ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2003; 42 (4): 393-401
0312-5963/03/0004-0393/$30.00/0

Pharmacokinetics of Methylphenidate After Oral Administration of Two Modified-Release Formulations in Healthy Adults

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Abstract

Objective: To compare the rate and extent of absorption of DL-*threo*-methylphenidate (MPH) from two modified-release MPH formulations at their respective recommended starting doses in healthy adult volunteers.

Design: Open-label, randomised, crossover, bioavailability study.

Participants: Twenty healthy adult male and female volunteers.

Methods: Subjects received single doses of two modified-release formulations of MPH, a 20mg capsule (Ritalin® LA) and an 18mg tablet (Concerta®). A total of 19 plasma samples was collected over 24 hours, and MPH plasma concentrations were determined by liquid chromatography-mass spectrometry (LC-MS/MS). These values were used to calculate standard noncompartmental pharmacokinetic parameters describing the rate (peak concentration and time to peak concentration) and extent (area under the concentration-time curve, AUC) of absorption of the two formulations. The relative bioavailability of the two drugs was assessed using a 90% confidence interval, based on the lower and upper endpoints of the confidence interval for the ratios of the geometric means (log transformed) being within the 0.80–1.25 equivalence criterion.

Results: Nineteen subjects, ten male and nine female, aged 21–34 years completed both treatment phases of the study. The Ritalin® LA formulation displayed a distinctly biphasic pharmacokinetic profile, with mean initial peak plasma concentration of 7 μg/L at an average of 2.1 hours after administration and a second peak of 9.3 μg/L occurring at 5.6 hours. In contrast, the profile of the Concerta® formulation rapidly reached an initial plateau concentration of 3.4 μg/L at 3.3 hours after administration and a second mean plateau concentration of 5.9 μg/L

approximately 6 hours after administration. Substantially more MPH was absorbed from Ritalin® LA than from Concerta® over the first 4 hours; the respective AUC_4 values were 18.5 and 9.3 μg • h/L ($p < 0.001$). The overall extent of absorption of MPH was similar between the two formulations. Oral clearance was identical between the two dosage forms.

Conclusions: The Ritalin® LA formulation exhibited more rapid initial absorption and reached significantly higher peak plasma concentrations compared with the Concerta® formulation, although the oral bioavailability of MPH was similar between the two formulations. The Ritalin® LA capsule demonstrated a distinctly bimodal plasma concentration-time profile. MPH plasma concentrations resulting from Concerta® reached a peak at 6 hours. These results indicate that the recommended starting dose of the Ritalin® LA 20mg capsule formulation provides more rapid absorption and higher peak plasma concentrations than the recommended 18mg starting dose of the Concerta® formulation.

Attention-deficit hyperactivity disorder (ADHD) is the most common neurobehavioural disorder of childhood affecting school-aged children, with a prevalence generally estimated to be 5–10% of the general population.[1-3] Although ADHD was thought to be a disorder largely limited to childhood, and self-resolving upon reaching adolescence, it now appears that up to 50% of children diagnosed with ADHD may have symptoms persisting into adolescence.[4] The cardinal behavioural features of ADHD include inattention, hyperactivity and impulsivity.[5] If left untreated, ADHD often leads to academic underachievement, poor interpersonal relationships with family members and peers, and low self-esteem.[2,6] Additionally, when compared with peers without the disorder, individuals with ADHD are at increased risk of comorbid psychiatric disorders such as oppositional defiant disorder, conduct disorder, depression, anxiety disorders and tic disorders.[7] The cause(s) of ADHD remain unknown but current research suggests that there are multiple factors involved in its aetiology.[8] The fact that the most widely used medications for ADHD have a prominent dopaminergic mechanism of action[9] further supports underlying dopaminergic dysfunction in ADHD. However, the demonstrated efficacy of noradrenergic agents in the treatment of ADHD points to broader neurochemical bases of this disorder.[10]

