Title
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Permalink
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Journal
PEDIATRICS, 72(1)

ISSN
0031-4005

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Publication Date
1983

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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. 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. The presence of food is thought to interfere with the absorption of the drug and thus reduce its potency. 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.

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. 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 and/or ritalinic acid 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.

**RESULTS AND DISCUSSION**

**Elimination Half-Life ($t_\text{1/2}$) for Methylphenidate**

The $t_{1/2}$ for methylphenidate did not differ significantly across the three different conditions studied.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Dose/Body Weight (mg/kg)</th>
<th>IV Fasted</th>
<th>Oral Fasted</th>
<th>Oral with Breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_{1/2}$ (h) Bioavailability</td>
<td>$t_{1/2}$ (h) Peak Concentration of Dose/Body Weight ([µg/L]/[mg/kg])</td>
<td>$t_{1/2}$ (h) Peak Concentration of Dose/Body Weight ([µg/L]/[mg/kg])</td>
<td>$t_{1/2}$ (h) Peak Concentration of Dose/Body Weight ([µg/L]/[mg/kg])</td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
<td>1.6 100</td>
<td>2.1 2.0</td>
<td>26.8 31.0</td>
</tr>
<tr>
<td>2</td>
<td>0.29</td>
<td>2.0 100</td>
<td>2.0 1.5</td>
<td>42.1 41.4</td>
</tr>
<tr>
<td>3</td>
<td>0.29</td>
<td>2.7 100</td>
<td>2.2 2.0</td>
<td>25.9 14.2</td>
</tr>
<tr>
<td>4</td>
<td>0.47</td>
<td>2.1 100</td>
<td>2.6 1.5</td>
<td>16.4 17.9</td>
</tr>
<tr>
<td>5</td>
<td>0.68</td>
<td>1.8 100</td>
<td>1.6 1.0</td>
<td>27.9 34.8</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>2.04 ±0.42</td>
<td>2.10 ±0.36</td>
<td>27.82 ±11.48</td>
</tr>
</tbody>
</table>

$P < .05$

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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Dose/Body Weight (mg/kg)</th>
<th>IV Fasted</th>
<th>Oral Fasted</th>
<th>Oral with Breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_{1/2}$ (h) Peak Concentration of Dose/Body Weight ([µg/L]/[mg/kg])</td>
<td>AUC of Dose/Body Weight</td>
<td>$t_{1/2}$ (h) Peak Concentration of Dose/Body Weight ([µg/L]/[mg/kg])</td>
<td>AUC of Dose/Body Weight</td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
<td>4.4 2.5</td>
<td>7429 3.2</td>
<td>2.5 660 49.1</td>
</tr>
<tr>
<td>2</td>
<td>0.29</td>
<td>4.8 1.5</td>
<td>6356 3.1</td>
<td>2.25 983 90.0</td>
</tr>
<tr>
<td>3</td>
<td>0.37</td>
<td>5.6 2.0</td>
<td>405 3.4</td>
<td>1.1 676 81.8</td>
</tr>
<tr>
<td>4</td>
<td>0.47</td>
<td>4.4 1.5</td>
<td>638 4.1</td>
<td>1.5 670 111.2</td>
</tr>
<tr>
<td>5</td>
<td>0.64</td>
<td>4.8 1.5</td>
<td>469 3.2</td>
<td>2.0 430 116.2</td>
</tr>
<tr>
<td>Mean</td>
<td>4.80</td>
<td>4.8 1.5</td>
<td>650 3.4</td>
<td>1.87 684 82.2</td>
</tr>
</tbody>
</table>

$±SD ±0.49 ±0.42 ±226 ±1,560.03 ±0.41 ±0.57 ±197 ±26.3 ±0.59 ±0.54 ±152.2 ±30.8 ±30.8
tered methylphenidate together with breakfast. The
methylphenidate during fasting, and (3) orally adminis-
trated methylphenidate together with breakfast. The
mean t\textsubscript{\text{pv}} 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.\textsuperscript{9,10}

**Peak Time for Methylphenidate**

Under the same conditions (ie, either with or
without food), the time required for plasma meth-
ylphenidate to reach a peak concentration was sim-
ilar among the five subjects. The peak time for
methylphenidate concentration decreased in three
of the five subjects when methylphenidate was ad-
ministered 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 meth-
ylphenidate.

**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 nor-
malized by dividing peak concentration by the ratio
of dose to body weight. The peak plasma concen-
tration varied by as much as 2.5-fold between in-
dividuals, but varied less within individuals (Table
2). The observed between-subject-variability sup-
ports the finding of Gualtieri et al,\textsuperscript{9} but the within-
subject-variability is less than that reported.\textsuperscript{9} The
peak concentrations of methylphenidate (normal-
ized for dose and body weight) following oral admin-
istration without or with breakfast were 27.82 ±
9.21 and 34.68 ± 14.81 \mu g/L divided by milligrams
per kilogram of body weight, respectively. The dif-
ference 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.\textsuperscript{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\textsubscript{1/2}) for Ritalinic Acid**

The t\textsubscript{1/2} values for ritalinic acid were much greater
after the intravenous rather than the oral admin-
istration of methylphenidate. The mean t\textsubscript{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 methylpheni-
date 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 concentra-
tion (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 concen-
tration 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 98.2% ± 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. They do not support the assumption that meals interfere with the metabolism or absorption of methylphenidate in hyperactive children. 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.

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.

REFERENCES

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