Published in final edited form as:

J Clin Psychopharmacol. 2015 August ; 35(4): 464–467. doi:10.1097/JCP.0000000000000348.

Comparative Ethanol-Induced Potentiation of Stimulatory Responses to Dexmethylphenidate versus Methylphenidate

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Abstract

The potentiation of positive subjective responses to immediate-release dexmethylphenidate (d-MPH) or dl-methylphenidate (dl-MPH) by ethanol was investigated over the time course of maximal drug exposure after a single dose. In a 4-way, randomized, crossover study design, 12 men/12 women normal volunteers received d-MPH (0.15 mg/kg) or dl-MPH (0.3 mg/kg) with or without ethanol (0.6 g/kg). Serial visual analog scales were used as surrogates for drug abuse liability: “high?”, “good?”, “like?”, “stimulated?” and “any drug effect?” Combining pure d-MPH with ethanol significantly ($P < 0.005$) increased the area under the effect curves ($AUC_{0-5.25h}$) of all 5 subscales. The dl-MPH-ethanol combination significantly ($P < 0.05$) increased these AUCs with the exception of “like?” ($P = 0.08$). Effects of the pure d-MPH-ethanol combination exhibited delayed potentiation relative to dl-MPH-ethanol. A pharmacokinetic interaction between the l-isomer of dl-MPH and ethanol has previously been shown to increase early exposure to d-MPH. Administration of the pure isomer d-MPH precludes this absorption phase pharmacokinetic interaction with ethanol. This notwithstanding, the pure d-MPH-ethanol combination resulted in comparable, if not greater, cumulative stimulant potentiation than the dl-MPH-ethanol combination. These findings provide evidence of a pharmacodynamic component to d-MPH-ethanol synergistic interactions and carry implications for the rational drug individualization in the treatment of attention-deficit/hyperactivity disorder.

Keywords

dexmethylphenidate; methylphenidate; ethanol; abuse

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AUTHOR DISCLOSURE INFORMATION: Funding support for this work was solely received from the NIH/NIAAA (KP). No other funding could be construed as a conflict of interest. KP is presently a consultant for ALZA, UCB, Shire, Endo and Johnson & Johnson and has been a consultant for Noven and Ortho-Janssen within the last 3 years. KP has had a provisional patent for isopropylphenidate (ritalinic acid isopropyl ester) as a novel psychotropic agent through the MUSC Foundation for Research Development, with a Notice of Abandonment Jan 2014. AS is a member of the Board of Directors for Cingulate Therapeutics and has consulted for Watson Pharmaceuticals. RM is funded through NIH/NIDA and has research funding from Janssen Pharmaceuticals. For the remaining authors none were declared.

INTRODUCTION

In the 12–17 years of age group, MPH is prescribed more often than any drug *regardless of therapeutic class*. Though most MPH products contain racemic dl-MPH, prescriptions for the enantiopure psychostimulant d-MPH have risen at least 10-fold over the last few years.¹ Many, if not most (> 90%), adolescent and adult MPH abusers co-abuse MPH with ethanol.² This pattern of MPH-ethanol co-abuse is consistent with the potentiating influence of ethanol on MPH stimulant/euphoric effects as demonstrated in controlled clinical studies.³

Administration of dl-MPH in combination with ethanol leads to carboxylesterase 1-mediated enantioselective transesterification of l-MPH to form l-ethylphenidate.⁴ This pathway competes with hydrolysis, resulting in a significantly greater rate and extent of d-MPH (and l-MPH) absorption.⁴ A steep rise in plasma d-MPH concentrations has correlated with potentiated euphoria³ in keeping with pharmacokinetic-pharmacodynamic correlations previously described for dl-MPH in the absence of ethanol⁵ or during early exposure to the d-MPH-ethanol combination.⁶ Administration of pure d-MPH precludes this metabolic interaction. Accordingly, we investigated the relative extent of ethanol-induced cumulative stimulant potentiation following immediate-release dl-MPH compared to pure d-MPH with the prospect of avoiding synergistic abuse liability by using the pure d-MPH-ethanol combination. The present investigation profiles the time course of pharmacodynamic effects during the overall period of high drug exposure (0 – 5.25 h post-dosing) and considers these findings in the context of both the pharmacokinetic and pharmacodynamic drug interactions which propel MPH-ethanol co-abuse.

METHODS

Subjects and drug administrations

Details regarding the subjects, experimental design and pharmacokinetic analysis associated with this investigation have been previously described.⁶ Briefly, in a 4-way, randomized, crossover study, normal volunteers (12 men/12 women completed of 35 total enrolled; treatment intervals were 1–3 weeks) received a light breakfast, then 1 h later were dosed with immediate-release dl-MPH·HCl (0.3 mg/kg; Ritalin®, Novartis Pharmaceuticals, Summit, NJ) or immediate-release d-MPH·HCl (0.15 mg/kg; Focalin®, Novartis), followed 0.5 h later by a juice drink, with or without ethanol (0.6 g/kg), consumed at a constant rate over 15 min.