Although multimodal treatment approaches are advocated, pharmacotherapy with psychostimulants remains a cornerstone of treatment for ADHD.[2,11-15] Of the available medications, the psychostimulant medication DL-*threo*-methylphenidate (MPH) is the most extensively studied and widely prescribed. Indeed, over 130 medication trials assessing MPH in ADHD have been performed,[16] and it is considered by many to be the drug of choice for ADHD. Numerous MPH formulations are presently available. The rapid metabolic de-esterification of MPH limits its half-life to only 2–3 hours,[9,17,18] thus usually necessitating multiple daily doses. In practice, giving medication throughout the school day poses numerous potential problems that may compromise medication compliance and, ultimately, treatment outcome. These problems include inconvenience, security issues with controlled substances at school, and potential stigmatisation of children who may be subject to ridicule by peers during the school day when additional doses are required. Additionally, schools may not administer a child's medication reliably, and adolescent patients may not comply with in-school administration schedules.[16]

In an initial attempt to provide the proven efficacy of immediate-release (IR) MPH in a single daily dosage form, sustained-release (SR) MPH was introduced in 1983. The SR tablet, formulated to contain MPH in a wax-matrix vehicle to achieve a slow release, provided a more gradual rate of absorption than IR MPH, then reached a relative

plateau or flat concentration-time profile, avoiding plasma troughs during the day. Finally, the subsequent plasma MPH concentration decay for SR forms occurred more gradually than that of IR forms.[19] However, clinical experience and formal study[20] have since suggested a potential therapeutic disadvantage of SR over conventional IR forms,[20,21] even though both formulations provide comparable extents of absorption.[19]

It has been observed that the greatest behavioural improvements in ADHD children treated with IR MPH corresponded to the absorption phase of the pharmacokinetics.[20-23] This pharmacodynamic correlation with rising blood concentrations has been referred to as the 'ramp'[24] or 'gradient'[9] effect. It has been proposed that a relatively constant blood concentration-time course of MPH, as produced by standard SR forms,[19] may induce an acute psychotherapeutic tolerance (i.e. tachyphylaxis) and compromise efficacy.[20,21,24] Additionally, conventional SR MPH may provide a slower onset of action than IR formulations. As a result of these limitations, many clinicians began to 'supplement' SR MPH with IR MPH formulations throughout the day. However, this common practice effectively defeats the purpose and benefit of a once-a-day MPH dosage form.[16]

It would appear that an ideal once-a-day MPH formulation should exhibit a rapid onset, present an overall absorption corresponding to peak activity during the periods in the child's day when control is most needed (at school and during homework), minimise lunchtime appetite suppression by offering an MPH plasma trough around noon, and allow for a normal dinner appetite and sleep schedule. With these considerations in mind, a number of newer once-a-day MPH formulations recently become available for general clinical use. The OROS®[1] (osmotic, controlled-release oral delivery system) MPH product (Concerta®) was the first of these newer dosage forms and was introduced in 2000. This tablet combines IR and controlled-release technology to provide for an initial rapid rise in circulating concentrations after the morning dose, followed by a short plateau appropriately preceding lunch, then a second rise.[25-28] The overall concentration increase characterising the first 6–8 hours after administration is postulated to offset acute behavioural tolerance.[20,21]

Although no clinical trial has been published comparing Concerta® with SR MPH, it is widely perceived to be superior to the older SR formulation. Nevertheless, supplementation with IR MPH still occurs with even the newer formulations.[29] Most recently (in 2002), Ritalin® LA, which uses the SODAS™ (spheroidal oral drug absorption system) technology, was introduced into clinical use. These capsules contain 50% IR MPH beads and 50% delayed-release beads. The latter are polymer-coated to offer an approximate 4-hour latency before gastrointestinal water erodes this coating to release the second pulse of MPH, and hence the resulting MPH blood profile becomes distinctly biphasic, as with IR MPH given twice daily. This modified-release MPH product offers an alternative pharmacokinetic profile, distinguished from that of the previously described Concerta® tablet by providing two distinct and robust absorption phases.

In order to delineate salient bioavailability differences between these modified-release formulations, a direct randomised crossover bioavailability study was conducted in healthy adult volunteers to unequivocally compare the pharmacokinetics of these two newer dosage forms. Such a crossover design would control for the well established inter-individual variability in the disposition of MPH.[9] Doses of 20mg of the Ritalin® LA formulation and 18mg of Concerta® were chosen, since they represent the initial dosage recommendations of the respective manufacturers for patients initiating MPH treatment.

