Methylphenidate Hydrochloride Given With or Before Breakfast: II. Effects on Plasma Concentration of Methylphenidate and Ritalinic Acid

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ABSTRACT. Methylphenidate HCl (Ritalin) is often prescribed for the treatment of hyperactivity and is usually administered orally 30 minutes to 1 hour before meals, based on an assumption that meals may interfere with the absorption or metabolism of the drug. Seven boys who were taking methylphenidate regularly for the treatment of hyperactivity were hospitalized and given their established dose of the drug intravenously or orally, either with breakfast or in a fasted state. Blood samples were taken to determine the pharmacokinetics of the drug in each condition. Few differences between the "fed" and "fasted" states were noted, but the statistically significant differences indicated that meals accelerate rather than impede the absorption of methylphenidate. *Pediatrics* 1983;72:56–59; *serum levels, methylphenidate, hyperactivity.*

Methylphenidate HCl (Ritalin) is prescribed in an oral dose for the management of hyperactivity.[1] After an oral dose, the amount of drug that reaches the circulation is dependent on gastrointestinal absorption and the first-pass effect of the liver. It is generally believed that methylphenidate should be taken on an empty stomach,[1,2] The presence of food is thought to interfere with the absorption of the drug and thus reduce its potency.[3,4] However, this has not been documented, and recent studies have shown no significant interference in the behavioral effect of methylphenidate when it is administered with meals.[5]

Received for publication May 10, 1982; accepted Oct 15, 1982.
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Administering methylphenidate before meals is troublesome for patients and their parents. The patient must be awakened early in the morning to take the medication, and then must wait one-half to one hour before eating breakfast. By then, the effect of the drug is apparent and may produce anorexia.

In this study, the effectiveness of oral-intravenous administration in the delivery of methylphenidate into the circulation was examined. Inasmuch as the effect of food on orally administered methylphenidate has not been reported, two oral administration conditions (in a fasted state or with breakfast) were established to examine the hypothesis that meals interfere with the absorption of this drug.

Methylphenidate and its metabolite, ritalinic acid, in the plasma were monitored following the three different modes of methylphenidate administration. Five criteria were examined: (1) elimination half-life of the compounds; (2) time required for the compounds to reach peak concentration in plasma; (3) peak concentration of the compounds; (4) bioavailability of methylphenidate; and (5) "area under the curve" (AUC) for ritalinic acid.

METHODS

The subjects were seven boys between 7 and 15 years of age who were receiving from 10 to 15 mg of methylphenidate (per administration) for the treatment of hyperactivity (see Table 1). These subjects had normal (>90) IQ scores, and scored more than 15 on the ten-item Conners parent rating scale.[6] Each subject underwent three days of testing in the Clinical Investigation Unit at The Hospital

for Sick Children under a protocol approved by the Human Subjects Committee of the University of Toronto. On the first day, methylphenidate was administered intravenously followed by a period of fasting. On the second and third day, methylphenidate was administered orally followed by either fasting or by breakfast in a counterbalanced fashion.

On the morning of testing, an intravenous catheter was inserted into the subject's arm. A predose blood sample was taken via the catheter. At 7:30 AM the subject was given a dose of methylphenidate (10 to 15 mg intravenously or orally). This was followed either by a period of continuous fasting until noon or by a standard breakfast (consisting of orange juice, milk, corn flakes, and toast).

Blood samples were collected via the catheter at 30, 45, 60, and 90 minutes, and at 2, 3, 4, 6, 8, and 10 hours after administration of the drug. The blood samples were immediately separated into plasma and the cell fraction was separated by centrifugation at 2,500 rpm for ten minutes. The plasma was analyzed for methylphenidate[7] and/or ritalinic acid[8] concentration, according to previously reported methods. For patients 6 and 7 only methylphenidate levels were measured. For patients 1 and 2 only ritalinic acid levels were measured. For the other patients, levels of both ritalinic acid and methylphenidate were measured.

TABLE 1. Clinical Data

Patient No.	Age (yr)	Body Weight (kg)	Dose of Methylphenidate Administered (mg)	Dose/Body Weight (mg/kg)
1	7	23.4	15	0.64
2	9½	26.8	10	0.37
3	10	32.0	15	0.47
4	8½	35.0	10	0.29
5	13	40.0	10	0.25
6	14½	50.9	15	0.29
7	7½	26.7	15	0.68

RESULTS AND DISCUSSION

Elimination Half-Life ($t_{½}$) for Methylphenidate

The $t_{½}$ for methylphenidate did not differ significantly across the three different conditions stud-

TABLE 2. Effects of Three Modes of Administration of Methylphenidate on Serum Concentration of Methylphenidate