Subjective effects

Using horizontal line scales with “0” labeled “not at all” and “100” labeled “extremely”, a vertical mark was made to indicate the intensity of the following drug effects: (1) Do you feel any drug effect?; (2) How high are you?; (3) Do the drugs have any good effects?; (4) Do the drugs have any bad effects?; (5) Do you like the drugs?; (6) Do you feel depressed?; (7) How anxious are you?; (8) How stimulated do you feel?; (9) How intoxicated do you feel? These scales were administered at baseline and following MPH dosing at times 0.75, 1.25, 2.25, 3.25, 4.25, 5.25 (and 11 h). These were used as surrogates for abuse liability.

Statistical analysis

Comparisons between VAS subscales were made using the student t-test assuming equal variance. VAS subscales were compared using analysis of variance (ANOVA) with treatment (dl-MPH versus dl-MPH-ethanol; d-MPH versus dexMPH-ethanol;) as a between (repeated measures) factor using the Latin square design to take into account sequence (carry-over) effect. The level of significance was set at $P = 0.05$.

RESULTS

Combining ethanol with pure d-MPH significantly potentiated the positive subjective effect subscale $AUC_{0-5.25h}$ values for (1) “stimulated” – Fig. 1; (2) “good” – Fig. 2; (3) “like”; (4) “high”, as well as for (5) “any drug effect” – Fig. 3 ($P < 0.005$). These effects of ethanol on dl-MPH were also significantly potentiated ($P < 0.05$) with the exception of the subscale “like” ($P = 0.079$) – Table 1. The degree of ethanol-induced potentiation of VAS subscales reached a maximum at 1.25 h for the d-MPH-ethanol combination while the maximum potentiation occurred at 0.75 h for dl-MPH-ethanol (e.g., Fig. 1–3).

The magnitude of the cumulative ethanol-induced positive subjective effect potentiation was consistently greater for the pure d-MPH-ethanol combination than for the dl-MPH-ethanol combination. However, these differences did not reach statistical significance (see Table 1).

The subjective effects of “bad”, “depressed”, and “anxious” were unremarkable in the four treatment groups. The extent of feeling “intoxicated”, i.e., the mean $AUC_{0-5.25h}$, was similar for the pure d-MPH-ethanol and dl-MPH-ethanol treatments, i.e., 94 (+/- 70) and 85 (+/- 79), respectively.

DISCUSSION

The present cumulative VAS high drug exposure time courses extend existing dl-MPH⁷ and dl-MPH-ethanol³ subjective effect characterization to that of the pure d-MPH isomer using dl-MPH as the comparator. Following dl-MPH, ethanol significantly increased the mean 0.75 h positive subjective effects while the pure d-MPH-ethanol combination generally required 1.25 h to reach statistically significant potentiation by ethanol, e.g., Fig. 1–3. This earlier onset for dl-MPH-ethanol potentiation occurs in concert with l-MPH-ethanol metabolism increasing the rate of d-MPH absorption, a rate influence obviated by dosing with the pure isomer d-MPH.⁴ In spite of the presystemic pharmacokinetic interactions with ethanol being limited to the dl-MPH, an overall trend toward more pronounced cumulative ($AUC_{0-5.25h}$) ethanol-induced behavioral potentiation occurred with d-MPH compared to dl-MPH (Table 1). The increased rate that d-MPH reaches the bloodstream when dl-MPH is combined with ethanol carries implications for dl-MPH-ethanol abuse liability.^{8–10} The tendency of the pure d-MPH-ethanol combination to induce even greater overall potentiation of stimulant effects compared to dl-MPH-ethanol indicates that the illicit popularity of concomitant MPH-ethanol² is unlikely to be limited to racemic dl-MPH. Regarding other pharmacokinetic differences between pure d-MPH versus dl-MPH, it is noted the absorption of d-MPH from the pure d-MPH formulation in the absence of ethanol occurs significantly faster than d-MPH from the dl-MPH formulation in the absence of ethanol.⁶