Materials and Methods

Study Subjects

Study subjects were recruited from the University of Tennessee Health Science Center, Mem-

1 Use of tradenames is for product identification only and does not imply endorsement.

phis, Tennessee, USA. All subjects had completed written informed consent previously approved by the institutional review board. A total of 20 healthy volunteer subjects (ten male, ten female) aged 21–34 years participated in this single-center study. All were healthy by history, physical examination and basic laboratory monitoring indices, and ECG. All subjects were non-smokers, were taking no prescription or over-the-counter medications, and abstained from caffeine and alcohol during the study period. Subjects were then randomly assigned to receive a sequential order of treatment with one modified-release MPH product, a 7-day wash-out period, and then the other formulation. A total of ten subjects per group per day were studied on two different occasions. Following the last blood draw for the second phase of the study, a follow-up visit occurred that included physical examination and vital signs.

Medication Administration and Administration

Subjects reported to the study clinic for baseline evaluations at least 1 hour prior to the initial administration on day 1 (period 1) and then again 1 week later on day 8 (period 2) following an overnight fast for a minimum of 10 hours. Baseline safety evaluation was conducted prior to the first administration. The first dose (Ritalin® LA 20mg capsule or Concerta® 18mg tablet) was administered orally with 240mL of room-temperature water, and water was then given at 2, 4, 6 and 8 hours post-dose to maintain all subjects on a uniform hydration schedule. These dosages were chosen as they represent the recommended starting doses of the respective formulations and are closest in mg strength. No food was provided until 4 hours post-dose, when a standard lunch was provided. A standard dinner was also provided 10 hours post-dose. Study subjects were confined to the clinic for at least 12 hours after the morning dose on days 1 and 8. Following an inter-dose interval of 7 days, each subject returned to the study site and crossed over to receive the other treatment. Immediately prior to each dose and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16 and 24 hours after each dose, a 7mL blood sample was obtained from each subject via heparin lock. The venous catheters were removed after the 16-hour sample was obtained, and the 24-hour sample was obtained by venipuncture. Blood samples were then promptly centrifuged at –4°C for 10 minutes, and the plasma was immediately aspirated into polypropylene vials and stored at –70°C until analysis of MPH.

Analytical Methods

All MPH determinations were performed by National Medical Services (Willow Grove, PA, USA) using liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS). Plasma (0.5mL) was internally standardised with [$^2H_3$]MPH, followed by automated extraction on Varian Bond Elut Certify cartridges. The analytical separations were performed on a Hewlett-Packard 1100 series high performance liquid chromatograph using a Zorbax SB-Phenyl analytical column with precolumn filter; the mobile phase was water with 0.1% formic acid/acetonitrile/isopropanol (75 : 12.5 : 12.5). The LC effluent was split 2 : 1 and passed into a Z-Spray configuration Micromass Quattro II LC/MS equipped with electrospray ionisation: cone at 25V, a capillary at 3KV, collision energy at 15eV, source at 120°C, and desolvation at 450°C. The MS/MS transition for MPH was m/z 234.3 (M + 1) to 83.97 (piperidyl), and 237.3 to 83.97 for [$^2H_3$]MPH. Calibrators at 20, 15, 10, 6, 3, 1.5, 0.5 and 0.25 μg/L MPH, and replicate quality control (QC) samples at 1, 5 and 14 μg/L, provided analytical control.

The QC samples (replicate pairs at each of the three levels), prepared from separate weighings of the MPH standard, were interspersed throughout each sample set. The lower limit of quantification (LLOQ) for this assay was 0.25 μg/L based on a 0.5mL aliquot of plasma. The performance statistics for this method at the LLOQ (using the lowest level standard values) over the course of the study (n = 12 sets) were: precision ±2.8% (coefficient of variation) and accuracy ±5.2%. The correlation coefficients (r^2) ranged from 0.9965–0.9999, typi-

cally 0.9995. The mean determinations for the QC samples (n = 12 sets of each) at the low (1 μg/L), mid (5 μg/L), and high (13 μg/L) levels were: 0.99 μg/L, precision ±4.1%, accuracy ±1.4%; 5.1 μg/L, precision ±3.3%, accuracy ±1.0%; and 14 μg/L, precision ±3.0%, accuracy ±0.41%, respectively.

