Commentary

Absorption Differences between Immediate-Release Dexamethasone and dl-Methylphenidate

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ABSTRACT

The postulate that twice the milligram/kilogram dose of dl-methylphenidate (dl-MPH) would result in equal exposure to d-MPH compared with half that milligram/kilogram dose of the chiral switch product dexamethasone (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 concentration-time curves (pAUC_{0-3h}) for d-MPH. The pAUC_{0-3h} is 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 area under the plasma concentration-time curve (AUC_{0-3h}) were within the 90% confidence interval (CI) regulatory range of 0.8-1.25, indicating that these two drugs were bioequivalent in terms of d-MPH. However, the pAUC_{0-3h} geometric mean ratio for d-MPH after IR dl-MPH versus IR d-MPH was 0.76 (P < 0.001; 90% CI, 0.67-0.87), showing significantly less early exposure to the d-isomer than IR d-MPH. The 1-hour d-MPH concentration after dl-MPH was 56% of that after 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), whereas the AUC_{0-3h} ratio of 0.89 was not significantly different (P = 0.21; CI, 0.98–1.13). The AUC_{0-3h} 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 after the pure d-isomer drug compared with the racemate may contribute to drug individualization/optimization in the treatment of attention deficit hyperactivity disorder.

Introduction

Patrick et al. (2013) previously reported that the administration of immediate-release (IR) dl-methylphenidate (dl-MPH) tablets (Ritalin; Novartis Pharmaceuticals, Summit, NJ) resulted in a 60% lower partial area under the plasma concentration-time curve [pAUC_{0-3h}, P < 0.01; confidence interval (90% CI), 0.49–0.79] and lower maximum plasma concentration (C_{max}, P < 0.05; 90% CI, 1.02–1.19) compared with half the milligram/kilogram dose of IR enantiopure dl-MPH tablets (Focalin; Novartis Pharmaceuticals). These findings were unexpected in view of the d-methylphenidate (d-MPH) product labeling, which indicates that capsules of enantiopure d-MPH, or twice the milligram dose of racemic dl-MPH, exhibit “comparable” d-MPH pharmacokinetics (PK) (Drugs@FDA, Focalin, Label Information, Supplement 018, April 17, 2015). Furthermore, the PK parameters for d-MPH capsules were reported to exhibit “similar values” to those of the to-be-marketed d-MPH tablets (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-278_Focalin.cfm).

The greater early exposure to d-MPH after IR d-MPH administration compared with 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 in the article by Patrick et al. (2013). However, these differences were not addressed in the discussion section associated with this 2013 methylphenidate (MPH)-ethanol interaction study. Knowledge of the greater initial d-MPH plasma exposure after the IR pure d-isomer relative to IR dl-MPH contributes to the pharmacological

ABBREVIATIONS: ADHD, attention deficit hyperactivity disorder; AUC, area under the plasma concentration-time curve; d-MPH, dexamethasone; CI, confidence interval; dl-MPH, dl-methylphenidate; FDA, U.S. Food and Drug Administration; IR, immediate-release; MPH, methylphenidate; pAUC, partial area under the plasma concentration-time curve; PK, pharmacokinetics.
characterization of PK-response relationships (Patrick et al., 2015) and carries translational implications for the drug and dose individualization of patients with attention deficit hyperactivity disorder (ADHD).

Materials and Methods

Details are found in the study by Patrick et al. (2013). Briefly, healthy normal volunteers (12 men and 12 women) aged 21–42 years were within 15% of ideal body weight. The subjects received a light breakfast 1 hour before dosing and a standard lunch 3.5 hours after MPH dosing. dl-MPH using IR dl-MPH HCl (0.3 mg/kg) was administered as 10- and 5-mg tablets (Ritalin; Novartis Pharmaceuticals), with the 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 hours 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 pAUC0–3h for IR dl-MPH versus IR d-MPH yielded geometric mean ratios of 0.76 (P = 0.001; 90% CI, 0.67–0.89); dl-MPH resulted in 76% less exposure to d-MPH over the 0- to 3-hour time period relative to pure d-MPH. However, in terms of total exposure to d-MPH, the racemate/pure isomer AUC0–tandem mass spectrometry

Discussion

Pharmacological benefits resulting from the chiral (or racemic) switch approach to drug discovery have many precedents, such as esomeprazole overcoming CYP2C19 polymorphism-based differences in peptic ulcer cure rates compared with omeprazole (Klieber et al., 2015) and the antidepressant escitalopram appearing to be more selective in targeting the serotonin reuptake transporter in the absence of the R-enantiomer of citalopram (Sánchez, 2006). Any potential therapeutic benefit of d-MPH over dl-MPH has been largely unknown in the literature, with the exception of overcoming absorption-phase drug interactions with ethanol (Patrick et al., 2013, 2015).

