for each of the fentanyl derivatives was abolished by quadazocine.

ANQ 3295 substituted for nalbuphine (*mu* agonist action) and also substituted for naltrexone (*mu* antagonist action). In contrast, ANQ 3463 did not substitute for naltrexone, but reversed naltrexone-lever responding in morphine deprived monkeys (*mu* agonist action). Like fentanyl and ANQ 3568, ANQ 3463 decreased respiratory frequency and its analgesic effects were antagonized by naltrexone. Like mirfentanil, ANQ 3295 did not decrease respiratory frequency and its analgesic effects were not antagonized by naltrexone. Analgesic effects of ANQ 3296 and ANQ 3326 were antagonized by quadazocine although the magnitude of antagonism was less than observed with other compounds (e.g., ANQ 3463). Thus, ANQ 3463 appears to be a high efficacy *mu* opioid whereas ANQ 3295 appears to be a low efficacy *mu* opioid with non-opioid analgesic effects; the opioid effects of ANQ 3296 and ANQ 3326 appear to be intermediate to those of ANQ 3295 and ANQ 3463 and the analgesic effects of these compounds appear to involve both opioid and non-opioid mechanisms.

COMPOUND	S/A[1]	NTX/DISCRIMINATION[2]	RESPIRATION[3]	ANALGESIA[4]
fentanyl	yes	agonist	decrease	opioid
ANQ 3568	yes	agonist	decrease	opioid
ANQ 3463	yes	agonist	decrease	opioid
ANQ 3326	yes	partial agonist	no effect	opioid/non-opioid
ANQ 3296	yes	no effect	no effect	opioid/non-opioid
ANQ 3295	yes	antagonist	no effect	non-opioid
mirfentanil	yes	antagonist	no effect	non-opioid

[1]Self administered. [2]Effect in naltrexone discrimination assay. [3]Effect on respiratory frequency. [4] Antagonism of analgesic effects by naltrexone.

Although the mechanism of analgesic action is not yet established for mirfentanil or ANQ 3295, these compounds might provide a novel approach to the treatment of pain, especially under conditions where the respiratory depressant effects of morphine-like opioids is contraindicated. Second, these results demonstrate that several compounds in this series vary markedly in opioid efficacy. Finally, these studies reinforce the utility of hypothesis testing based on receptor theory, especially as that theory applies to behavioral effects of drugs.

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