ETHYLPHENIDATE FORMATION IN HUMAN SUBJECTS AFTER THE ADMINISTRATION OF A SINGLE DOSE OF METHYLPHENIDATE AND ETHANOL

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ABSTRACT:

Ethylphenidate was recently reported as a novel drug metabolite in two overdose fatalities where there was evidence of methylphenidate and ethanol coingestion. This study explores the pharmacokinetics of ethylphenidate relative to methylphenidate and the major metabolite ritalinic acid, in six healthy subjects who received methylphenidate and ethanol under controlled conditions. Subjects (three males, three females) received a single oral dose of methylphenidate (20 mg; two 10-mg tablets) followed by consumption of ethanol (0.6 g/kg) 30 min later. Methylphenidate, ritalinic acid, and ethylphenidate were quantified using liquid chromatography-tandem mass spectrometry. Ethylphenidate was detectable in the plasma and urine of all subjects after ethanol ingestion. The mean (±S.D.) area under the concentration versus time curve for ethylphenidate was 1.2 ± 0.7 ng/ml/h, representing 2.3 ± 1.3% that of methylphenidate (48 ± 12 ng/ml/h). A significant correlation was observed between the area under the concentration versus time curve of methylphenidate and that of ethylphenidate. In view of the known dopaminergic activity of racemic ethylphenidate, it remains possible that under certain circumstances of higher level dosing, e.g., in the abuse of methylphenidate and ethanol, the metabolite ethylphenidate may contribute to drug effects.

Methylphenidate (Ritalin, (dl)-threo-α-phenyl-2-piperidineacetic acid methyl ester) is the most commonly used psychostimulant in the United States for the treatment of attention-deficit hyperactivity disorder (ADHD) and is perhaps the most frequently prescribed psychotropic medication in children (Robison et al., 1999). In humans, the majority of orally administered methylphenidate has been reported to be stereoselectively deesterified (Buggé et al., 1996; see Patrick and Markowitz, 1997) to the inactive metabolite ritalinic acid (Patrick et al., 1985). This metabolite reaches plasma concentrations one to two orders of magnitude greater than that of the parent drug (Redalieu et al., 1982; Wargin et al., 1983). Other metabolites (Fig. 1) include corresponding lactams (Bartlett and Egger, 1972) and a small amount of p-hydroxymethylphenidate (Patrick et al., 1985).

Methylphenidate use has increased dramatically in recent years (Robison et al., 1999) and is increasingly being prescribed to adult patients with residual symptoms of ADHD (Spencer et al., 1995; Elia et al., 1999). Methylphenidate, a schedule II drug, is considered to be a medication of high abuse potential with documented abuse via oral, i.e., in the abuse of methylphenidate and ethanol, the metabolite ethylphenidate may contribute to drug effects.

Recently, the first detection of ethylphenidate (ritalinic acid ethyl ester; Fig. 1) was reported in two overdose victims who had ingested large quantities of methylphenidate with evidence of ethanol consumption (Markowitz et al., 1999). Ethylphenidate formation has previously been reported in vitro using a rat liver preparation incubated with methylphenidate and ethanol (Bourland et al., 1997). This biotransformation appears to be a carboxylesterase-dependent trans-esterification process (Bourland et al., 1997). This mechanism may be analogous to that involved in the formation of cocaethylene (benzylecgonine ethyl ester) by human hepatic esterase(s) after concomitant cocaine and ethanol abuse (Jatlow et al., 1991; Boyer and Peterson, 1992). X-ray crystallography indicates that both methylphenidate and cocaine appear to display a common, superimposable pharmacophore consisting of an amine, phenyl ring, and methyl ester (Fromowitz et al., 1995). Cocaine (Sonders et al., 1997), cocaethylene (Jatlow et al., 1991), methylphenidate (Volkow et al., 1995), and (dl)-threo-ethylphenidate (Schweri et al., 1985) all exhibit appreciable dopamine transporter binding activity believed to underlie their central nervous system (CNS) stimulant effects, i.e., through the uptake inhibition of impulse released dopamine.

