Profiles of lisdexamfetamine and methylphenidate in rats trained to discriminate d-amphetamine from saline

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INTRODUCTION

Lisdexamfetamine (LDX) (Vyvanse®) and methylphenidate are Schedule 2 Controlled Drugs used in the treatment of ADHD in North America. LDX is an inactive prodrug comprising d-amphetamine (d-AMF) covalently bound to the amino acid, L-lysine. It is metabolized to yield the stimulant, d-AMF, primarily in red blood cells (Pennick 2010). In contrast, methylphenidate is a pharmacologically active stimulant. Data from studies in drug-experienced human volunteers (Jasinski & Krishnan, 2009a,b) suggest that the unusual pharmacokinetics of LDX may reduce some aspects of its liability for abuse.

The aim of this study was to determine the subjective effects of LDX in rats that had been trained to distinguish d-AMF from saline in a two-choice, operant drug-discrimination procedure and compare them with those of immediate release (IR)-methylphenidate. LDX and methylphenidate were tested after dosing by the oral (po) and intraperitoneal (ip) routes to evaluate the effects on their potency of switching to a non-clinical route of administration.

METHODS

Groups of 6-9 young adult female PVG rats were trained to discriminate d-AMF (0.5 mg/kg ip) from saline in a 2-lever operant procedure (partial generalization = 28-74%; full generalization ≥75% responding on the appropriate lever) using an FR-5 schedule of food rewards. It is a well established model for determining similarities between the subjective effects of test compounds in comparison to reference drugs with known abuse liability profiles. LDX was tested at various times (15, 60 and 120 min) after administration, methylphenidate and d-AMF were tested after 15 min.

To facilitate comparisons between LDX and d-AMF, doses of both drugs are expressed as mg/kg d-AMF base.

RESULTS

References


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• Fifteen (15) min after po dosing, LDX (equivalent to 0.5-1.5 mg/kg d-AMF base) generalized to saline. At 60 min, LDX partially generalized to d-AMF (26-74%) at 0.5-1.0 mg/kg and fully generalized (≥75%) at 1.5 mg/kg. At 120 min, LDX (0.5 and 0.75 mg/kg) generalized to saline and LDX (1.0 and 1.5 mg/kg) generalized partially to d-AMF (Fig. 1, Table 1).

• When tested 15 min after dosing, orally administered d-AMF (0.1-1.5 mg/kg) dose-dependently generalized to the d-AMF cue (Fig. 2). At this time-point, IR-methylphenidate (3.0-10 mg/kg, po) also dose-dependently generalized to the d-AMF cue (Fig. 2).

• Switching to the ip route reduced the time interval required for LDX (0.5-1.5 mg/kg) to be recognised as d-AMF-like, but it did not alter its potency (Fig. 3; top).

• Intraperitoneal administration of d-AMF (0.1-0.5 mg/kg) produced a dose-dependent generalization to the d-AMF cue. However, the dose required for full generalization decreased from 1.5 mg/kg po to 0.5 mg/kg ip (Fig. 3; middle).

• After ip administration, IR-methylphenidate (0.75 3.0mg/kg) dose-dependently generalized to d-AMF, but the dose required for full generalization decreased from 10 mg/kg po to 3.0 mg/kg ip (Fig. 3; bottom).

CONCLUSIONS

• LDX’s amphetamine-like subjective effects were delayed in onset after oral dosing and of relatively short duration.

• By contrast, generalization to d-AMF occurred rapidly after po or ip administration of IR-methylphenidate.

• The potency of LDX was not increased by switching to the ip route.

• The potencies of IR-methylphenidate and d-AMF were increased ~3 fold when dosing was switched from oral administration to the ip route.

• Consistent with Jasinski and Krishnan’s human findings (2009a,b), these data support the hypothesis that unlike IR-methylphenidate or d-AMF, the recreational abuse potential of LDX cannot be enhanced by switching to the more harmful injection route. This finding is relevant to the abuse of psychostimulants where more hazardous routes, eg intravenous injection or nasal insufflation, are often employed to increase the speed of penetration of drugs into the brain.

Fig 1. Profiles of oral LDX in d-AMF-cued drug-discrimination testing determined at various times after compound administration.

Fig 2. Generalization to the d-AMF cue by oral LDX 15 min after dosing.

Fig 3. Comparison of oral vs intraperitoneal potency of LDX, d-AMF and methylphenidate.