INTRODUCTION

Lisdexamfetamine dimesylate (LDX; Vyvanse®) is a novel prodrug consisting of L-lysine covalently bonded to d-amphetamine (d-AMP). LDX is a medication that is approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in the USA and Canada. After ingestion and absorption from the gut, the metabolism of LDX to yield the active moiety, d-AMP, is via rate-limited, enzymatic hydrolysis that probably occurs exclusively in red blood cells (Pennick, 2010). The Culex Bambino (BAS i/c) allows the simultaneous collection of intracranial microdialysis samples from freely-moving rats together with independently programmable blood sampling and locomotor activity measurements.

We have used this instrument to compare the pharmacodynamic (PD) and pharmacokinetic (PK) profiles of LDX and immediate release d-AMP (IR d-AMP) on the extracellular concentration of dopamine (DA) in the striatum and locomotor activity.

An in-depth evaluation of the results by hysteresis analysis (the relationship between the ascending and descending components of a concentration-time curve and a functional response) has been performed and the findings are presented at this meeting (See Poster 775.11/S6 - this session).

METHODS

Adult, male Sprague Dawley rats (250–350 g; Charles River, UK) were anesthetized with isoflurane in O₂:N₂O. A 4 mm concentric microdialysis probe (CMA, UK) was stereotaxically implanted into the striatum (AP: +0.2 mm; L: -3.0 mm; V: -7.8 mm; Paxinos and Watson, 1986). A catheter was implanted into the jugular vein and exteriorized between the rats’ shoulder blades.

Following surgery, rats were individually housed in the Culex Bambino dialysis balls and allowed to recover for at least 16 h with ad libitum food and water. Probes were continuously perfused with aCSF (sodium 150 mM; potassium 3 mM; magnesium 0.8 mM; calcium 1.4 mM; phosphate 1.0 mM; chloride 155 mM) at a flow rate of 1.2 μl/min.

LDX and IR d-AMP were tested at an equivalent dose as mg/kg d-AMP base. ie 1.5 mg/kg. LDX and IR d-AMP were administered to the rats (n = 5–6/group) by intraperitoneal (i.p.) injection.

Dialysate samples were collected at 15 min intervals, 1 h before to 8 h after drug administration. Blood samples (0.3 ml/sample) were collected into sterile saline/heparin (10 IU/ml) vials at 0, 15, 30, 60, 120, 180, 240, 360 and 480 min.

DA concentrations in dialysate samples were measured by Hplc-ecd (Rowley et al, 2000). Blood samples were spun at 8,000 g for 5 min and the plasma aliquots were stored at -80°C until being shipped to CEDRA Corporation (Texas, USA) for analysis of d-AMP and LDX.

AUC, Tmax, and % of baseline were calculated for plasma d-AMP, but with a 50% lower Cmin, and significantly delayed T1/2. At an equivalent dose, LDX produces a smaller and more sustained increase in striatal DA efflux than IR d-AMP and substantially less locomotor activation.

The PK/PD findings are consistent with the reports that equivalent molar doses of LDX were experienced as less stimulant than IR d-AMP by drug-experienced human volunteers (Jasinski & Krishnan, 2009 a,b). This finding also has other important clinical implications. The greater separation between increased striatal dopaminergic neurotransmission and locomotor activation with LDX predict that it will have a greater "therapeutic window" than IR d-AMP, because it is less likely to produce undesirable stimulant side-effects.

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RESULTS

Fig 1. Lisdexamfetamine

Fig 2. Effects of LDX and IR d-AMP on extracellular DA levels in the striatum

Fig 3. Effects of LDX and IR d-AMP on locomotor activity

Fig 4. Comparison of the relationship between plasma d-AMP and striatal DA efflux for LDX and IR d-AMP

Fig 5. Comparison of the relationship between striatal DA efflux and locomotor activity for LDX and IR d-AMP

CONCLUSIONS

• The PK of LDX is consistent with the characteristics of a prodrug that is converted to a pharmacologically active moiety, d-AMP, by a rate-limited enzymatic process, i.e. compared with the IR d-AMP, there was an identical AUC0-160 min, but with a 50% lower Cmin, and significantly delayed T1/2.

• At an equivalent dose, LDX produces a smaller and more sustained increase in striatal DA efflux than IR d-AMP and substantially less locomotor activation.

• The PK/PD findings are consistent with the reports that equivalent molar doses of LDX were experienced as less stimulant than IR d-AMP by drug-experienced human volunteers (Jasinski & Krishnan, 2009 a,b).

• This finding also has other important clinical implications. The greater separation between increased striatal dopaminergic neurotransmission and locomotor activation with LDX predict that it will have a greater "therapeutic window" than IR d-AMP, because it is less likely to produce undesirable stimulant side-effects.

REFERENCES