During cocaine and ethanol abuse, cocaethylene blood concentrations may approach or exceed that of cocaine (Jatlow et al., 1996), and cocaethylene has been reported to be more lethal than cocaine (Hearn et al., 1991). The toxicology of ethylphenidate has not been estab-

1 Abbreviations used are: ADHD, attention-deficit hyperactivity disorder; CNS, central nervous system; LC, liquid chromatography; MS, mass spectrometry; AUC, area under the concentration versus time curve; \( t_{1/2} \), terminal phase half-life.
ml of soda water. Subjects consumed this drink within 15 min to minimize intersubject variability in ethanol pharmacokinetics. This dose of ethanol approximated doses used in recent clinical studies of cocaethylene formation (Farré et al., 1997; McCance-Katz et al., 1998). The sequence of methylphenidate and ethanol administration was designed to favor their coabsorption. Additional blood samples were taken at 1, 1.5, 2, 3, 4, and 6 h after methylphenidate dosing. Ten-milliliter plastic syringes were used for this purpose, and catheter lines were cleared of residual heparin solution before sampling. The blood was transferred to green-stopped heparinized glass blood collection tubes (Vacutainers; Becton Dickinson, Rutherford, NJ) previously stored in an ice bath, centrifuged at 4°C for 5 min, and the plasma was immediately aspirated into plastic vials and stored at −80°C until analysis. Cumulative urine was collected for 6 h after methylphenidate dosing and the total volume was recorded. An aliquot of urine was retained for analysis of methylphenidate and metabolites.

**Materials and Methods.**

**Subjects.** All subjects gave written informed consent before participating in the study. The study population consisted of six individuals (three females, three males) aged 24 to 32 years, who were healthy as assessed by medical history, physical examination, 12-lead electrocardiogram, and routine laboratory tests including complete blood count, serum electrolytes, blood glucose, and liver function indices. Additionally, all subjects were nonsmokers and abstained from the use of caffeine-containing beverages for the duration of the study. The study was conducted in compliance with the current National Institute on Alcohol Abuse and Alcoholism (NIAAA) Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation (June, 1989) and did not involve the administration of ethanol to alcohol-naive subjects. Subjects were specifically questioned about any alcohol or substance use history and were asked to answer questions from the Brief Michigan Alcoholism Screening Test (MAST) with an exclusion criteria of scoring 2 or greater.

**Drug Administration and Sampling.** All subjects fasted for 8 h before drug administration, and were then fed a standard breakfast consisting of a bagel, cream cheese, and orange juice. An indwelling venous catheter was placed into a forearm vein for serial blood sampling. After obtaining baseline blood pressure, heart rate, and alcohol breathalyzer (Alco-Sensor III; Intoximeters Inc., St. Louis, MO) readings, subjects voided their bladders and were given 20 mg of methylphenidate administered orally as two 10-mg immediate release tablets (Ritalin; Novartis Pharmaceuticals, Summit, NJ) followed by 180 ml of water.

Blood samples (10-ml) were obtained predose and 0.5 h after methylphenidate administration. Immediately after the 0.5-h blood sample was obtained, patients were given an alcoholic drink containing 0.6 g/kg of body weight of ethanol (0.66 mL/kg 95% ethanol) mixed with 180 ml of orange juice and 60
concentration versus time data. Other pharmacokinetic parameters were noted directly from the data or calculated by standard methods (Rowland and Tozer, 1989). The assumption was made that ethanol elimination in the concentration range observed was first order. Calculating ethanol apparent half-lives on this basis using linear regression could overestimate the true “half-life” of ethanol if this assumption is invalid. However, in comparison to previously published values (Holford, 1987), the assumption of first order elimination appears reasonable for the observed data and allowed a practical means of comparison with pharmacokinetic estimates for the other compounds of interest in this study. Correlations between parameters for individuals were assessed by linear regression analysis (Instat 3.01; GraphPad Software, San Diego, CA). Differences between means of parameters were assessed by the paired Student’s t test (Instat) or repeated measures ANOVA. The level of significance was set at P < .05.

Results

The methylphenidate and ethanol combination was well tolerated by all research subjects with no adverse events noted. Ethylphenidate was only detected in plasma after ethanol intake (post 0.5 h), whereas ritalinic acid was detected at the 0.5-h time point immediately before ethanol dosing (Fig. 3). Noncompartmental pharmacokinetic parameters for the compounds of interest are shown in Table 1. As with other pharmacokinetic studies of methylphenidate, ritalinic acid was the major metabolite of methylphenidate (see Patrick and Markowitz, 1997). The mean area under the concentration versus time curve (AUC) for ritalinic acid was 23 ± 4 times greater than that of methylphenidate, whereas the ethylphenidate AUC was only 2.3% ± 1.3 of the mean methylphenidate AUC (Table 1).