Pharmacokinetic Analysis

The pharmacokinetics of MPH were evaluated by noncompartmental model analysis. Peak concentration (C_{max}) and the time to C_{max} (t_{max}) were recorded as observed. The terminal elimination rate constant (k_{el}) was calculated by log-linear regression of the plasma concentration versus time for the terminal data points (derived from a semilogarithmic plot of concentration versus time) and the estimation of this constant was used to calculate the terminal elimination half-life ($t_{½\beta}$). The area under the plasma concentration-time curve (AUC) from time 0 to the last measured timepoint was calculated by the trapezoidal method (AUC_t). The residual area from time t to infinity was estimated based on the final measured plasma concentration divided by k_{el}. This area was added to AUC_t to produce the total AUC_∞. Apparent (oral) clearance (CL/F) was calculated as dose (20mg for Ritalin® LA or 18mg for Concerta®) divided by AUC_∞.

Results

Nineteen healthy subjects, ten male and nine female, aged 21–34 years (mean ± SD: age, 24 ± 3 years; weight, 70 ± 11.7kg), completed both treatment phases of the study. One subject discontinued the study due to some discomfort experienced related to difficulty in obtaining blood samples from the catheter line.

The Ritalin® LA formulation displayed a distinctly biphasic pharmacokinetic profile over the 24-hour sampling period, whereas Concerta® demonstrated an ascending pharmacokinetic profile with plateau concentrations at about 3.3 and 6 hours. The capsule formulation exhibited a more rapid rise in plasma MPH concentration and higher peak concentrations over the course of the first 8 hours when compared with the Concerta® formulation. The mean concentration-time curves of the Ritalin® LA and Concerta® formulations are provided in figure 1. To provide a further comparison between these two formulations, figure 1 also depicts a third theoretical profile where the 18mg Concerta® formulation was 'dose adjusted' by multiplying the mean values by 20/18 to approximate the profile of a 20mg dose of the tablet, were such a dose available for direct comparison. This adjustment was made assuming linearity of MPH absorption and disposition, and is consistent with published data.[9,17-21] As with most pharmacokinetic studies of MPH, interindividual differences in concentration-time curves were noted. Figure 2 depicts profiles from two individual subjects to illustrate the variability observed in the present study.

The associated pharmacokinetic parameters generated from this study are displayed in table I. The mean peak plasma concentration for the first 4 hours after administration of the Ritalin® LA capsule occurred at 2.1 hours, and was approximately twice the plasma concentration of Concerta® observed at this time (7.0 vs 3.4 μg/L; $p < 0.001$). Further, the mean AUC_4 for Ritalin® LA was also approximately twice that of Concerta®

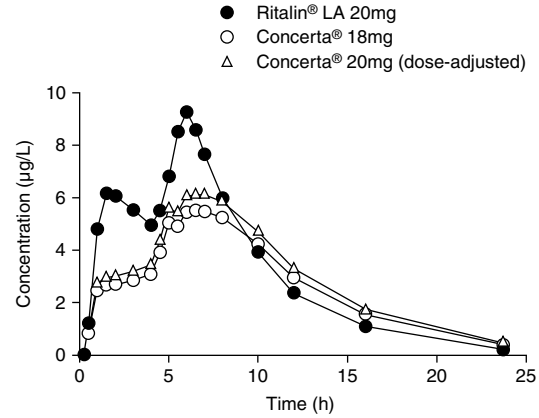

Fig. 1. Mean concentration-time profiles of DL-*threo*-methylphenidate after administration of Ritalin® LA 20mg and Concerta® 18mg to healthy adult volunteers.

