Invited Commentary

Absorption differences between immediate-release dexmethylphenidate and dl-methylphenidate

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Number of text pages: 8

Tables: 0

Figures: 1

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Words in discussion: 1,342

NON-STANDARD ABBREVIATIONS: ADHD, attention-deficit/hyperactivity disorder; AUC, area under the plasma concentration-time curve; $AUC_{0\text{-}inf}$, AUC zero to infinity; d-MPH, dexmethylphenidate; CI, confidence interval; dl-MPH, dl-methylphenidate; FDA, U.S. Food and Drug Administration; IR, immediate-release; $C_{max,}$ maximum plasma concentration; pAUC, partial AUC; PK, pharmacokinetic.

ABSTRACT

The postulate that twice the mg/kg dose of dl-methylphenidate (dl-MPH) would result in equal exposure to d-MPH when compared to half that mg/kg dose of the chiral switch product dexmethylphenidate (d-MPH) was tested. Using a randomized, crossover study design, 12 men and 12 women received either immediate-release (IR) dl-MPH (0.3 mg/kg) or IR d-MPH (0.15 mg/kg). Relative bioavailability comparisons included partial area under the plasma d-MPH concentration curves ($pAUC_{0\text{-}3\ hours}$) – a new regulatory metric presently only required for bioequivalence testing of a specific dl-MPH *modified-release* product. The geometric mean ratios for both the C_{max} and $AUC_{0\text{-}inf}$ were within the 90% confidence interval (CI) regulatory range of 0.8-1.25, indicating these two drugs were bioequivalent in terms of d-MPH. However, the $pAUC_{0\text{-}3\ hours}$ geometric mean ratio for d-MPH following IR dl-MPH versus IR d-MPH was 0.76 ($P < 0.001$; CI 0.67-0.87), i.e., showing significantly less early exposure to the d-isomer than IR d-MPH. The 1 hour d-MPH concentration following dl-MPH was 56% of that following the enantiopure drug. The maximum d-MPH plasma concentration (C_{max}) for dl-MPH was also significantly lower for dl-MPH ($P < 0.05$; CI 1.02-1.19), while the $AUC_{0\text{-}inf}$ ratio of 0.89 was not significantly different ($P = 0.21$; CI 0.98-1.13). The $AUC_{0\text{-}3\ hours}$ difference reported here points to the potential limitations of using bioequivalence for sound predictions of dose-response relationships. Knowledge of the greater early exposure to d-MPH following the pure d-isomer drug compared to the racemate may contribute to drug individualization/optimization in the treatment of attention-deficit/hyperactivity disorder (ADHD).

Introduction

In 2013, Patrick et al. reported that the administration of immediate-release (IR) dl-methylphenidate (dl-MPH; Ritalin, Novartis Pharmaceuticals, Summit, NJ) tablets resulted in a 60% lower partial area under the plasma-concentration curve ($pAUC_{0.5\text{-}2\ hours}$; $P < 0.01$; CI 0.49-0.79), and lower maximum plasma concentration (C_{max}; $P < 0.05$; CI 1.02-1.19), when compared to one-half the mg/kg dose of IR enantiopure d-methylphenidate (dl-MPH; Focalin, Novartis Pharmaceuticals, Summit, NJ) tablets. These findings were unexpected in view of the d-MPH product labeling which indicates that capsules of enantiopure d-MPH, or twice the mg dose of racemic dl-MPH, exhibit "comparable" d-MPH pharmacokinetics (PK) (Focalin 2015). Further, the PK parameters for d-MPH capsules were reported to exhibit "similar values" to those of the to-be-marketed d-MPH tablets (FDA 2001).

The greater early exposure to d-MPH following IR d-MPH administration compared to dl-MPH (equimolar with regard to d-MPH) was determined in the course of a broader study focused on the influence of ethanol consumed 0.5 hours after either d-MPH or dl-MPH in normal volunteers. Data demonstrating these differences between d-MPH and dl-MPH in the absence of ethanol are found within the summary PK tables and figures (Patrick et al., 2013). However, these differences were not addressed in the discussion section associated with this 2013 MPH-ethanol interaction study. Knowledge of the greater initial d-MPH plasma exposure following the IR pure d-isomer relative to IR dl-MPH contributes to the pharmacological characterization of PK-response relationships

(Patrick et al., 2015) and carries translational implications for the drug and dose individualization of attention-deficit/hyperactivity disorder (ADHD) patients.