Patient No.	Dose/Body Weight (mg/kg)	IV Fasted		Oral Fasted				Oral with Breakfast			
		$t_{½}$ (h)	Bioavailability	$t_{½}$ (h)	Peak Time (h)	Peak Concentration of Dose/Body Weight ([μg/L]/[mg/kg])	Bioavailability	$t_{½}$ (h)	Peak Time (h)	Peak Concentration of Dose/Body Weight ([μg/L]/[mg/kg])	Bioavailability
5	0.25	1.6	100	2.1	2.0	26.8	31.0	2.1	1.0	50.8	39.3
4	0.29	2.0	100	2.0	1.5	42.1	41.4	2.0	1.5	50.7	52.4
6	0.29	2.7	100	2.2	2.0	25.9	14.2	2.5	1.0	20.7	10.5
3	0.47	2.1	100	2.6	1.5	16.4	17.9	2.4	0.5	26.2	23.2
7	0.68	1.8	100	1.6	1.0	27.9	34.8	1.7	1.0	25.0	31.6
Mean ±SD		2.04 ±0.42	100 ±0	2.10 ±0.36	1.60* ±0.42	27.82 ±9.21	27.86 ±11.48	2.14 ±0.32	1.00* ±0.35	34.68 ±14.81	±31.40 ±15.87

* $P < .05$

TABLE 3. Effects of Three Modes of Administration of Methylphenidate on Serum Concentration of Ritalinic Acid

Patient No.	Dose/Body Weight (mg/kg)	IV Fasted				Oral Fasted				Oral with Breakfast			
		$t_{½}$ (h)	Peak Time (h)	Peak Concentration of Dose/Body Weight ([μg/L]/[mg/kg])	AUC of Dose/Body Weight	$t_{½}$ (h)	Peak Time (h)	Peak Concentration of Dose/Body Weight ([μg/L]/[mg/kg])	AUC Relative to IV (%)	$t_{½}$ (h)	Peak Time (h)	Peak Concentration of Dose/Body Weight ([μg/L]/[mg/kg])	AUC Relative to IV (%)
5	0.25	4.4	2.5	960	7429	3.2	2.5	660	49.1	3.1	2.0	540	38.2
4	0.29	4.8	1.5	776	6356	3.1	2.25	983	90.0	3.0	1.75	845	70.2
3	0.37	5.6	2.0	405	4235	3.4	1.1	676	81.8	4.0	1.0	568	78.7
2	0.47	4.4	1.5	638	4329	4.1	1.5	670	111.2	4.3	0.75	660	93.5
1	0.64	4.8	2.0	469	3877	3.2	2.0	430	113.9	3.2	1.7	442	122.2
Mean ±SD		4.80 ±0.49	1.9 ±0.42	650 ±226	5,245.20 ±1,560.03	3.40 ±0.41	1.87 ±0.57	684 ±197	89.2 ±26.3	3.52 ±0.59	1.44 ±0.54	611 ±152.2	80.6 ±30.8

ied: (1) intravenously administered methylphenidate during fasting, (2) orally administered methylphenidate during fasting, and (3) orally administered methylphenidate together with breakfast. The mean $t_{1/2}$ for methylphenidate was calculated to be 2.04 ± 0.42 hours, 2.10 ± 0.36 hours, and 2.14 ± 0.32 hours, respectively (Table 2). These values are a little lower than in previous studies.[9, 10]

Peak Time for Methylphenidate

Under the same conditions (ie, either with or without food), the time required for plasma methylphenidate to reach a peak concentration was similar among the five subjects. The peak time for methylphenidate concentration decreased in three of the five subjects when methylphenidate was administered orally with breakfast (Table 1). In the remaining two subjects, no difference was observed between "fed" and "fasted" states. The mean "peak time" was 1.60 ± 0.42 hours in the absence of food and 1.00 ± 0.35 hours in the presence of food, respectively. The fasting state increased the peak time significantly by 60% ($P < .05$ by paired t test), relative to the fed state. These data are contrary to the general belief that food interferes with the absorption of methylphenidate. Instead, these data indicate that food enhances the absorption of methylphenidate.

Peak Concentration of Methylphenidate in Plasma

To facilitate the comparison among subjects who had taken different doses of methylphenidate, the plasma concentration of methylphenidate was normalized by dividing peak concentration by the ratio of dose to body weight. The peak plasma concentration varied by as much as 2.5-fold between individuals, but varied less within individuals (Table 2). The observed between-subject-variability supports the finding of Gualtieri et al,[9] but the within-subject-variability is less than that reported.[9] The peak concentrations of methylphenidate (normalized for dose and body weight) following oral administration without or with breakfast were 27.82 ± 9.21 and 34.68 ± 14.81 μg/L divided by milligrams per kilogram of body weight, respectively. The difference is not statistically significant ($P > .1$ by paired t test). Thus, food did not alter the maximum concentration of methylphenidate in the serum of these patients.