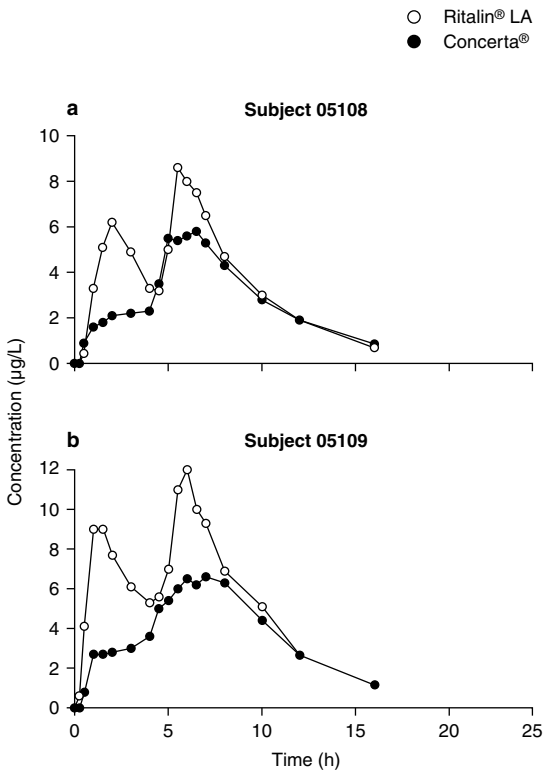

Fig. 2. Representative concentration-time profiles of DL-*threo*-methylphenidate from two healthy adult volunteers after administration of Ritalin® LA 20mg and Concerta® 18mg.

(18.5 vs 9.3 µg • h/L; $p < 0.001$). The second mean peak plasma concentration for the Ritalin® LA capsule occurred at 5.6 ± 0.5 hours compared with 6.4 ± 1.2 hours for Concerta® ($p < 0.001$). The 90% confidence interval for the geometric mean ratio of AUC_∞ (unadjusted for dose) of Concerta® compared with Ritalin® LA was 0.77–0.91. Calculated oral clearance (CL/F) was essentially identical (approximately 4.5 L/kg/h) between the two dosage forms.

Discussion

The pharmacokinetics of the Ritalin® LA and Concerta® formulations of MPH have previously been documented in separate healthy volunteer studies. However, the present investigation was a direct comparison of rate and extent of absorption of MPH from these two modified-release formulations within the same study population in a crossover fashion. Based on the dose strengths available for these two MPH product lines (18, 27, 36 and 54mg for Concerta®, and 20, 30 and 40mg for Ritalin® LA), the recommended starting doses for each was chosen in the present study, i.e. 20mg for Ritalin® LA versus 18mg for Concerta®.[28,30]

The drugs were administered to fasting subjects. The effect of fed versus fasted state on the rate of absorption of IR MPH[31,32] and SR MPH[33] have been formally assessed previously and appear to be minimal, although food has been reported to increase the extent of absorption of both IR and SR MPH formulations, as well as to delay the C_{max} of IR MPH.[33] With regard to the two modified-release formulations utilised in the present study, both the Concerta® formulation[26] and the capsule formulation[34] have been likewise assessed; food effects appear to be limited to a slightly delayed C_{max} for both preparations and no 'dose dumping' has been observed. Multiple-dose pharmacokinetic comparisons were not pursued in the present study in view of the rapid metabolic clearance of MPH,[9] which limits accumulation, and the established similarity of pharmacokinetic parameters found between single- and multiple-dose administration of the Concerta® tablet.[25]

As background, a head-to-head bioavailability comparison has been previously been conducted between the Concerta® formulation utilised in the present study and a second newer modified-release MPH capsule formulation, Metadate® CD.[35] The Metadate® CD 20mg capsule '30/70' formulation utilises Diffucaps® technology and is designed to mimic a twice-daily schedule of IR MPH. The disparate nature of the MPH-containing beads within the capsule allow for rapid dissolution of 30% of the MPH dose while the remaining 70% of the dose is released in an extended fashion. The resulting MPH time course in plasma somewhat resembles that of earlier SR MPH products (time courses for such earlier products compared with two doses of IR MPH are illustrated in figure 3), but provides

Table I. Pharmacokinetic parameters of DL-*threo*-methylphenidate following the administration of single doses of Ritalin® LA 20mg and Concerta® 18mg to healthy adult volunteers

