Pharmacokinetics and Pharmacodynamics of Lisdexamfetamine Compared with D-Amphetamine in Healthy Subjects.

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Rationale:
Lisdexamfetamine is a prodrug of D-amphetamine used for the treatment of attention-deficit/hyperactivity disorder (ADHD). Lisdexamfetamine is thought to have a prolonged pharmacokinetic profile compared with oral D-amphetamine, possibly associated with lower drug liking and a lower risk of oral misuse. However, differences in the pharmacokinetics and pharmacodynamics of lisdexamfetamine and D-amphetamine have not been directly compared.

Methods:
Equimolar doses of D-amphetamine (40 mg) and lisdexamfetamine (100 mg), and placebo were administered in 24 healthy subjects in a randomized, double-blind, placebo-controlled, cross-over study. Plasma concentrations of amphetamine, subjective effects, and vital signs were repeatedly assessed. The pharmacokinetic parameters were determined using compartmental modeling.

Results:
The increase in plasma concentrations of amphetamine had a 0.6 ± 0.6 h (mean ± SD) longer lag time and reached peak levels 1.1 ± 1.5 h later after lisdexamfetamine administration compared with D-amphetamine administration, but no differences in maximal concentrations or total exposure (AUC) were found between the two treatments. Consistent with the pharmacokinetics, the subjective and cardiovascular stimulant effects of lisdexamfetamine also occurred later compared with D-amphetamine. However, no differences in peak ratings of potentially abuse-related subjective drug effects (e.g., drug liking, drug high, stimulation, happy, well-being, and self-confidence) were observed after lisdexamfetamine administration compared with D-amphetamine administration. Lisdexamfetamine and D-amphetamine also produced similar peak increases in mean arterial blood pressure, heart rate, body temperature, pupil size, and adverse effects.

Conclusion:
The pharmacokinetics and pharmacodynamics of lisdexamfetamine are similar to D-amphetamine administered 1h later. Lisdexamfetamine is likely associated with a similar risk of oral abuse as D-amphetamine.

The study was registered at ClinicalTrials.gov (NCT02668926).