Effects of Food on the Pharmacokinetics of Methylphenidate

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Purpose. To test the hypothesis that the pharmacokinetics of d-methylphenidate (d-MPH) would be altered by food ingested before administration of an immediate release formulation (dl-MPH- IR) but not when food is ingested before a slow release formulation (dl-MPH-SR).

Methods. A randomized, four-phase, open label, crossover design was conducted in 24 healthy men who each received, on separate occasions, dl-MPH-IR and dl-MPH-SR taken after an overnight fast and 15 min after a standardized breakfast (20% protein, 21% fat, 59% carbohydrate). Plasma MPH levels were monitored by a validated, stereoselective, GLC-ECD method.

Results. For plasma d-MPH, there were significant differences (ANOVA) between dl-MPH-IR and dl-MPH-SR in tmax, Cmax (peak exposure), and Cmax/AUC (sensitive to rate of absorption). Dl-MPH-SR on average delayed tmax from 2.3 to 3.7 h and lowered Cmax 34%. There was no significant difference between the formulations in AUC (extent of absorption). For dl-MPH-IR, food significantly increased Cmax (23%) and AUC (15%) and for dl-MPH-SR the corresponding increases were Cmax (17%) and AUC (14%). After dl-MPH-IR, food delayed average tmax from 2.0 to 2.5 but had no effect on tmax after dl-MPH-SR. There was no effect of food on Cmax/AUC (rate of absorption).

Conclusions. Food caused a significant increase in extent of absorption but had no effect on rate of absorption of d-MPH after either dl-MPHIR or dl-MPH-SR.

KEY WORDS: d-methylphenidate; immediate release; slow release; pharmacokinetics; food effects.

INTRODUCTION

dl-*threo*-Methylphenidate (dl-MPH) is a drug that is subject to extensive enantioselective presystemic metabolism in humans (1,2) with no evidence of interconversion between the enantiomers (3). In ADHD children, it was established (4) that the pharmacodynamic activity of dl-MPH resides entirely with the d-enantiomer. The major metabolic pathway is ester hydrolysis to form ritalinic acid (1). Only trace amounts of oxidative and conjugative metabolites have been detected in humans (5), and recently it was shown that CYP2D6 has little or no effect on the pharmacokinetics of dl-MPH (6).

Two early speculative reports (7,8) suggested that dl-MPH should be administered before meals because of the possibility that the drug may be unstable in the acidic milieu of the stomach. Subsequently, however, two small studies in children (9) and healthy adults (10) showed that the presence of food did not impede the absorption of MPH from the gastrointestinal tract, although neither study had sufficient statistical power to detect any pharmacokinetic difference between the fasted and fed states.

Patrick and coworkers (11) performed a three-way crossover bioavailability study in 18 healthy male volunteers to compare a formulation of immediate release dl-MPH (dl-MPH-IR) with two formulations of slow release dl-MPH (dl-MPH-SR). On each of the three dosing days, the appropriate formulation of dl-MPH was administered immediately before the consumption of a standard high-fat breakfast. The authors reported the extents of absorption, as determined from the areas under the plasma concentration vs. time curves (AUCs), of the three products were within 5% of each other. There was no significant difference between the two SR formulations in rate or extent of absorption. The study showed that a high-fat meal did not prevent absorption of MPH but, unfortunately, did not include comparison between the fed and fasted states.

Recently, Modi and coworkers (12) examined the effect of food on the pharmacokinetics of MPH after administration of an osmotic controlled release formulation of MPH that was administered either in the fasting state or within 30 min of consuming a high-fat breakfast (approximately 15% protein, 60% fat, and 25% carbohydrate). The results showed a non-significant tendency for AUC in the fed state to exceed that in the fasted state. The authors pointed out that the high-fat meal was not a typical breakfast for children and speculated that meals with a lower fat content would not represent a greater change in absorption after administration of the controlled release formulation than that reported in their study (12).

