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Comparison of the Relative Reinforcing Effects of Heroin, Remifentanil and Morphine using Fixed and Progressive Ratio Schedules of Reinforcement in Rat IntravenousSelf-Administration

Intravenous self-administration models are commonly used for rapid drug delivery to the CNS to mimic drug abuse. Diamorphine (heroin), remifentanil and morphine are opioids used clinically for severe pain relief, but are Schedule II Controlled Drugs (C-II) as they have high abuse liability. This study compared the reinforcing effect of the three drugs in a rat intravenous self-administration test using a fixed ratio 2 (FR2) schedule of reinforcement. Their relative reinforcing effect was evaluated using a progressive ratio (PR) schedule of reinforcement where animals press operant levers on an ascending scale within sessions to receive drug rewards.

This study was conducted according to the Animals (Scientific Procedures) Act 1986 / ASPA Amendment Regulations 2012.Adult, male Sprague Dawley rats ~~were~~(175-200g; Charles River, UK) were mildly food restricted and trained to press levers for food rewards on FR2 schedule. 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 by >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.

On a FR2 schedule, morphine served as a positive reinforcer at doses of 0.0075, 0.0225 and 0.075 mg/kg/inj [maximum 12.0 ± 1.4 inj/session at 0.075 mg/kg/inj, n = 10], remifentanil at 0.0001, 0.001, 0.003, 0.01, 0.015 mg/kg/inj(maximum 20.0 ± 0.0 inj/session at 0.01 mg/kg/inj; n = 8) and heroin at 0.0005, 0.0025, 0.01 and 0.025 mg/kg/inj(maximum 18.7 ± 0.8 inj/session at 0.0025 mg/kg/inj; n = 5). Saline did not serve as a positive reinforcer(5.8 ± 0.4 inj/session; n = 18). On PR schedule, break-points for the most reinforcing doses of heroin (0.025 mg/kg/inj = 61.8± 17.7; n = 8) and remifentanil (0.015 mg/kg/inj = 48.1 ± 18.2; n = 5) were not significantly different. PR break-points of operant responding 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 = 11.6 ± 2.1; n = 10).

When tested on FR2 schedule, all three drugs served as positive reinforcers in the test reflecting their known profiles as sedative, euphoriantreinforcers 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. In summary, heroin and remifentanil are better opioid reference comparators than morphine for use in rat intravenous self-administration tests.

References

Heal D.J., et al., 2013, Neuropharmacology, 73: 348-358.