Materials and Methods

Details are found in Patrick et al. (2013). Briefly, Healthy normal volunteers (12 men, 12 women) aged 21-42 years were within 15% of ideal body weight. One hour prior to dosing, the subjects received a light breakfast and a standard lunch 3.5 h after MPH dosing. dl-MPH used IR dl-MPH HCl (0.3 mg/kg) administered as 10 and 5 mg tablets (Ritalin®, Novartis Pharmaceuticals, Summit, NJ) with the 5 mg tablets halved when appropriate; d-MPH using oral IR d-MPH HCl (0.15 mg/kg) administered as 5 and 2.5 mg tablets (Focalin®, Novartis Pharmaceuticals) with the 2.5 mg tablets halved when appropriate. Plasma samples were obtained 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h after MPH dosing. Plasma analysis used chiral liquid chromatography-tandem mass spectrometry (see Patrick et al., 2007 for details). PK analyses used standard methods.

Results

Comparison of the $pAUC_{0\text{-}3\ hours}$ for IR dl-MPH versus IR d-MPH yielded geometric mean ratios of 0.76 (P = 0.001; 90% CI 0.67-0.89), i.e., dl-MPH resulted in 76% less exposure to d-MPH over the 0-3 hour time period relative to pure d-MPH. However, in terms of total exposure to d-MPH, the racemate/pure isomer $AUC_{0\text{-}inf}$ d-MPH ratio was not significantly different: 0.89 (P = 0.206; 90% CI 0.98-1.13). The corresponding C_{max} ratio was 0.84 (P <0.05; 90% CI 1.02-1.19).

Within our data set, the 1 hour and 1.5 hour d-MPH plasma concentration ratios following dl-MPH compared to d-MPH were 0.56 (P = 0. 001; 90% CI 0.40-0.73) and

0.65 ($P < 0.001$; 90% CI 0.52-0.81), respectively. The mean 2 and 2.5 hour d-MPH plasma concentration was also significantly lower for the racemate compared to the pure d-isomer ($P < 0.01$), though the mean 0.5 hour d-MPH concentrations were not significantly different – Fig. 1.

Discussion

Pharmacological benefits resulting from the chiral (or racemic) switch approach to drug discovery have many precedents, such as esomeprazole overcoming cytochrome P_{450} 2C19 polymorphism-based differences in peptic ulcer cure rates when compared to omeprazole (Klieber et al., 2015); and the antidepressant escitalopram appearing to more selective in targeting the serotonin reuptake transporter in the absence of the R-enantiomer of citalopram (Sanchez 2006). Any potential therapeutic benefit of d-MPH over dl-MPH has been largely unknown to the literature, with the exception of overcoming absorption phase drug interactions with ethanol (Patrick, et al., 2013; Patrick et al., 2015).

The present commentary brings recognition to the significant differences in the relative d-MPH bioavailability during early exposure to the racemic drug compared to half the mg/kg dose of the pure d-isomer. Extrapolating to a clinical context, drug dependent differential d-MPH exposure can be expected to apply to the 3 hours following the breakfast time dose and the 3 hours following the lunch time dose when using a standard twice daily MPH regimen for the treatment of ADHD. Knowledge of these d-MPH PK differences between dl-MPH versus d-MPH offers the potential to assist in the drug and dose optimization/individualization, as consistent with the

established MPH dose-response relationships for both stimulatory effects (Swanson and Volkow, 2002; Volkow and Swanson 2003, Spencer et al., 2006) and treatment emergent side effects (Patrick et al., 1987b; Kollins et al., 1998).