Parameter and unit	Ritalin® LA 20mg		Concerta® 18mg			Geometric mean ratio as % (CI)[a]	p-Value[b]
	mean (%CV)	range	mean (%CV)	range	dose-adjusted mean[c]		
AUC_4 (μg • h/L)	18.5 (44)	7.8–43.1	9.3 (51)	4.3–20.6	10.3	49.2 (45–54)	<0.001
AUC_t (μg • h/L)	75.0 (54)	30.7–192.8	61.6 (50)	30.7–141.7	68.4	83.8 (78–91)	<0.001
AUC_∞ (μg • h/L)	78.7(54)	34.5–204.4	66.9 (49)	40.2–154.5	74.3	87.6 (80–96)	0.024
$C_{max,4}$ (μg/L)	7.0 (47)	3.0–17	3.4 (44)	1.7–6.7	3.8	48 (44–53)	<0.001
C_{max} (μg/L)	9.9 (41)	4.7–20	5.9 (37)	3.4–11	6.5	60.8 (56–66)	<0.001
$t_{max,4}$ (hr)	2.1 (48)	0.9–4.0	3.3 (36)	0.9–4.0			0.007
t_{max} (h)	5.5 (15)	3.0–6.4	6.0 (28)	0.9–10			0.086
CL/F (L/kg/h)	4.6 (47)	1.2–10.4	4.6 (36)	1.5–7.3			>0.999
$t_{½\beta}$ (h)	3.4 (24)	2.5–5.4	4.3 (35)	2.6–8.4			0.001

a Calculated on dose-unadjusted values.

b Computed from the exact distribution of the Wilcoxon signed rank test on dose-unadjusted values.

c Adjusted to 20mg dose assuming linear kinetics.

AUC_t = area under the concentration-time curve from time zero to the last measured timepoint; **AUC_4** = area under the concentration-time curve during the first 4 hours after administration; **AUC_∞** = area under the concentration-time curve from time zero to infinity; **CL/F** = apparent ('oral') clearance; **C_{max}** = peak plasma concentration observed during the complete concentration-time profile; **$C_{max,4}$** = peak plasma concentration observed during the first 4 hours after administration; **t_{max}** = time to C_{max}; **$t_{max,4}$** = time to $C_{max,4}$; **$t_{½\beta}$** = terminal elimination half-life; **%CV** = percentage coefficient of variation.

for a more rapid onset. Two studies were carried out; one was a single-dose, randomised, two-period crossover trial comparing Metadate® CD 20mg with Concerta® 18mg (n = 36), and the other was a single-dose, randomised, four-way crossover trial comparing Metadate® CD 40mg with Concerta® 36mg and Metadate® CD 60mg with Concerta® 54mg (n = 24).[35] MPH plasma concentration profiles were found to be biphasic for both formulations, with a sharp initial slope followed by a second steep absorption phase, and exhibited dose proportionality.[35] Although the plasma MPH concentration profiles from the Metadate® CD and Concerta® formulations were similar in the early hours of the time course, the Metadate® CD capsule provided higher early plasma MPH concentrations (at 1.5, 3 and 4 hours) and the Concerta® tablet yielded significantly higher concentrations at later time points.[35] The half-life of MPH following Metadate® CD was longer than that after Concerta® 18mg (mean ± SD: 6.24 ± 1.32 vs 3.58 ± 0.68 hours, respectively), perhaps due to delayed dissolution of MPH from the coated particles in this capsule formulation.[35] The AUC of MPH for both formulations was comparable. Gonzalez and associates noted that although these two modified-release products may have comparable total and maximum exposure as determined from AUC and C_{max}, the different degrees of early and late exposure dictate that they not be considered bioequivalent.[35]

In the present study, the modified-release Ritalin® LA capsule formulation demonstrated rapid initial and subsequent absorption phases, and reached substantially higher peak plasma concentrations over most of the plasma concentration-time curve when compared with Concerta®. Ritalin® LA exhibited a distinctly bimodal plasma concentration-time profile, with the peaks at 2.1 and 5.6 hours approximating those of a twice-daily schedule of IR MPH (see figure 3). In contrast, plasma concentrations of Concerta® showed a plateau over the 1–4 hour period, then ascended to a peak concentration at 6 hours post-dose. Although the mean values for the time of the second peak concentration (which ranged from 4 to 12 hours) were not significantly different between Ritalin® LA and Concerta®, the coefficients of variation