The present balanced, four-phase, crossover study in 24 healthy volunteers was undertaken to examine the possible effects of food on the rates and extents of absorption of d-MPH after administration of an immediate release formulation (dl-MPH-IR), a slow release formulation (dl-MPH-SR) both in the fasting state and after a standardized breakfast. The meal was a high-carbohydrate breakfast (20% protein, 21% fat, and 59% carbohydrate) based on that selected by Chan and coworkers (9) and is intended to represent a typical breakfast consumed by North American children.

MATERIALS AND METHODS

Materials

Racemic dl-*threo*-methylphenidate (Ritalin and Ritalin SR, Novartis Pharmaceuticals Canada Inc.) were purchased commercially through the Royal University Hospital Dispensary, Saskatoon, SK, Canada. Ethylphenidate Hydrochloride (internal standard) was prepared in house by ethylation of ritalinic acid. Dl-*threo*-methylphenidate was purchased from

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ABBREVIATIONS: MPH, methylphenidate; dl-MPH-IR, immediate release methylphenidate; dl-MPH-SR, slow release methylphenidate; GLC-ECD, gas-liquid chromatography with electron capture detection; ADHD, attention deficit hyperactivity disorder; LLOQ, lower limit of quantification.

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the USP Convention Inc. Solvents and all other reagents were of analytic grade and were used without further purification.

Subjects

Subjects who took part in this study were recruited from the student population at the University of Saskatchewan. Selection of volunteers was contingent on successful physical examination and clinical laboratory tests that included hematology, blood chemistry, and urinalysis. Twenty-four nonsmoking, healthy men aged 18–50 years, weighing no more than 15% from the ideal weight for height according to the Metropolitan Life Insurance Company Bulletin (1983) entered the study after giving informed consent. All subjects were required to refrain from drinking alcoholic beverages from 24 h before each drug administration, during the study, and until 24 h after the last blood sample was obtained. In addition, consumption of caffeine-containing products was not permitted on the day of drug administration, and the subjects were required to avoid exercise for 24 h after drug administration.

Drug Administrations

The study was a balanced, four-phase, four-sequence, open label, crossover design in which each subject received the following: A: 40 mg of Ritalin (dl-MPH-IR) taken with 150 mL of water 15 min after consumption of a standardized breakfast; B: 40 mg of Ritalin (dl-MPH-IR) taken with 150 mL of water after an overnight fast; C: 40 mg of Ritalin SR (dl-MPH-SR) taken with 150 mL of water 15 min after consumption of a standardized breakfast; and D: 40 mg of Ritalin SR (dl-MPH-SR) taken with 150 mL of water after an overnight fast. There was a washout period of 1 week between doses. Each subject was randomized to one of four sequences: sequence 1 = ABCD; sequence 2 = CADB; sequence 3 = DCBA; sequence 4 = BDAC. This arrangement of sequences meant that any given treatment was followed by each of the other treatments in some subjects.

Standardized Breakfast

The standardized breakfast consisted of the following: boiled egg (50 g); white bread (50 g); margarine (20 g); grape jelly (20 g); skimmed milk (500 mL); orange juice (250 mL). The subjects were instructed to consume the entire meal, which provided a total energy of 600 kcal (20% protein, 21% fat, and 59% carbohydrate). On each day of study, 12 subjects were randomized to receive breakfast in the balanced study design for a total of 48 breakfasts over the 4 days of study. The meal was prepared and served in a room on a different floor, well away from the room in which the fasting subjects were housed so that it was impossible for the latter to see or smell the food.

Blood Samples

Blood samples (10–15 mL) were drawn from the cubital vein into heparinized evacuated tubes (Vacutainers) without allowing the blood to come into contact with the rubber stopper at any time. The blood sampling schedule included a sample taken immediately before dosing (0 h) and at 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 16.0 h postdose. Plasma was separated immediately by centrifugation and stored at –20°C until analysis.

Analysis of Samples

Plasma samples were analyzed by an enantioselective GLC-ECD method modified after a published procedure (13). Briefly, the secondary amino group of MPH was reacted with heptafluorobutyryl-l-prolyl chloride to form a pair of diastereomeric amide derivatives that were then separated on a nonchiral OV225 column. Ethylphenidate was used as internal standard. The day-to-day performance of the assay was monitored by the analysis of quality control samples (analyst blind) run in parallel with test samples and standard curve samples in each analytic run. The test samples were bracketed by standard curve samples and quality control samples in all cases. The LLOQ was 0.1 ng/mL for each isomer.