The labeling information for d-MPH tablets recommends using half the previous mg dose when converting a patient receiving a maintenance dose of dl-MPH to the new drug entity d-MPH. In addition, the labeling includes d-MPH absorption data based on a range of doses delivered from d-MPH capsules. According to the labeling, d-MPH reaches a C_{max} at "about 1 - 1.5 hours", with "comparable levels" of plasma d-MPH concentrations attained following twice the mg/kg doses of dl-MPH in capsules (Focalin®, 2015). Further, MPH capsules were reported to exhibit "similar" PK as the tablets (FDA 2001). In the Patrick et al., 2013 study, the respective 1 and 1.5 hour d-MPH plasma mean concentrations were significantly less for the racemate compared to the pure isomer (see Results).

In the context of this overall 0-3 hour time frame, it is noted that the recommended dosing interval for IR d-MPH or dl-MPH is 4 hours. Our reported $AUC_{0\text{-}3\ hours}$ differences notwithstanding, the comparisons of C_{max} and $AUC_{0\text{-}inf}$ for d-MPH versus dl-MPH fell within the statistical range for regulatory bioequivalence – were it not for the fact that dl-MPH and d-MPH are considered separate drugs and technically cannot be FDA bioequivalent. Nonetheless, this active (Patrick et al., 1987) d-isomer PK comparison does point to the potential limitations of using only C_{max} and $AUC_{0\text{-}inf}$ 80-125% CIs for comprehensive studies of PK-pharmacodynamic correlations (Patrick et al., 2013; 2015).

The explanation for the PK differences we reported between dl-MPH and the "new drug entity" d-MPH is subject to conjecture, though the following factors may be pertinent: (1) Different tableting processes are used in the manufacture of the dl-MPH and d-MPH formulations; (2) Eleven of our 24 subjects received a minor portion of their d-MPH dose in the form of a half tablet when this aided in more accurate mg/kg dosing. The d-MPH tablets were not specifically designed to be halved, i.e., the 2.5 mg d-MPH tablet is not scored. Accordingly, the resulting cut tablet surface difference from that of an intact tablet may have influenced the dissolution rate; (3) The dl-MPH and d-MPH products use different chiral excipients, e.g., tragacanth in dl-MPH (Ritalin® 2015) and microcrystalline cellulose in d-MPH (Focalin® 2015). Nonequivalent chiral environments alter physicochemical properties of chiral drugs; (4) Solubility differences between d-MPH and dl-MPH may influence dissolution rates. Most racemic compounds are more soluble than their corresponding enantiomers (Eliel and Wilens, 1994), the so-called "double solubility" rule (Collet et al., 1980), though any greater solubility of dl-MPH over d-MPH would simplistically be expected to accelerate, not retard, absorption (Fig. 1).

No head-to-head PK study has specifically been designed to compare the relative d-MPH bioavailability of commercial IR dl-MPH tablets compared to IR d-MPH tablets. Unlike our findings, an earlier study of dl-MPH versus d-MPH PK reported comparable plasma d-MPH concentrations (Quinn et al., 2004). A range of experimental design differences between the 2004 study and our 2013 study limit direct comparisons. Such differences include: (a) The 2004 study administered d-MPH or dl-MPH in extemporaneously compounded capsules. The mean T_{max} for d-MPH from capsules has been reported to be 1.8 h (n = 30), compared to 1.1 h (n = 9) for tablets (FDA 2001); (b)

The earlier study dosed the subjects with breakfast; the 2013 study provided a light breakfast 1 hour before dosing. Food has been reported to delay the d-MPH time to maximum plasma concentration (T_{max}) and may increase total MPH exposure (Midha et al., 2001; Teo et al., 2004). (c) The earlier study used ADHD children (n = 32). Exposure to d-MPH has been reported to be "somewhat lower" in children than in adults (Focalin®, 2015). The present study used normal adults. (d) The earlier study subjects were all male. The 2013 study used 12 men and 12 women. Significant PK sex dimorphisms have been reported for a range of MPH formulations (Markowitz et al., 2003; Patrick et al. 2007); (e) The Quinn study used relatively few plasma sampling times during the period of high drug exposure: 0.5, 1, 1.5, 2, 4 hour (and 8, 10 hour); The 2013 study included these sampling times in addition to 2.5, 3, 5, 6 hour (and 8, 10, 12 hour) samples; (f) Differences in the two analytical methods may have contributed to the different results (see Lim et al., 1986; Zhu et al., 2011).

