INTRODUCTION

Lisdexamfetamine dimesylate (LDX, Vyvanse®) is a produg, which has been approved for the management of attention deficit hyperactivity disorder (ADHD) in children, adolescents and adults in the USA and Canada. LDX comprises L-lysine covalently bonded to d-amphetamine (d-AMP) via an amide linking group. After ingestion and absorption, LDX is metabolized exclusively in red blood cells by rate-limiting hydrolysis to d-AMP and L-lysine (Pernick, 2010).

The Culex Bambino (BAS Inc) was developed to combine the automatic collection of intracerebral microdialysis samples in freely-moving rats together with independently programmable blood sampling and locomotor activity monitoring. The aim of this investigation was to employ the Culex Bambino to explore the pharmacodynamic (PD) and pharmacokinetic (PK) relationships for the actions of LDX and immediate-release (IR) d-AMP sulphate on the extracellular concentration of dopamine (DA; in the striatum, locomotor activity and plasma drug levels. The microdialysis, locomotor activity and pharmacokinetic results are reported in Poster 775.23/T6 (this session).

A hysteresis analysis determines the relationship between the ascending and descending components of a concentration-time curve and a functional response. In this study, we have used hysteresis analysis to explore 3 different relationships for LDX and d-AMP:

- Plasma d-AMP concentration and locomotor activity
- Plasma d-AMP concentration and extracellular DA concentration in the striatum
- Extracellular DA concentration in the striatum and locomotor activity

METHODS

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 rat’s shoulder blades.

Following surgery, rats were individually housed in the Culex Bambino dialysis bowls 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 in terms of d-AMP base, i.e. 1.5 mg/kg, and were administered to the rats (n = 5/4/group) by intraperitoneal (ip) injection. Jasinski & Krishnan (2009a,b) reported that when given at equivalent doses in terms of quantity of d-AMP base, LDX was experienced as substantially less stimulating than IR d-AMP by drug experienced volunteers. For this reason, we also tested LDX at the higher dose of 5 mg/kg (n = 5).

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 μl/ml) vials at 0, 15, 30, 60, 120, 180, 240, 360 and 480 min. DA concentrations in dialysate samples were measured by hplc-eqc (Rowley et al., 2000). Blood samples were centrifuged 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.

RESULTS

**Fig 1.** Hysteresis analysis of the relationship between the plasma concentration of d-AMP and extracellular dopamine in the striatum

**Fig 2.** Hysteresis analysis of the relationship between the plasma concentration of d-AMP and locomotor activity

**Fig 3.** Hysteresis analysis of the relationship between extracellular dopamine concentrations and locomotor activity

LDX and IR d-AMP - Hysteresis analyses revealed antirhythmic relationships between plasma d-AMP and striatal DA efflux (Fig 1) or locomotor activity (Fig 2). They showed that the increases in extracellular DA or locomotor activity were smaller as the plasma concentration of the d-AMP was rising, but these effects were maintained for longer when concentration of drug was declining. Antirhythmic hysteresis is consistent with IR d-AMP having to cross the blood-brain barrier enthril striatal nerve terminals before it can release the neurotransmitter, i.e DA, to produce the functional outcome, i.e locomotor activity. The effects of the 2 drugs were not statistically different from one another.

CONCLUSIONS

- **Antirhythmic hysteresis relationships between the plasma concentration of d-AMP and striatal DA efflux or locomotor activity were observed with LDX and IR d-AMP.**
- **An unexpected finding was the temporal relationship between the two interlinked pharmacodynamic parameters, i.e extracellular striatal DA (neurochemical mediator) and locomotor activity (functional outcome).** After LDX administration there was an antirhythmic hysteresis relationship, whereas after administration of IR d-AMP, there was a clockwise hysteresis relationship.
- **The difference in the direction of the hysteresis may partially explain why at equivalent doses LDX is less stimulant in man than IR d-AMP (Jasinski & Krishnan, 2009a,b). This finding also has other important clinical implications.** The sustained increase in extracellular DA and reduced locomotor activation predict that LDX is likely to have an enlarged therapeutic window compared with IR d-AMP. Moreover, the maintenance of LDX’s pharmacodynamic effect under circumstances when extracellular DA concentrations in the CNS are declining indicates that the unusual PK of LDX optimizes the pharmacologic utilization of its active metabolite, d-AMP

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REFERENCES