There were highly significant correlations between plasma methylphenidate and both metabolite plasma concentrations (r² = .48, P < .001 for ethylphenidate and r² = .70, P < .001 for ritalinic acid). Hysteresis was observed in three subjects (one clockwise, two counterclockwise) in time series plots of plasma concentration data for methylphenidate and ethylphenidate. Significant correlations between the AUC values of methylphenidate/ethylphenidate and methylphenidate/ritalinic acid (r² = .70, P = .037 and r² = .66, P = .048, respectively) were also found (Table 1). Ethylphenidate and ethanol plasma concentrations were not significantly correlated (r² = .11, P = .14). Five of the six subjects showed clear hysteresis but not consistent between individuals (two clockwise, three counterclockwise) in time series plots of plasma ethylphenidate versus ethanol plasma concentration data.

Furthermore, there was no significant correlation between: 1) eth-
ethylphenidate and ethanol AUC values ($r^2 = .05$, $P = .86$); 2) the mean half-lives of ethanol and ethylphenidate ($P = .76$, paired Student’s $t$ test); 3) the individual half-life values ($r^2 = .0008$, $P = .96$; 4) differences between $t_{\text{max}}$ values for the analytes of interest ($P = .52$, repeated measures ANOVA). The $t_{1/2}$ of ethylphenidate was significantly shorter than that of methylphenidate ($P = .0123$), but there was no significant correlation between the individual values ($r^2 = .096$, $P = .55$). The amounts of methylphenidate, ethylphenidate, and ritalinic acid excreted in the urine from 0- to 6-h postmethylphenidate were $1.4 \pm 0.8, 0.02 \pm 0.1$, and $19.9 \pm 10.8\%$ of the methylphenidate dose, respectively.

**Discussion**

These data confirm the presence of ethylphenidate as a minor metabolite of methylphenidate when given at a normal clinical dose, followed by a moderate intake of ethanol. The concentration of ethylphenidate detected after ethanol administration appeared to be dependent more on methylphenidate plasma concentration than ethanol concentration. Similarly, cocaethylene formation after cocaine and ethanol intake correlates poorly with blood ethanol concentrations (Bailey, 1996; Brookoff et al., 1996). Surprisingly, the mean $t_{1/2}$ of ethylphenidate was significantly lower than that of methylphenidate. This result may be partly an artifact of a brief sampling time after single dose administration, as methylphenidate concentration in plasma rapidly declines below the level of assay sensitivity. The elimination rate of ethylphenidate may be dependent on its rate of formation from methylphenidate. In this situation the apparent elimination of ethylphenidate should occur with a half-life similar to methylphenidate. However, after a single oral dose of methylphenidate, the observed plasma concentration of ethylphenidate is the sum of the metabolite formed by first-pass elimination during absorption of methylphenidate and metabolite continuously formed from the absorbed drug. The result is the temporary disappearance of the metabolite at a rate seemingly faster than that of the parent compound. A separate administration of preformed ethylphenidate would be required to clarify the issue of whether the elimination of the metabolite is rate-limited by its formation from methylphenidate. Finally, until chiral chromatographic methods are applied to ethylphenidate determinations, the influence of enantioselective transesterification and/or deesterification on pharmacokinetic parameters cannot be definitively described. The potential significance of this consideration has precedents in the disparate rates of methyl ester hydrolysis for both methylphenidate (see Patrick and Markowitz, 1997) and cocaine (Gatley et al., 1990) enantiomers.

The elimination of ethanol was not significantly different from that of ethylphenidate. These data also imply that increasing the intake of ethanol may not necessarily increase the amount of ethylphenidate formed at a given dose of methylphenidate. However, in the case of cocaethylene formation, it has been suggested that continual intake of ethanol in the presence of cocaine could prolong the elimination of cocaethylene by providing an ongoing source of ethanol for ester exchange (Bourland et al., 1998).

Ethanol has been reported to increase circulating plasma concentrations of cocaine in human subjects (McCance-Katz et al., 1993; Roberts et al., 1993; Farré et al., 1997; McCance-Katz et al., 1998). In view of what may be a prolonged long half-life (mean = 3.6 h) observed for methylphenidate in this study (otherwise typically reported to be in the 2- to 3-h range; see Patrick and Markowitz, 1997), it may be possible that the ethanol interaction with esterases could reduce the rate of conversion of methylphenidate to ritalinic acid, i.e., the process primarily responsible for the short half-life of methylphenidate. A similar hypothesis has recently been advanced by Farré et al. (1997) to explain the observed elevating effects of ethanol on plasma cocaine concentrations. A crossover study design with a methylphenidate only phase, which includes a greater number of subjects, may be appropriate to confirm such a drug-drug interaction.