This commentary brings recognition to the significant differences in the relative d-MPH bioavailability during early exposure to the racemic drug compared with half the milligram/kilogram 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 after the breakfast-time dose and the 3 hours after 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 milligram 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 Cmax at “about 1–1.5 hours,” with “comparable levels” of plasma d-MPH concentrations attained after twice the milligram/kilogram doses of dl-MPH in capsules (Drugs@FDA, Focalin, Label Information, Supplement 018, April 17, 2015). Furthermore, MPH capsules were reported to exhibit “similar” PK as the tablets (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/21-278_Focalin.cfm). In the study by Patrick et al. (2013), the respective 1- and 1.5-hour d-MPH plasma mean concentrations were significantly less for the racemate compared with the pure isomer (see the Results).

In the context of this overall 0- to 3-hour time frame, it is noted that the recommended dosing interval for IR dl-MPH or dl-MPH is 4 hours. Our reported AUC0–3h differences notwithstanding, the comparisons of Cmax and AUC0–tandem mass spectrometry

![Fig. 1. Significantly higher mean plasma d-MPH concentrations resulted over the 0–3 hour period after d-MPH (0.15 mg/kg; circles) compared with dl-MPH (0.3 mg/kg; squares) in 24 normal volunteers. **P < 0.01; ***P < 0.001. Adapted from Patrick et al. (2013).](image-url)
The explanation for the PK differences we reported between dl-MPH and the “new drug entity” d-MPH is subject to conjecture, although the following factors may be pertinent. First, different tableting processes are used in the manufacture of the dl-MPH and d-MPH formulations. Second, 11 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 milligram/kilogram 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. Third, the dl-MPH and d-MPH products use different chiral excipients, such as tragacanth in dl-MPH (Drugs@FDA, Ritalin, Label Information, Supplement 80, April 17, 2015) and microcrystalline cellulose in d-MPH (Focalin, 2015). Nonequivalent chiral environments alter physicochemical properties of chiral drugs. Finally, solubility differences between d-MPH and dl-MPH may influence dissolution rates. Most racemic compounds are more soluble than their corresponding enantiomers (Eliel and Wilen, 1994), the so-called “double solubility” rule (Collet et al., 1980), although 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 with 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 the following. First, Quinn et al. (2004) administered d-MPH or dl-MPH in extemporaneously compounded capsules. The mean time to maximum plasma concentration for d-MPH from capsules has been reported to be 1.8 hours (n = 30), compared with 1.1 hours (n = 9) for tablets (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-278_Focalin.cfm). Second, the study by Quinn et al. (2004) dosed the subjects with breakfast; the study by Patrick et al. (2013) provided a light breakfast 1 hour before dosing. Food has been reported to delay the d-MPH time to maximum plasma concentration and may increase total MPH exposure (Midha et al., 2001; Teo et al., 2004). Third, the earlier study by Quinn et al. (2004) used children with ADHD (n = 32). Exposure to d-MPH has been reported to be “somewhat lower” in children than in adults (Focalin, 2015). Our current study used normal adults. Fourth, the earlier study subjects were all male. The study by Patrick et al. (2013) 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). Fifth, the study by Quinn et al. (2004) used relatively few plasma sampling times during the period of high drug exposure: 0.5, 1, 1.5, 2, and 4 hours (and 8 and 10 hours). The study by Patrick et al. (2013) included these sampling times in addition to 2.5, 3, 5, and 6 hours (and 8, 10, and 12 hours). Finally, 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 milligram dose of IR dl-MPH. Compared with 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 data from Wigal et al. (2004) led to the cautious suggestion that clinician and teacher ratings of patient improvement were greater after d-MPH than after 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” (Weiss et al., 2004). 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, although 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 with 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 (Jackson, 2014; http://www.fda.gov/drugs/drugsafetyucm422569.htm). Approval of generic versions of this osmotic branded product will now require testing of pAUC0–3 h and pAUC3–7 h in the fasted state, as well as pAUC0–4 h and pAUC4–8 h in the fed state. These new metrics are in addition to the customary bioequivalence parameter comparisons (although they 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, this article 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).

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Authorship Contributions

Participated in research design: Patrick, Straughn.
Conducted experiments: Patrick.
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References


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