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Abstract

BACKGROUND/PURPOSE:
Ethanol co-administered with immediate-release dl-methylphenidate (dl-MPH) or dexmethylphenidate (d-MPH) significantly increases the geomean maximum plasma concentration (Cmax) of d-MPH 22% and 15%, respectively, and elevates overall drug exposure and psychostimulant effects. We asked the question: Are these ethanol-MPH interactions based more fundamentally on (1) inhibition of post-absorption d-MPH metabolism or (2) acceleration of MPH formulation gastric dissolution by ethanol in the stomach? This was investigated using the pulsatile, distinctly biphasic, spheroidal oral drug absorption systems of dl-MPH and d-MPH.

METHODS:
In a randomized, 4-way crossover study, 14 healthy subjects received pulsatile dl-MPH (40 mg) or d-MPH (20 mg), with or without ethanol (0.6 g/kg), dosed 4 hours later. These 4 hours allowed the delayed-release second MPH pulse to reach a more distal region of the gut to preclude gastric biopharmaceutical influences. Plasma was analyzed using a highly sensitive chiral method. Subjective/physiological effects were recorded.

FINDINGS/RESULTS:
Ethanol increased the second pulse of d-MPH Cmax for dl-MPH by 35% (P < 0.01) and the partial area under the plasma concentration curve from 4 to 8 hours by 25% (P < 0.05). The respective values for enantiopure d-MPH were 27% (P = 0.001) and 20% (P < 0.01). The carboxylesterase 1-mediated transesterification metabolite ethylphenidate served as a biomarker for co-exposure. Ethanol significantly potentiated stimulant responses to either formulation.

IMPLICATIONS/CONCLUSIONS:
These findings support drug dispositional interactions between ethanol and MPH as dominant over potential biopharmaceutical considerations. Understanding the pharmacology underlying the frequent co-abuse of MPH-ethanol provides rational guidance in the selection of first-line pharmacotherapy for comorbid attention-deficit/hyperactivity disorder-alcohol use disorder.