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PHARMACOKINETICS OF METHYLPHENIDATE IN HYPERKINETIC CHILDREN

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1 Pharmacokinetic study has been carried out following oral administration of 10–20 mg of methylphenidate hydrochloride to four behaviorally disordered children.

2 It is indicated that the drug is metabolized to ritalinic acid with an apparent plasma half life of 2.5 h.

3 The variability in magnitude of plasma concentration seems to be due not to its metabolism to ritalinic acid but due to the variability in the apparent volume of distribution.

4 The brief half life of methylphenidate which parallels the short duration of action of methylphenidate in behaviorally disordered children may be explained in part by its low protein binding which results in high percentage of free drug being made available for metabolism to pharmacologically inactive metabolites.

Introduction

Methylphenidate is a sympathomimetic agent with stimulant effects on the central nervous system, the pharmacology of which was first described by Meier and associates (Meier, Gross & Tripod, 1954). It is administered orally in the treatment of mild psychiatric disorders, narcolepsy and hyperactivity in children. In general, the pharmacological properties are similar to those of amphetamines and other phenyl isopropylamines, but methylphenidate differs from these in having only moderate effects in the peripheral circulatory system and minor anorexic effects.

Methylphenidate is generally considered to be the drug of choice for the treatment of behaviorally disordered children (Winsberg, Yepes & Bialer, 1976) and is approved for this use by United States Food and Drug Administration (Eisenberg & Conners, 1971; Rappaport, Quinn, Bradhard, Riddle & Brooke, 1974). Various surveys indicate that approximately one-third of hyperkinetic children are treated with psychostimulants, and of this group, 67% receive methylphenidate (Krager & Safer, 1974).

However, little information is available on the metabolism and pharmacokinetics in children, and except for detailed investigations in adults using radioactive methylphenidate, all data on methylphenidate are derived from animal studies. In adult man, methylphenidate is completely and quickly absorbed as shown by the pattern of urinary excretion and minimal faecal elimination. Rapid and nearly complete metabolism was deduced since a) during the absorption phase, plasma metabolite levels were several-fold those of parent drug, b) urinary ^{14}C excretion was rapid and c) most (78%) of the ^{14}C in urine was found in metabolites. The major metabolite is the deesterified product, ritalinic acid, α-phenyl-2-piperidine acetic acid (Perel & Dayton, 1977). Following oral administration of methylphenidate ^{14}C to four adult subjects, peak plasma levels at 2 h with an apparent $T_{\frac{1}{2}}$ ranging from 2 to 7 h were observed for methylphenidate ^{14}C. Fifty to 90% of the ^{14}C was excreted in urine in 8 and 48 h respectively, suggesting complete absorption of methylphenidate (Faraj, Israili, Perel, Jenkins, Holzman, Cucinell & Dayton, 1974). Ritalinic acid accounted for 80% of the dose. Other metabolites of methylphenidate have been identified and include para-hydroxy-methylphenidate, para-hydroxyritalinic acid; oxoritalinic acid and oxomethylphenidate (Perel & Dayton, 1977). Methylphenidate appears to be responsible for most of the therapeutic effect although para-hydroxymethylphenidate, which is relatively lipid soluble and penetrates the blood-brain barrier to a greater extent than the parent compound (Segal, Cunningham, Dayton & Israili, 1976), has also been demonstrated to have marked pharmacologic activity (Perel & Davis, unpublished results). Ritalinic acid has poor lipid

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solubility. Faraj and co-workers conclude that in view of low plasma levels in human subjects, the potency of the drug appears considerable although the clinical effectiveness of the drug may also be due in part to pharmacologically active lipid soluble metabolites (Faraj *et al.*, 1974).

With respect to methylphenidate metabolism in hyperkinetic children Wells and co-workers (Wells, Hammond & Rodgerson, 1974) reported that after a single 10 mg oral dose, between 35 and 98% of the dose could be recovered from urine collected during 6 h after ingestion and that of the total amount excreted 8% to 11% could be recovered as unchanged methylphenidate with the remainder excreted as ritalinic acid. Milberg and associates reported that amounts of excreted methylphenidate in urine appeared to be lower for a non-reactor and a poor reactor (Milberg, Rinehart, Sprague & Sleator, 1975). However, because of methodological problems in analysis, which include thermal decomposition (Flamm & Gal, 1975), the quantitative estimation of methylphenidate and ritalinic acid in these latter two studies suffer from major drawbacks, accurate determination of the parent compound and its principal metabolite and the subsequent correlations of these determinations with behavioral and toxic effects have not been possible.