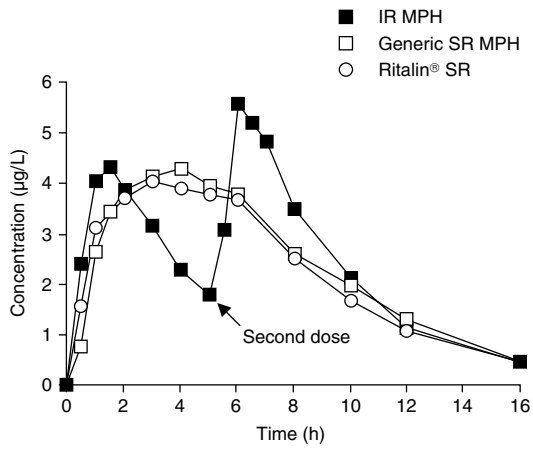

Fig. 3. Mean (n = 18) concentration-time profiles for DL-*threo*-methylphenidate (MPH) after administration of immediate-release MPH (IR MPH; Ritalin®) and two forms of sustained-release MPH (SR MPH; generic and Ritalin®-SR) [reproduced from Patrick et al.,[19] with permission].

suggest potentially more variability in this parameter with the Concerta® formulation.

The apparent differences in the terminal half-life of MPH from the two formulations in the present study may be attributed to the prolonged release characteristics of the Concerta® tablet compared with the Ritalin® LA capsule. It would appear that based on the formulation design specifications, both products performed according to theory. However, the substantially different MPH concentration profiles produced by these two formulations could have important clinical implications. For example, in view of reports that rapid absorption of MPH correlates with improved behavioural response,[9,20-22] the profile of the Ritalin® LA dosage form may offer an advantage. This capsule formulation might be expected to minimise any theoretical 'acute tolerance' associated with the MPH blood concentration plateau seen with SR MPH formulations (figure 3).[19-21] Conversely, the severity of MPH adverse effects has been correlated with high blood MPH concentrations, underscoring the need for careful titration of an individual's dose,[36] although clinical trials with both the Ritalin® LA and Concerta® formulations did not find any significant differences between these modified-release formulations and IR MPH in terms of adverse effects.

The concentration-time profile of Ritalin® LA, when compared with Concerta® (figure 1) or with older SR MPH formulations (figure 3),[19] more closely approximates a typical IR MPH administration regimen, limiting the MPH concentration trough to a period of time approximately coinciding with a typical lunch schedule, but now allowing a single daily dose. Although both formulations have been proven effective in the treatment of ADHD, direct head-to-head studies between these two MPH formulations at comparable doses are required to draw firm conclusions about the relative efficacy of one formulation over the other.

Conclusion

Ritalin® LA exhibited a distinctly bimodal plasma concentration-time profile, with peaks at 2.1 and 5.6 hours post-dose. Plasma concentrations of Concerta® ascended, with a plateau at 1–4 hours, to achieve a mean peak concentration at 6 hours. Although the overall extent of MPH absorption was similar, Ritalin® LA clearly exhibited more rapid initial absorption and reached significantly higher peak plasma concentrations compared with Concerta®. Although the present bioavailability study was limited to a healthy adult population, a review of both paediatric and adult MPH pharmacokinetic studies has revealed no significant pharmacokinetic differences related to patient age.[9] Accordingly, the findings have implications for the selection of MPH formulations for use in children and adolescents.

Acknowledgements

This study was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. The authors would like to acknowledge Dr Bernd Meibohm and Dr Ryan Yates for their assistance in the conduct of the clinical protocol. The authors further acknowledge the analytical assay development and support of Dr Fred Brill of National Medical Services, Willow Grove, PA, USA. The authors have provided no information on conflicts of interest directly relevant to the content of this study.

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