Bioavailability

The bioavailability of methylphenidate following an oral dose varies as much as fivefold between individual subjects (Table 2). Further, the amount of methylphenidate present in the circulation was only 10.5% to 52.4% of that present following an identical intravenous dose. This suggested that only a small portion of an oral dose is absorbed as methylphenidate. The majority of the dose was either degraded before it reached the circulation or was not absorbed at all. The bioavailability was not systematically related to the dose administered. Thus, it is unlikely that such an observation was an artifact caused by different doses. The data indicate individual differences between subjects in the ability to absorb an oral dose of the drug exits, and support the similar results of Gualtieri et al.[9]

The mean bioavailability of orally administered methylphenidate without breakfast was 27.86% ± 11.48% and 31.40% ± 15.87%, respectively. This difference is not statistically significant. Thus, the amount of methylphenidate absorbed following an oral dose was not altered by taking it with breakfast.

Elimination Half-Life ($t_{1/2}$) for Ritalinic Acid

The $t_{1/2}$ values for ritalinic acid were much greater after the intravenous rather than the oral administration of methylphenidate. The mean $t_{1/2}$ values for ritalinic acid were 4.80 ± 0.49 hours, 3.40 ± 0.41 hours, and 3.52 ± 0.59 hours for IV, oral (fasted), and oral (with breakfast), respectively (Table 2). The differences between the IV data relative to either set of oral data are statistically significant ($P < .01$ by paired t test), but there is no difference between oral-fasted or oral-fed conditions ($P > .10$).

Peak Time for Ritalinic Acid

When methylphenidate was administered with breakfast, the mean peak time for plasma ritalinic acid was 1.44 ± 0.54 hours (Table 3). This was significantly shorter than the mean of 1.87 ± 0.57 hours observed when the same subjects fasted ($P < .01$). A decrease in peak time was observed in four of the five subjects. The data are in agreement with evidence derived from plasma methylphenidate peak time. Both variables indicate that the presence of food facilitates the absorption of methylphenidate from the gastrointestinal tract.

It was also observed that plasma ritalinic acid concentration (Table 3) was maximal at a slightly later time than plasma methylphenidate concentration (Table 2). The mean differences were 0.27 hours (without food) and 0.44 hours (with food).

It is interesting to note that the peak concentration of ritalinic acid following IV methylphenidate occurred at 1.90 ± 0.42 hours, which is significantly longer than the "oral with breakfast" time of 1.44 ± 0.54 hours ($P < .05$, by paired t test).

Peak Ritalinic Acid Concentration in Plasma

The peak concentration for ritalinic acid was normalized for dose and body weight to facilitate comparison among the five subjects. A significantly smaller peak of ritalinic acid concentration was observed when the drug was orally administered together with food than when the same oral dose was taken in a fasted state ($P < .05$, by paired t test). The mean peak concentration for ritalinic acid following IV methylphenidate was not significantly different from either of the two oral conditions (Table 3).

Area Under the Curve (AUC) for Ritalinic Acid

After oral administration of methylphenidate, the mean AUC for plasma ritalinic acid was 89.2% ± 26.3% (fasted) and 80.6% ± 30.8% (with breakfast) relative to that following an IV dose (100%). The difference between fasted and fed conditions was not statistically significant ($P > .05$).

DISCUSSION

The data from this study of the effect of food on the absorption and subsequent metabolism of methylphenidate suggest that the administration of an oral dose of methylphenidate with a meal does not impede the rate of methylphenidate absorption and subsequent appearance of ritalinic acid as compared with administration of the drug in a fasted state. Differences in the bioavailability and peak plasma concentration of methylphenidate and its metabolite were not found. The data on serum concentrations are consistent with the observed lack of significant difference in behavioral effects of methylphenidate when it is given with or before breakfast.[5] They do not support the assumption that meals interfere with the metabolism or absorption of methylphenidate in hyperactive children.[1-4] Similar results have been reported in adults (C. T. Gualtieri, W. Wargin, R. Kanoy, et al, personal communication, 1982).

The only significant effect in the predicted direction was that the peak ritalinic acid concentration was higher when methylphenidate was taken in a fasted state than when it was taken with breakfast. The AUC for ritalinic acid was not significantly different in these two conditions, but the nonsignificant trend was in the predicted direction. This pattern of nonsignificant trend also occurred in the evaluation of behavioral effects of methylphenidate given with or before meals.[5]

The bioavailability of orally administered methylphenidate was found to be low (10.5% to 52.5%) and large individual differences were observed in the patients' ability to absorb oral doses of methylphenidate. The large individual differences with respect to methylphenidate bioavailability may account for the differences in dose requirements among hyperactive children. These between-subject differences in bioavailability were stable across the two conditions and greater than the within-subject differences between the fed and fasted states.

The results of this study do not support the current practice of administering methylphenidate before meals. However, because of the small sample size of this study, these results merely raise questions about the current practice and may not be sufficiently definitive to alter that practice.

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