Evaluation of remifentanil and morphine as reference reinforcers in a rat intravenous self-administration procedure

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AIMS

Intravenous self-administration (IVSA) in rats is an established test to predict whether CNS active compounds have potential abuse liability in humans. We have reported that the relative reinforcing effect of stimulants can be determined by comparing their break-points after progressive ratio testing (Heal et al, 2014, CPDD Meeting, Abst 89). In this study, we investigated morphine and remifentanil to see whether this approach can be extended to assessing the relative reinforcing effects of sedative euphoriant.

METHODS

Adult, male, Sprague-Dawley rats (Charles River, UK) were mildly food-deprived and trained to lever-press for food rewards on a fixed ratio 2 (FR2) response requirement. When the rats had learned to lever-press consistently for food, they were switched to self administer morphine (75 µg/kg/injection, iv) on FR2 schedule of reinforcement. After saline extinction, morphine (7.5, 22.5, 75, and 225 µg/kg/inj) and remifentanil (0.1, 1.0, 3.0 and 10 µg/kg/inj) were evaluated. All drugs were dosed as free base. When self-administration was stable in each rat, where a dose of morphine or remifentanil served as a positive reinforcer (mean >5 infusions/session in last 3 consecutive tests), the break-point for operant responding was determined using an ascending progressive ratio (PR) schedule of reinforcement in 4.0hr sessions (Richardson & Roberts, 1996). In the statistical analysis, a break-point of 4 lever-presses was assigned to any dose of drug, ie morphine or remifentanil, that did not serve as a positive reinforcer in an individual rat. The scientific rationale for this decision was that all rats took >1 infusion of the opioid agonists on the FR2 schedule of drug reinforcement and 4 lever-presses was the break-point immediately above 2 in the PR schedule.

RESULTS

- The chemical structures of the potent µ-opioid receptor agonists, morphine and remifentanil are shown in Figure 1.
- Four doses of remifentanil (0.1, 1.0, 3.0 and 10 µg/kg/inj) and 2 doses of morphine (25 and 75 µg/kg/inj) served as positive reinforcers by maintaining >8.0 infusions/session and at a level significantly greater than saline (Figure 2). The total infusions of remifentanil (3.0 µg/kg/inj) taken were significantly (P<0.001) greater than all doses of morphine.
- The break-point of operant responding for remifentanil (3.0 µg/kg/inj [n = 9]) was significantly greater than the break-points for all doses of morphine including the most reinforcing dose of morphine (75 µg/kg/inj [n = 10]) (Figure 3).
- A survival analysis of operant responding for remifentanil (3.0 µg/kg/inj [n = 9]) compared with the most reinforcing dose of morphine (75 µg/kg/inj [n = 10]) is shown in Figure 4.
- A comparison with our previous results revealed that the break-point of remifentanil (3.0 µg/kg/inj) was not significantly different from the most reinforcing doses of cocaine (0.29 µg/kg/inj [n = 7]) or methylphenidate (0.1 µg/kg/inj), but the break-point for morphine (75 µg/kg/inj) was significantly lower than all 3 other drugs (Figure 5).

CONCLUSIONS

Various doses of remifentanil and morphine served as positive reinforcers in a rat IVSA model. However, as indicated by the break-point analysis, the relative reinforcing effect of morphine was lower than remifentanil, methylphenidate or cocaine. Thus, remifentanil is a better opioid reference comparator than morphine for use in rat IVSA tests.

REFERENCES