Ethylphenidate is probably best recognized as an internal standard for methylphenidate quantitation from biological samples, as has been reported in numerous pharmacokinetic studies (see Patrick et al., 1985). In view of these findings, any ethanol consumption by subjects whose samples were subsequently assayed using ethylphenidate as the internal standard could potentially lead to an underestimation of methylphenidate concentrations.

Ethylphenidate has not been pharmacologically well characterized. However, it is known that ethylphenidate possesses significant CNS activity. Schweri et al. (1985) found that relative to methylphenidate, (dl)-three-ethylphenidate exhibits approximately 50% the potency of methylphenidate in the inhibition of $[^3H]$methylphenidate binding to rat striatal synaptosomal membranes. Portoghese and Malpeis (1961) reported that (dl)-three-ethylphenidate was 80% as active as methylphenidate in inducing locomotor activity in mice. However, it is important to consider that these comparisons were based on the synthetic racemate of ethylphenidate, which may not serve appropriately as an authentic reference standard of metabolically formed ethylphenidate. In that methylphenidate is subject to enantioselective deesterification, which greatly reduces the oral bioavailability of l-methylphenidate relative to d-methylphenidate (see Patrick and Markowitz, 1997), and that the d-methylphenidate enantiomer is primarily responsible for CNS and peripheral activity (Patrick et al., 1987), it is quite possible that such esterase stereoselectivity general-

**TABLE 1**

Pharmacokinetic parameters for methylphenidate (MPH), ethylphenidate (EPH), ritalinic acid (RA), and ethanol (EtOH). AUC, terminal elimination phase half-lives, time to maximum concentration ($t_{\text{max}}$), and maximum concentration ($C_{\text{max}}$) for MPH, EPH, RA, and EtOH for six healthy subjects administered a single oral dose of MPH followed 30 min later by 0.6 g/kg EtOH over 15 min.

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*Note: Values are presented as mean ± standard deviation.*
izes to substrate transesterification as well. Accordingly, the enantio-
meric disposition of circulating ethylphenidate may be distorted (from
50:50) and thus prevent any definitive correlation between the estab-
lished pharmacology of racemic ethylphenidate and the potential
pharmacological contribution of the metabolically formed ethylpheni-
date of unknown stereochemistry.

Although the toxicity of ethylphenidate has not been examined,
the low concentrations of ethylphenidate detected in this study indi-
cate that a single clinically relevant dose of methylphenidate in
combination with moderate intake of ethanol is unlikely to result in
substantial generation of this metabolite relative to the parent drug.
However, this study raises the possibility that at higher doses of
methylphenidate, larger ethylphenidate concentrations might contri-
but to pharmacological effects. Similarly, some controlled studies of
cocaine formation in humans have found 80% lower concentra-
tions of cocaine than those detected in clinical and forensic
cases, a disparity likely attributable to the bing use of cocaine and the
longer elimination half-life of cocaethylene (Jatlow et al., 1996).

Among alcohol consuming individuals, ethylphenidate formation
may have clinical implications in patients receiving doses of methyl-
phenidate in the upper range of clinically useful doses (>1.5 mg/kg/
day), patients with a relatively low clearance of methylphenidate
compared with the population average, or, finally, persons abusing
methylphenidate. With regard to the latter group, there are a number of
documented cases of intranasal abuse of methylphenidate (Jaffe,
1991; Garland, 1998; Massello and Carpenter, 1999), some with fatal
consequences (Falzon and Ward, 1996; Massello and Carpenter,
1999). Although never examined under controlled conditions, intra-
nasal methylphenidate would be expected to allow for a much more
rapid and perhaps more complete absorption, resulting in much higher
blood concentrations (Falzon and Ward, 1996) than by the oral route,
where bioavailability is low (see Patrick and Markowitz, 1997).

In conclusion, the detection of ethylphenidate as a metabolite in
plasma and urine of the six human subjects studied opens the possi-
bility that such a CNS active metabolite may contribute to the cat-
echolaminergic effects in certain individuals, depending on their
methylphenidate dose and ethanol consumption. The increased rec-
ognition, diagnosis, and pharmacological treatment of adult ADHD is
well documented (Spencer et al., 1995; Elia et al., 1999). Many of
these individuals may consume moderate amounts of ethanol in social
conditions. Additionally, it is known that a greater risk for sub-
stance abuse exists in this population (Biederman et al., 1995). Fur-
thermore, methylphenidate is well recognized as a drug of high abuse
potential in the general population (Drug Enforcement Administra-
tion, 1995), and cases of ethanol and methylphenidate coabuse have
been documented (Jaffe et al., 1991). Taken together, it appears that
coingestion of methylphenidate and ethanol may frequently occur on
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