Pharmacokinetic Calculations

The maximum plasma concentration (Cmax) and time to Cmax (tmax) were determined directly from the plasma concentration vs. time curves. Terminal elimination rate constants (Kel) were estimated (SAS v 6.12) from the terminal portion of the natural log transformed plasma concentration vs. time curves by linear regression using at least three data points. Area under the plasma concentration vs. time curve (AUClast) to the last measurable concentration (Clast) were calculated (SAS v 6.12) by the linear trapezoidal rule for ascending portions of the curve and the log trapezoidal rule for descending portions of the curve. AUClast was extrapolated to infinite time (AUC) by adding to AUClast the quotient of Clast and Kel. Half-life was calculated as the quotient of ln 2 and Kel

Statistical Calculations

The natural log transformed pharmacokinetic parameters Cmax, AUC, and the quotient of Cmax and AUC (Cmax/AUC) were examined by ANOVA (SAS v 6.12) in which the effects in the model were as follows: Formulation; Food; Phase; Sequence; Subject (Sequence). The subject (Sequence) mean square was used as an error term for Sequence. The overall within-subject (WSV) and the between-subject (BSV) coefficients of variation were estimated by equations A and B respectively:

$$WSV = \sqrt{\exp^{S_W^2} - 1} \times 100\% \quad \text{(A)}$$

$$BSV = \sqrt{\exp^{[(S_B^2 - S_W^2)/2]} - 1} \times 100\% \quad \text{(B)}$$

Wilcoxon's signed rank test was used to evaluate the effects of food and/or formulation on tmax.

RESULTS

Both formulations of dl-MPH were well tolerated by all volunteers, with or without breakfast. Mean plasma concentrations vs. time profiles of d-MPH are shown in Fig. 1. Plasma concentrations of l-MPH were relatively very low or not measurable and were not considered further.

The plasma concentration-dependent pharmacokinetic parameters, Cmax, AUC, and the ratio Cmax/AUC are

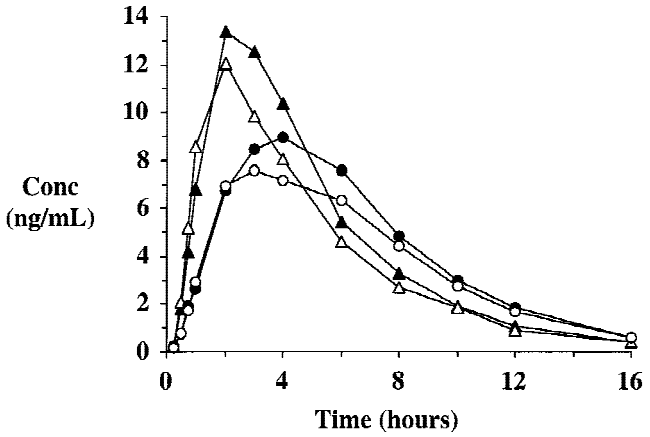

Fig. 1. Arithmetic mean plasma concentrations of d-MPH vs. time curves: for dl-MPH-IR with food (solid triangles), and without food (open triangles); and for dl-MPH-SR with food (solid circles), and without food (open circles).

shown in Table I as their geometric means together with minimum and maximum values. The wide ranges for Cmax and AUC were attributable to one individual (#17) who was one of two subjects (with #12) who exhibited very high values for these parameters and who contributed to very large overall between-subject coefficients of variation in Cmax (47.5%) and AUC (54.6%). The overall within-subject coefficients of variation were much smaller, however, for Cmax (21.8%) and AUC (13.6%). For the ratio Cmax/AUC, the BSV was 9.6% and the WSV was 13.6%).

Table II shows that there was a tendency for the presence of food to prolong average tmax of d-MPH by approximately 0.5 h after administration of dl-MPH-IR. This was confirmed by Wilcoxon's signed rank test ($P = 0.0184$), whereas there was no such effect of food after administration of dl-MPH-SR. However, the presence of food had no significant effect on terminal elimination half-life after administration of either dl-MPH-IR or dl-MPH-SR.