Another important pharmacological parameter to consider in evaluating drug effects is protein binding, since the amount of drug bound to proteins is essentially unavailable, i.e., inactive at receptor sites (Koch-Wesser & Sellers, 1976). In a previous report we have shown how measures of plasma protein binding might prove helpful to the understanding of the therapeutic action and toxicity of imipramine in children with behavior disorders (Winsberg, Perel, Hurwic & Klutch, 1974). In the present paper, we report on the application of a recent analytical procedure (Hungund, Hanna & Winsberg, 1978) to the study the pharmacokinetics of methylphenidate and ritalinic acid in a group of children receiving methylphenidate for their hyperkinetic disorder. In addition, we report on the protein binding of methylphenidate and discuss the relationship of these findings to the relatively brief duration of therapeutic effect of methylphenidate and to the comparatively low oral doses of methylphenidate (e.g., 10–20 mg per dose) required for its therapeutic effect in the treatment of behaviorally disordered children.

Methods

Subjects and specimens

Four behaviorally disordered children who participated in this study received the diagnosis of 'Behavior Disorder of Childhood' based upon parent and teacher evaluations and on interview with a child psychiatrist. The children were 7 to 11 years old, and informed consent was provided by their parents. They were receiving methylphenidate in doses appropriate to their clinical condition (10 to 20 mg orally, two times a day). Specimens were obtained in EDTA tubes to inhibit the plasma esterases that metabolize methylphenidate to ritalinic acid *in vitro*. Specimens were immediately centrifuged and stored at −20°C until the assay.

Procedure

1. *Protein binding study* Plasma binding was determined in eight children by a micromethod modification of standard equilibrium dialysis at 37°C (Perel, Snell, Chen & Dayton, 1964). The mixture of plasma and drug was incubated, in duplicate, in a cellulose dialyzer tubing (0.39, Fisher Scientific) immersed in an outer phase (OPh) buffer. Twenty-four hours of incubation time was allowed to establish the equilibrium. At that time duplicate aliquots were counted in an Intertechnique Beta Scintillation Spectrometer.

The inner phase (IPh) consisted of a dialyzing tube closed with a double knot containing a glass bead and filled with 1.25 ml of plasma to which 0.25 ml of IPh buffer was added. The tubing was then closed with another knot, leaving an air bubble over the meniscus. The inner phase buffer consisted of 1/15 M Sorensen buffer, pH 7.4 containing 1.25 μg methylphenidate Hcl (carbonyl-C^{14}, California Bionuclear Corp. specific activity 2.03 mci/mM). The outer phase buffer consisted of 4.3 ml 1/15 M Sorensen buffer, pH 7.4 with tracer amounts of ^{14}C labelled drug. The tube was closed with Parafilm and tape and incubated at 37°C in a water bath for 24 h. Both IPh and OPh buffers contained 5×10^{-6} mol EDTA/ml, the pH's being determined before and after incubation. At the end of dialysis, the outer phase (buffer) was also tested for leakage and bacterial growth by adding 10% trichloracetic acid to an aliquot of the dialysate. Values obtained are the mean of duplicate determinations.

2. *Plasma levels and plasma half life study* The weights of the four children were as follows: Subject A weighed 21 kg, subject B, 38 kg, subject C, 33 kg, and subject D, 37 kg, respectively. All subjects were receiving oral methylphenidate for at least 3 weeks prior to the study. Subject A was receiving 10 mg twice a day, subject B was receiving 15 mg twice a day, subject C, 10 mg a day and subject D 15 mg twice a day, respectively. Parent, teacher or nurse reports confirmed behavioral improvement for each of the children.

Plasma disappearance curves were determined as follows: At 08.00 h of the day that blood samples

were drawn, patients received their morning doses of methylphenidate. At 09.00 h, 10.00 h, 11.00 h, 13.00 h and 15.00 h, 10 ml of blood were drawn for determination of methylphenidate and ritalinic acid levels. Blood was collected in EDTA tubes and immediately centrifuged, and stored at −20°C until assayed. Determinations of methylphenidate and ritalinic acid were performed using a gas chromatographic method employing a nitrogen-phosphorus detector described elsewhere (Hungund *et al.*, 1978). This method has a sensitivity of < 1 ng/ml.