Clinical trials have evaluated the relative efficacy of IR d-MPH versus twice (Quinn et al., 2004), or nearly twice (Wigal et al., 2004), the mg dose of IR dl-MPH. Compared to placebo, these studies reported significant ADHD symptom reduction within the 4 hour duration of action for both the pure isomer and the racemate. Post hoc analysis of the Wigal data led to the cautious suggestion that clinician and teacher ratings of patient improvement were greater following d-MPH than following dl-MPH (Weiss et al., 2004). It was theorized that this apparent disparity in efficacy could be based on MPH isomeric composition differences influencing "bioavailability, potency or metabolism". To our knowledge, findings of any potential therapeutic differences between IR d-MPH and dl-MPH have not been replicated.

Subsequent to our earlier report of the significant difference between IR d-MPH and IR dl-MPH (Patrick et al., 2013), pAUC metrics have become a timely new MPH PK regulatory parameter, though limited to bioequivalence testing of specific generic *modified-release* dl-MPH formulations versus the branded osmotic-release dl-MPH product. Anecdotal reports of diminished afternoon efficacy for these generic products compared to the osmotic formulation prompted the FDA to further review approval histories and culminated in a change of the therapeutic equivalence rating for these specific generic products from AB to BX. The consequence is that BX MPH products cannot be automatically substituted for this branded product (FDA 2014; Jackson 2014). Approval of generic versions of this osmotic branded product will now require testing of $pAUC_{0\text{-}3\ hours}$ and $pAUC_{3\text{-}7\ hours}$ in the fasted state, as well as $pAUC_{0\text{-}4\ hours}$ and $pAUC_{4\text{-}8\ hours}$ in the fed state. These new metrics are in addition to the customary bioequivalence parameter comparisons (though include additional in vitro studies). The FDA did not extend this AB-to-BX coding change to other modified-release MPH products (for examples see Patrick et al., 2009).

The PK differences between IR d-MPH and dl-MPH discussed in this commentary are offered for a better understanding of pharmacological options in treating ADHD. In addition, it addresses potential confounds relevant to developing definitive bioavailability protocols as applied to both IR and racemic switch drugs. To underscore the challenge of appropriately designing PK comparisons of MPH, the FDA changed the Orange Book coding of IR dl-MPH products from “AA” to “AB” after using the novel approach of including intrasubject variability in an overall experimental design (Meyer et al., 2000).

Acknowledgement

The authors express gratitude for the contributions of Joshua M. Knight to this commentary.

Authorship contributions:

Participated in research design: Patrick, Straughn

Conducted experiments: Patrick

Performed data analysis: Straughn, Patrick

Wrote or contributed to the writing of the manuscript: Patrick, Straughn

Financial disclosure:

Funding support for this work was solely received from the National Institutes of Health (KP). No other funding could be construed as a conflict of interest. KP has been a consultant for Janssen, ALZA, Shire, Noven and UCB 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 in Jan 2014. AS is a member of the Board of Directors for Cingulate Therapeutics and has been a consultant for Watson.

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Footnotes

This publication was supported by the National Institutes of Health Institute of Alcohol and Alcoholism [grant R01AA016707]; and the South Carolina Clinical & Translational Research Institute, with an academic home at the Medical University of South Carolina, via use of the Clinical & Translational Research Center, National Institutes of Health [grant UL1 TR000062, UL1 RR029882].

Fig. 1. Significantly higher mean plasma d-MPH concentrations resulted over the 0 – 3 hour period following d-MPH (0.15 mg/kg; Δ) compared to dl-MPH (0.3 mg/kg; □) in 24 normal volunteers; ****** $P < 0.01$; ******* $P < 0.001$; adapted from Patrick et al., 2013.

DMD Fast Forward. Published on January 4, 2016 as DOI: 10.1124/dmd.115.067975
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