A summary of the results of ANOVA of the natural log transformed pharmacokinetic parameters is shown in Table III. The fixed effects of both formulation and food were highly significant for Cmax; for AUC, the effect of food was significant, whereas that for formulation was not significant. By contrast, the effect of formulation was significant for Cmax/AUC, whereas the effect of food was not. As anticipated, the effect of subject nested within sequence was significant for all three parameters because of large between-subject variability especially in terms of Cmax and AUC. The reason for the significant phase effect in Cmax is unknown.

Table I. Summary of Concentration-Dependent Pharmacokinetic Data for d-MPH after Administration of dl-MPH-IR or dl-MPH-SR with or Without Food

	Geometric Mean	Minimum	Maximum
Cmax (ng/mL)			
IR with food	14.30	5.12	28.18
IR no food	11.65	4.11	33.19
SR with food	9.19	4.62	18.20
SR no food	7.83	3.39	17.69
AUC (ng · h/mL)			
IR with food	68.10	24.82	131.44
IR no food	59.09	19.94	161.53
SR with food	66.29	27.23	118.28
SR no food	58.09	26.39	138.51
Cmax/AUC			
IR with food	0.210	0.159	0.341
IR no food	0.200	0.160	0.326
SR with food	0.138	0.116	0.170
SR no food	0.135	0.098	0.187

Table II. Data for d-MPH (Mean ± SD) After Administration of dl-MPH-IR or dl-MPH-SR with or Without Food

Treatment	Tmax (h)	Half-life (h)
IR with food	2.54 ± 0.88	2.67 ± 0.51
IR no food	2.00 ± 0.66	2.92 ± 1.40
SR with food	3.62 ± 1.13	2.70 ± 0.44
SR no food	3.71 ± 1.37	2.73 ± 0.59

DISCUSSION

Over the past 20 years, a vast amount of literature on the effects of food on the pharmacokinetics of a variety of drugs has accumulated. After a recent comprehensive review (14) of 491 manuscripts, however, it was concluded, "there is still no rational scientific basis to predict the effect of food for a particular chemical entity or a chemical class of therapeutic agents." Much of the pioneering work in this area has been performed with propranolol, but other drugs that exhibit a food effect are like propranolol in that they are also subject to extensive metabolism during the first pass through the gut wall and liver before reaching the systemic circulation. Briefly, the following are three of the possible mechanisms by which food effects may arise. (a) The ingestion of food may produce a transient increase in liver blood flow that would be expected to produce an increase in AUC of concomitantly administered drug due to decreased first-pass metabolism. In one study, however, an increase in liver blood flow induced by postural changes did not produce a comparable increase in AUC of propranolol compared with that produced by administration of food (15). (b) Dietary amino acids compete with drug for oxidative or conjugative metabolic pathways in the liver. In a study with isolated, perfused rat livers, amino acids increased steady-state concentrations of propranolol and reduced steady-state concentrations of a variety of phase I and phase II metabolites (16). *In vivo* experiments in humans, however, showed that a decrease in AUC of propranolol gluc-

Table III. Pr > F Values From ANOVA of Log Transformed Pharmacokinetic Parameters[a]

	Cmax	AUC	Cmax/AUC
Formulation	0.0001	NS[d]	0.0001
Food	0.0001	0.0001	NS
Phase	0.0151[b]	NS	NS
Sequence[c]	NS	NS	NS
Subject (sequence)	0.0001	0.0001	0.0183

[a] $\alpha = 0.05$
[b] Significant phase effect: phase 1 is highest; phase 3 is lowest.
[c] Subject (squence) mean square was used as an error term for Sequence.
[d] NS = not significant.

uronide was insufficient to account for the increase in AUC of the parent drug (17), and there was no significant decrease in the AUC of 4-hydroxypropranolol (18). Moreover, a high-carbohydrate, low-protein meal increased propranolol AUC in humans without producing an increase in liver blood flow (19). (c) The food effect involves neurologic and hormonal factors associated with the whole process of eating and digestion. Power and coworkers (20) conducted a study in which propranolol was administered to healthy humans after an overnight fast and on another occasion in which the volunteers were allowed to see and smell an appetizing meal without eating it. This teasing protocol produced a significant increase in tmax, and there was a strong trend toward an increase in AUC. These data suggest that a variety of influences are brought to bear on the phenomenon often referred to as the "food effect."

