The Clinical Pharmacokinetics of Amphetamines Utilized in the Treatment of Attention-Deficit/Hyperactivity Disorder.

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Abstract

Amphetamine (AMP), an indirectly acting psychostimulant approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults, is among the most long-standing therapeutic agents in all of clinical psychopharmacology. This review focuses on AMP absorption, metabolism, and elimination brought to bear on comparative pharmacokinetics in its various formulations. A comprehensive search of the published literature was conducted using MEDLINE (PubMed) and Google Scholar databases through April 2017 to retrieve all pertinent in vitro and human studies for review and synthesis. Additionally, Food and Drug Administration (FDA) databases were accessed for otherwise unavailable data when possible. Initially available as racemic (dl)-AMP, this drug was later supplanted by enantiopure (d)-AMPH or enantioenriched (75:25 dl)-AMP formulations; although racemic AMP returned as an approved drug to treat ADHD in 2014. Presently, there are several immediate-release (IR) formulations available, including d-AMP, dl-AMP, and mixed amphetamine salts, which are neither racemic nor the pure d-enantiomer (i.e., a 3:1 mixture of d-AMP and l-AMP). Furthermore, new modified-release AMP formulations, including an oral suspension and an orally disintegrating tablet, are now available. A lysine-bonded prodrug form of d-AMP also serves as a treatment option. Oral AMP is rapidly absorbed, with high absolute bioavailability, followed by extensive metabolism involving multiple enzymes. Some metabolic pathways exhibit stereoselective biotransformations favoring the l-isomer substrate. Drug exposure exhibits dose-proportional pharmacokinetics. Body weight is a fundamental determinant of differences in observed AMP plasma concentrations. IR formulations typically provide a Tmax from 2 to 3 hours. In replicated studies, children exhibit a shorter plasma T1/2 (~7 hours) relative to adults (~10 to 12 hours). There are few documented pharmacokinetic drug interactions of clinical significance beyond influences of drug-induced alteration of urinary pH. The array of AMP formulations addressed in this review offer flexibility in dosing, drug onset, and offset to assist in individualized pharmacotherapy of ADHD.