Comparison Of The Relative Reinforcing Efficacy of Heroin, Morphine And Remifentanil Using Fixed And Progressive Ratio Schedules Of Reinforcement In Rat Self-Administration

GE Oakley, SC Cheetham, DJ Heal, SL Smith

Aims
Self-administration models enable sensitive and reliable detection of reinforcing drugs (eg Mead, 2014). Intravenous self-administration is commonly used for rapid drug delivery to the central nervous system (CNS) to mimic methods of drug abuse. Morphine, diamorphine (heroin) and remifentanil are clinically used for severe pain relief. The chemical structures are shown in Fig. 1. They are commonly abused, CNS-acting opioids and are Schedules II Controlled Drugs (C-II). We have previously reported that remifentanil is a more powerful positive reinforcer than morphine in rat intravenous self-administration using fixed ratio 2 (FR2) and ascending progressive ratio (PR) testing (Heal et al., 2015). This study investigated the reinforcing effect of morphine, heroin and remifentanil on FR2 schedule and evaluated their relative reinforcing effect using PR schedule.

Methods
Adult, male Sprague Dawley rats (Charles River, UK) were mildly food restricted and trained to press levers on a FR2 schedule for food rewards in a specialised self-administration box (Fig. 2). Once responding was stable, animals were implanted with a jugular vein catheter. After recovery, a dose-response test for heroin (0.0005, 0.0025, 0.01, 0.025, 0.05 mg/kg/inj; n=3-13), remifentanil (0.0001, 0.001, 0.003, 0.01, 0.015 mg/kg/inj; n=4-21) or morphine (0.0075, 0.0225, 0.075, 0.225 mg/kg/inj; n=7-10) was conducted on FR2 schedule. After morphine testing, saline extinction was performed. When responding was stable (number of injections (inj) did not vary >20% over previous 3 sessions; Heal et al., 2013) and where each drug dose was positively reinforcing (mean >8 inj/session for last 3 sessions), a 4 hr PR schedule was used to determine break-point of operant responding. For statistical analysis, a break-point of 4 lever presses was assigned to any drug dose that was not reinforcing in an individual rat.

Results
• On FR2 schedule (Fig. 3), morphine served as a positive reinforcer at doses of 0.0075, 0.0225 and 0.075 mg/kg/inj, remifentanil at 0.0001, 0.001, 0.003, 0.01, 0.015 mg/kg/inj and heroin at 0.0005, 0.0025, 0.01 and 0.025 mg/kg/inj.
• Saline did not serve as a positive reinforcer on FR2 schedule (Fig. 3).
• On PR schedule, break-points for the most reinforcing doses of heroin (0.025 mg/kg/inj) and remifentanil (0.015 mg/kg/inj) were not significantly different (Table 1).
• PR break-points of operant responding (Fig. 4) for both heroin (0.01, 0.025, 0.05 mg/kg/inj) and remifentanil (0.0001, 0.003, 0.01, 0.015 mg/kg/inj) were significantly greater (P<0.05; 0.001) than the most reinforcing dose of morphine (0.075 mg/kg/inj).
• A survival analysis of operant responding on PR testing for the most reinforcing doses of remifentanil (0.015 mg/kg/inj) and heroin (0.025 mg/kg/inj) compared with the most reinforcing dose of morphine (0.075 mg/kg/inj) is shown in Fig. 5.

Conclusions
• On a FR2 schedule, all three drugs were positively reinforcing, reflecting their known profiles as sedative, euphoriant reinforcers in humans.
• Using an ascending PR schedule, the relative reinforcing effects of heroin and remifentanil were comparable. However, both were more powerful reinforcers than morphine.
• The weak reinforcing effect of morphine does not fit well with its C-II status.
• Heroin and morphine would, therefore, be better opioid reference comparators than morphine for use in rat intravenous self-administration tests.

References
Heal D.J. et al. (2013). Neuropharmacol. 73, 348-358.
Heal D.J. et al. (2015). Abstract No. 286, CPDD, Phoenix, USA.