The maximum plasma concentration (Cmax) is arguably one of the most important pharmacokinetic parameters as far as physicians are concerned because of its association with maximum exposure/toxicity of the drug. Cmax depends on both rate and extent of absorption drug from the gastrointestinal tract, whereas AUC depends on extent of absorption but is not affected by rate of absorption. On the other hand, it has been shown that the ratio Cmax/AUC is sensitive to rate but not extent of absorption (21,22). Thus, the results of ANOVA (Table III) may be interpreted to indicate that, in comparison with results obtained with dl-MPH-IR, administration of dl-MPH-SR led to significant effects on rate of absorption (Cmax/AUC and Cmax) but not on extent of absorption (AUC). Table I indicates that Cmax was considerably (52%) higher after dl-MPH-IR compared with Cmax after the same dose of dl-MPH-SR. It has been reported that chewing Ritalin SR tablets increases rate of absorption (dose dumping) and effectively changes the pharmacokinetic profile into one similar to that obtained after administration of immediate release Ritalin (2). This phenomenon was a result of the disruption of the waxy matrix of Ritalin SR tablets brought about by chewing. The potential clinical significance of this observation in adverse effects (abdominal pains, nausea, and extreme anorexia) were described in the case of a child who chewed Ritalin SR tablets before swallowing (23). This situation arose when the child was switched from two daily doses of regular Ritalin tablets (where chewing before swallowing has little or no effect) to a once daily dose Ritalin SR containing twice the dose of dl-MPH.

Earlier work (9,10) showed that the presence of food did not impede the absorption of MPH from the gastrointestinal tract, although neither study had sufficient statistical power to detect any pharmacokinetic difference between the fasted and fed states. The present food effects study in 24 healthy adult volunteers was based on a standardized high-carbohydrate breakfast similar to that used in children by Chan and coworkers (9) and also reflective of the present day trend away from the traditional high-fat breakfast. It is possible, however, the effect of food may be as great or greater after a high-fat meal than under the present conditions.

Table III shows that the presence of food had a statistically significant effect on extent of absorption (AUC), but no significant effect on rate of absorption (Cmax/AUC). A clinically relevant outcome of the presence of food was a 23% increase in Cmax after dl-MPH-IR and a 17% increase in Cmax after dl-MPH-SR swallowed whole (Table I). If the Ritalin SR tablets were to be chewed before swallowing, however, there is potential for a 49% increase in Cmax when the formulation is taken after an overnight fast, or a 56% increase in Cmax when the formulation is taken after breakfast.

In addition to effects on Cmax, the food-induced increase in extent of absorption led to statistically significant effects on AUC (Table III). Table I shows a 15% increase in AUC after dosing with dl-MPH-IR and a 14% increase in AUC after dosing with dl-MPH-SR. These results confirm that the extent of absorption d-MPH was modestly enhanced when either formulation was administered after breakfast. The discovery that dl-MPH-SR exhibited a significant food effect was unexpected in principle but may be understood by inspection of Fig. 1, which shows that the dosage form, in fact, behaves poorly as a sustained release formulation.

CONCLUSIONS

Patient compliance is a very important factor in the effective use of MPH in the treatment of attention-deficit hyperactivity disorder in children and adults. In practical terms, a requirement that a drug is to be taken at a fixed interval before breakfast is often difficult to remember in a busy household. The present study shows that MPH can be taken after breakfast with enhanced extent of absorption. The resulting increase in Cmax could conceivably lead to adverse effects such as abdominal pains and nausea, particularly when a child chews a slow release product before swallowing. These observations suggest that a regular morning routine should be established while the patient is being "titrated" to find the optimal dose for that individual. Three advantages of taking the medication after breakfast are that it is easier to remember, the possibility of gastric discomfort is diminished after a meal, and that the patient will already have had a meal before taking the drug; therefore, the effects of anorexia on the bodily economy will be diminished.

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