Oral vs. Intraperitoneal Dosing in the Rat Drug Discrimination Model

INTRODUCTION

The regulatory agencies guidance for the assessment of abuse liability in preclinical models recommend using preferably the clinical route of administration although different routes may be considered depending on the model used and the context of non-medical use. For the drug discrimination the routes of administration with fast onset of action, such as intraperitoneal (IP) or subcutaneous (SC) injection, are largely used. The present study aimed at investigating the effects of some drugs of abuse given through different routes of administration in a two choice drug discrimination operant task.

METHODS

The Training

- Study 1: 12 male Sprague Dawley rats were trained to discriminate cocaine (COC) at 10 mg/kg from its vehicle (VEH), given IP 10 minutes before the start of the session.
- Study 2: 10 female Lister Hooded rats were trained to discriminate lorazepam (LZP) at 1 mg/kg from its VEH, given IP 60 minutes before the start of the session.

The Generalization Testing

- During generalization session both levers were actively delivering a pellet upon 10 consecutive lever presses on one of the two levers.
- Study 1: rats received COC 1, 3, 10 mg/kg or VEH given IP (Testing 1; Figure 1A and Table 1A) at 10 min; then COC 8, 16, 32 mg/kg or VEH given orally (PO). Testing 2. Figure 1B and Table 1B) at 60 min.
- Study 2: rats received LZP 0.1, 0.2, 0.5, 1 mg/kg or VEH given IP (Testing 1; Figure 2A and Table 2A) at 60 min; then LZP 0.5, 1 and 3 mg/kg or VEH given PO (Testing 2; Figure 2B and Table 1B) at 60 min.

RESULTS

- **Study 1**: COC was given IP (Figures 1A and 1B). Lower panels show the rate of responding (i.e. total lever presses/min). *= P<0.05, ** = P<0.01 vs. VEH, Dunnett’s test.
- **Study 2**: LZP was given PO (Figures 2A and 2B).

DISCUSSION AND CONCLUSIONS

- The different routes of administration used for the training or generalization testing do not affect the robustness of the discriminative stimulus effect.
- The choice of the route of administration is not critical as long as testing is conducted at Tritan.
- The oral route, which is often the proposed therapeutic route, can be suitable for drug discrimination studies despite the route used for the training drug.
- However the possibility of production of different active metabolites depending on the route of administration used needs to be taken into account.

**Table 1A**: Generalization Testing: Effect of COC following IP administration.

**Table 1B**: Generalization Testing: Effect of COC following PO administration.

**Figure 1**: Generalization Testing: Effect of COC.

**Figure 2**: Generalization Testing: Effect of LZP.