The mechanism of action by which d-MPH produces both therapeutic and euphoric effects appears to occur through indirect dopaminergic (and noradrenergic) agonism. d-MPH binds to the dopamine transporter to inhibit reuptake of impulse-released dopamine by presynaptic terminals.¹¹ Imaging studies indicate that extracellular d-MPH concentrations high enough to inhibit at least 50–60% of dopamine transporter function¹² appear to be required to reach a threshold for euphoric response.¹⁰ In addition, imaging studies reveal that even a single exposure to d-MPH causes some persistent changes in the regulation of dopamine synthesis in humans. Accordingly, while the randomized, cross-over study design used in the present study should control for potential carryover effects, drug effects subsequent to the initial exposure in each study subject may reflect some degree of compensatory response to prior treatment(s).¹³

In animal models we have previously reported that (1) a sub-stimulatory dose of dl-MPH potentiates a stimulatory dose of ethanol,¹⁴ (2) a depressive dose of ethanol strongly potentiates a stimulatory dose of dl-MPH¹⁵ and (3) combining dl-MPH with ethanol potentiates ataxia.¹⁶ Integrating these preclinical investigations with the present human behavioral time course studies using pure d-MPH-ethanol support an underlying neuropharmacological component to this drug combination synergism. Theoretically, the indirect release of extracellular dopamine by ethanol^{17–20} increases the synaptic pool of dopamine subject to reuptake inhibition by d-MPH^{5,8,9,21} to amplify postsynaptic signaling and propel MPH-ethanol co-abuse.

In summary, our present behavioral findings using ethanol and pure d-MPH, with dl-MPH as a comparator, provide evidence that a pharmacodynamic mechanism underlies d-MPH-ethanol interactions in addition to the established pharmacokinetic interactions.⁴ Accordingly, pure d-MPH avoids pharmacokinetic influences on plasma d-MPH by ethanol during the absorption phase (time to maximum plasma d-MPH concentration: 2.1 h⁶), while still exhibiting highly significant potentiation of stimulant effects within this same period of time. The ethanol-induced potentiation of positive subjective effects by either pure d-MPH or racemic dl-MPH contributes to understanding the popularity of this drug combination by drug abusers,² and underscores the importance of discerning drug selection in rational attention-deficit/hyperactivity treatment individualization.

Acknowledgments

This publication was supported by NIH grant R01AA016707 (KSP) with additional support from the South Carolina Clinical & Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, via use of the Clinical & Translational Research Center, NIH UL1 TR000062, UL1 RR029882, as well as support via the Southeastern Pre-doctoral Training in Clinical Research Program, NIH TL1 RR029881. The authors express their appreciation for the statistical analysis by Dr. Paul Nietert and for help offered by Cristina Murphy, Timothy Corbin, Catherine Fu, Joshua Knight and Dalton Dunaway in the development of this manuscript.

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FIGURE 1.

Visual analog subscale "stimulated": 0 = not at all; 100 = extremely.

($\pm$ SEM); * $P < 0.05$; ** $P < 0.01$.

FIGURE 2.

Visual analog subscale for "good": 0 = not at all; 100 = extremely.

(+/- SEM); * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

FIGURE 3.

Visual analog subscale for "any drug effect": 0 = not at all; 100 = extremely.
 (+/- SEM); *** $P < 0.001$.

TABLE 1Visual Analog Subscale Treatment Comparisons: AUC_{0-5.25h} (n=24)

Racemate	dl-MPH	dl-MPH+EtOH	Potentiation by EtOH	
	Mean (SD)	Mean (SD)	Mean	P Value
“Stimulated”	69 (65)	93 (68)	23	0.023
“Like”	71 (83)	93 (86)	21	0.0787
“Good”	60 (64)	83 (78)	20	0.0411
“High”	27 (39)	67 (62)	39	<0.0001
“Effect”	70 (60)	95 (66)	24	0.031

d-Isomer	d-MPH	d-MPH+EtOH	Potentiation by EtOH	
	Mean (SD)	Mean (SD)	Mean	P Value
“Stimulated”	60 (57)	105 (77)	45	<0.0001
“Like”	67 (77)	103 (101)	38	0.0024
“Good”	56 (59)	97 (80)	42	0.0002
“High”	35 (52)	82 (59)	47	0.0001
“Effect”	68 (52)	105 (64)	38	0.0009

Trends in Ethanol-induced Potentiation of Subjective effects:
AUC_{0-5.25h} d-MPH > dl-MPH (% greater change).

	Difference	P Value
“Stimulated”	23 (+44%)	0.1084
“Like”	17 (+23%)	0.3304
“Good”	20 (+35%)	0.2008
“High”	8 (+14%)	0.5438
“Effect”	14 (+18%)	0.3659

Influence of EtOH (0.6 g/Kg) on positive subjective effects of dl-MPH (0.3 mg/kg) or d-MPH (0.15 mg/kg)

AUC, area under the curve; EtOH, ethanol; dl-MPH, dl-methylphenidate; d-MPH, dexamethylphenidate.