Results

1. *Protein binding study*

The mean values for free and protein bound methylphenidate in eight children were found to be 84.1 ± 2.3 (s.d.) % and 15.2 ± 5.2 (s.d.) % respectively. These values are almost identical to those we obtained using adult human plasmas from two patients, 83.8 ± 1.1 (s.d.) and 16.2 ± 1.1 (s.d.), respectively. The mass balance for methylphenidate after the separations and measurements in each phase was essentially quantitative: mean recovery of all experiments = 94.2 ± 2.2 (s.d.) accounting for almost the entire added drug. These data are also in agreement with information from prior reports (Segal *et al.*, 1976; Perel & Dayton, 1977) which noted that although the half life of the deesterification to ritalinic acid, at 37°C, by plasma or serum was similar; 11.5 h (range 9.0–14.3 h) the addition of EDTA prevents the occurrence of this hydrolytic process for at least 24 h. It is of interest that a previous communication reported that methylphenidate was bound to human albumin (crystaline 4% W/V) to the extent of 12% (Faraj *et al.*, 1974). This would suggest that most, but not all, of the plasma protein binding occurs with the albumin fraction of plasma. The low degree of binding indicates that relatively significant amounts of the total methylphenidate are available for penetration into the CNS, (brain/plasma ratio = 3.4, Faraj *et al.*, 1974) for interaction with receptor sites as well as to metabolic enzymes.

2. *Pharmacokinetic measurements*

A linear least-squares regression analysis of the $\log_{10}$ plasma-methylphenidate was carried out on the single-dose data obtained from each patient. The results of this analysis were used to calculate a series of pharmacokinetic parameters for each patient. These parameters were derived according to a one-compartment (monoexponential) pharmacokinetic model. Although the pharmacokinetics of methylphenidate have been adequately described in the rat by a two-compartment open model (Gal, Hodshon, Pintauro, Flamm & Cho, 1977), the use of a one-compartment equation has been shown to introduce negligible (1% to 5%) errors in the calculation of drug clearances for many drugs, including lipophilic psychoactive agents (Dvorchik & Vesell, 1978). The pharmacokinetic parameters calculated for each patient are listed in Table 1.

The area under the curve (to $t = \infty$) was calculated by the use of the Romberg equation (Wilf, 1975). In the absence of comparative intravenous plasma disappearance curves, the value of F is arbitrarily assumed to be 1.0. An examination of the pharmacokinetic parameters (Table 2), which were calculated by assuming a total absorption of methylphenidate reveals that $V_d\,\beta$ values show a three-fold range, whereas the rates of plasma disappearance, $T_{1/2}\,\beta$, are remarkably similar for all four children. The pharmacokinetic results show a half-life of $T_{1/2}\,\beta$ 2.6 h. Since the rate of disappearance in the four children is almost identical ($T_{1/2}\,\beta = 2.6$; s.d. 0.16), we consider that metabolism

Table 1 List of pharmacokinetic parameters

$(C_o)_\beta$ = extrapolated zero-time intercept of the β-phase

β = est. hybrid rate constant determined during the mono-exponential terminal portion of the curve, after a single dose by linear regression

$T_{1/2}\,\beta$ = apparent half-life of the β-slope = 0.693

$V_d\,\beta$ = apparent volume of drug distribution at pseudodistribution equilibrium

s.d. = standard deviation of the mean

$$V_d\,\beta = \frac{f \times \text{dose (mg)}}{\beta \times \text{AUC} \times \text{wt (kg)}}\ ;\ f = \text{fraction of drug absorbed assumed to be 1}$$

$$\text{AUC} = \int (C(t))\,dt = \text{area under the plasma concentration (C) curve from zero to infinite time using the Romberg equation}$$

$$\text{Plasma clearance rate; also total body clearance} = \frac{\text{dose (mg/kg)}}{\text{AUC}}$$

to ritalinic acid by deesterification is not the primary reason for the variability in the magnitude of plasma concentrations, rather, this variability is readily explained by the scatter in the apparent volumes of distribution which are the main contributing factors to the observed range in plasma clearances (3.1–8.5).

As in previous findings with adult subjects (Faraj *et al.*, 1974), most of the circulating drug in plasma is in the form of ritalinic acid (Table 3). An exmination of the ratio of ritalinic acid/methylphenidate in plasma reveals a range from 4.6 to 20.8 and suggests a linear trend as a function of time. Thus, high regression coefficients were observed with patients A, B and D (0.71 to 0.93) and a moderate trend with patient C (0.59).

Discussion

The relatively smaller oral doses of methylphenidate required to treat behaviorally disordered children as compared to imipramine, could be explained in part by the greater amounts of free drug available provided that both drugs have similar clinical potency. The brief half-life of methylphenidate (Swanson, Kinsbourne, Roberts & Zucker, 1978) in behaviorally disordered children may be explained in part by its low protein binding which results in a high percentage of free drug being made available for metabolism to pharmacologically inactive metabolites (Koch-Weser & Sellers, 1976). It is also of interest to note that ampheramine, which has similar therapeutic effects as methylphenidate in children (Winsberg, *et al.*, 1976) and which likewise has a brief course of clinical action (3 to 4 h), also shows relatively low binding, 22% (Franksson & Anggard, 1970).

