Investigation of the possible reinforcing effects of samidorphan and naltrexone by fixed and progressive ratio intravenous self-administration testing in rats

David J Heal ¹, Sharon L Smith ¹, Reginald L Dean ² and Mark S Todtenkopf ²

¹ Renasci Ltd, BioCity, Nottingham NG1 1GF, UK. ² Alkermes, Inc, Waltham, MA 02451, USA.

Invited guest of Prof J Henningfield

BACKGROUND

Samidorphan (SAM) is a µ-opioid receptor antagonist. SAM is being developed in combination with buprenorphine as an adjunct treatment for major depressive disorder (ALKS 5461) and in combination with olanzapine for the treatment of schizophrenia (ALKS 3831).

We investigated whether SAM or naltrexone (NTX; another opioid receptor antagonist) served as positive reinforcers in rats trained to self-administer a low dose of a Schedule 1 (C-I) opiate, heroin, using a fixed ratio (FR) schedule of reinforcement. We also evaluated their relative motivational properties using a progressive ratio (PR) schedule to determine break-points and compared them to heroin.

The use of FR schedules of reinforcement to assess the abuse potential of novel CNS-active drugs is recommended by the FDA (FDA Guidance, 2017). The use of PR/break-point determinations to assess the relative reinforcing effects of novel CNS-active drugs is recommended in the EMA guidelines on assessing the abuse potential of novel drugs for human use (GHMP/EMA, 2006).

METHOD

Male Sprague Dawley rats (200-225 g; Charles River, UK) were mildly food restricted and trained to lever press for food rewards. Once responding was stable, rats were implanted with a jugular vein catheter. Rats were trained to self-administer heroin (15 µg/kg/injection [inj]), followed by saline extinction, before being divided into 3 groups for further testing: a) doses of heroin (7.5 and 25 µg/kg/inj), b) dose response for SAM (13.6, 40.8 and 68 µg/kg/inj) and c) dose response for NTX (13.6, 40.8 and 68 µg/kg/inj).

Training and testing were on a fixed ratio-5 (FR5) schedule in 2 hr sessions. When stable self-administration was observed over 3 consecutive sessions (inj/session) did not vary by ≥25%, or ≤50% in-session for non-reinforcement), the break-point for operant responding was determined in a 4 hr PR session.

Data were analysed parametrically after angular transformation, with each test compound compared to saline and heroin by separate Dunnett’s tests. Results are reported as mean ± SEM for ≥7 rats/group.

RESULTS

- On FR5, heroin maintained self-administration at levels significantly (p<0.001) greater than saline at all doses (Figure 1).
- SAM did not serve as a positive reinforcer on FR5 at 13.6 or 40.8 µg/kg/inj, but the number of injections per session of SAM (68 µg/kg/inj) was significantly (p<0.01) greater than saline (9.2 ± 2.1 vs 4.3 ± 0.2 inj/session) (Figure 1).
- NTX did not serve as a positive reinforcer on FR5 at any dose. However, self-administration of NTX (13.6 µg/kg/inj) almost reached statistical significance (p = 0.053) versus saline (8.1 ± 2.3 vs 4.3 ± 0.2 inj/session) (Figure 1).
- On PR, the break-points for self-administration of heroin were all significantly (p<0.001) greater than saline (Figure 2).
- The break-points of all doses of SAM and NTX were significantly (p<0.001) lower than those of all doses of heroin (Figure 2).
- None of the break-points for SAM and NTX with the exception of SAM (68 µg/kg/inj) were significantly different from saline (17.9 ± 3.3 vs 10.4 ± 0.8 lever presses/injection) (Figure 2).
- The break-points for SAM were not significantly different from those of NTX (Figure 2).

CONCLUSIONS

- SAM and NTX gave weak and equivocal signals, respectively, as positive reinforcers at a single dose in heroin-maintained rats.
- All of the break-points for SAM and NTX were significantly lower than those for heroin. Only a single dose of SAM differed from saline on relative reinforcing efficacy. The relative reinforcing effects of SAM and NTX were not different from one another.
- Based on the results of this head-to-head comparison results, it can be concluded that the rewarding properties of SAM and NTX are virtually identical. If these results translate to man they predict that SAM poses a minimal risk for recreational abuse.

REFERENCES


FUNDING STATEMENT

CONFLICTS OF INTEREST

This research carried out by RenaSci Ltd and was funded by Alkermes, Inc.

David Heal is an employee and shareholder of RenaSci Ltd. Sharon Smith is an employee of RenaSci Ltd. Reginald Dean and Mark Todtenkopf are employees and shareholders of Alkermes, Inc.