The main probable reason for the small inter-individual variability of plasma disappearance rates, is that metabolism of methylphenidate occurs mostly with non-microsomal hydrolytic enzymes which are widely distributed in different forms and activities throughout the body. This pattern of metabolism is different than the one found for amphetamine and imipramine. The latter two are metabolized mostly by hepatic mixed function oxygenases which activites are under genetic control hence the large interindividual variability observed in plasma levels. Thus, methyl-

Table 2 Summary of pharmacokinetic data

Patient	*OBS peak level after drug (ng/ml)*	*Extrapolated zero-time intercept of g-slope (ng/ml)*	*β = rate constant = slope of terminal phase (h^{-1})*	$T_{1/2}\,\beta$ *(h)*	$V_d\,\beta$ *(l/kg)*	*Plasma clearance ($l\,kg^{-1}\,h$)*	*AUC ($ng\,h^{-1}\,ml$)*
A	22.3	39.6	−0.2921	2.37	18.6	5.68	89.58
B	17.9	37.0	−0.2525	2.75	18.0	4.54	88.07
C	7.71	12.8	−0.2565	2.70	33.2	8.53	36.26
D	22.5	48.5	−0.2850	2.43	10.7	3.11	133.82
Mean	17.6	34.48	−0.2715	2.56	20.13	5.47	86.93
±s.d.	± 6.0	±13.22	−0.0127	±0.162	± 8.98	±2.18	± 34.55

Table 3 Rate of *in vivo* conversion of methylphenidate to ritalinic acid as measured in plasma samples*

Time after administration (h)	*Patients* A	B	C	D
1	10.4	12.0	11.3	5.8
2	10.0	8.3	16.7	4.6
3	9.6	11.5	14.4	8.0
5	15.4	11.3	14.6	13.8
7	20.8	16.0	16.7	12.0
Regression coefficients	0.933	0.711	0.585	0.863

*Data expressed as the ratio of the plasma concentrations of ritalinic acid over methylphenidate

phenidate is a more predictable therapeutic agent, provided that the variability due to distribution is compensated in dosage administration by taking into account either weight (mg/kg) or surface area (mg/m^2). The apparent linear increase of the ritalinic acid/methylphenidate plasma ratio as a function of time is noteworthy in view of the reports which indicate a significant decrease of hyperkinetic control after long time chronic administration of methylphenidate. It would, of course, be valuable to compare the ratios of methylphenidate resistant groups with those of the responders. Other drugs that presumably have similar dispositions are the lipid-soluble ester-type local anesthetics, where duration of action and metabolism have been demonstrated to be related to differences in plasma protein bindings and, in turn, distribution parameters (Covino, 1971). Thus compartmentalization of the methylphenidate would also be expected to account for degrees of responsivity among children with severe behavior disorders.

It is of interest that Swanson and co-workers (Swanson *et al.*, 1978) have reported that a parameter of clinical response to methylphenidate based on a laboratory learning task administered to hyperactive children, performance was maximal 1 to 2 h after administration of a single dose, which closely corresponds to the present findings on methylphenidate peak plasma levels following oral ingestion.

For a number of drugs, measurement of plasma levels has proven most helpful for safe and effective clinical management of various medical and psychiatric disorders (Davies & Prichard, 1972). Within the area of psychiatric disturbances, measurement of plasma levels of the tricyclic antidepressants promises to provide more effective clinical management of depression as well as understanding and classification of the heterogenous disorders classified as depression (Braithwaite, Goulding, Theano, Barley & Coppen, 1972; Glassman, Perel, Shostak, Kantor & Fleiss, 1977; Gram, Reisby, Ibsen, Nagy, Dencker, Peterson & Christiansen, 1976; Kragh-Sorenson, Asberg & Eggert-Hansen, 1973).

Furthermore, measurement of plasma levels of pharmacologically active agents can help elucidate their mechanisms of action. For example, Brown, Ebert & Hunt (1978) have demonstrated that peak behavioral effects and peak plasma levels of (+)-amphetamine occur between hours 1–4, following oral doses of (+)-amphetamine, and that the behavioral response to (+)-amphetamine was related particularly to the actual level present in the plasma. This suggested to them that the behavioral effects are most marked when (+)-amphetamine is most active in catecholamines release.

We are presently examining the relationship between methylphenidate plasma levels and clinical response in hyperactive children.

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