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Bioequivalence of a methylphenidate hydrochloride extended-release preparation: comparison of an intact capsule and an opened capsule sprinkled on applesauce

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Key words
methylphenidate – ADHD – Medikinet retard – Medikinet XL – bioequivalence – food effect

Abstract. Objective: To assess bioequivalence between an intact capsule and the content of a capsule sprinkled on applesauce. Materials: Medikinet retard 20 mg capsules were obtained from Medice (Iserlohn, Germany). Methods: This was a single-center, completely randomized, open, 2-period, 2-sequence, balanced crossover study with a washout period of 1 week between administrations, in 12 healthy male and female subjects, aged 18 – 45 years. Blood samples were collected over 24 hours and methylphenidate plasma concentration-time data were used to calculate pharmacokinetic parameters for both administrations. The main parameters were (confirmatory) $AUC_{0\text{-}tz}$ (extent of BA), C_{max}, t_{max} (rate of BA) and (descriptively) $AUC_{0\text{-}}$ and $t_{1/2}$. Equivalence was concluded if the 90% confidence interval (CI) for the ratio between test and reference was 0.80 – 1.25 ($AUC_{0\text{-}tz}$). Results: All 12 dosed subjects finished both treatment periods and were included in pharmacokinetic and safety analyses. 90% geometric confidence intervals for $AUC_{0\text{-}tz}$ and C_{max} data were well within accepted bioequivalence limits. The study has shown that both treatment modes lead to similar pattern of absorption and elimination following single-dose administration in the fed state. The test treatment (content of capsule sprinkled over 15 ml applesauce) is bioequivalent to the reference treatment (intact capsule) in terms of extent and rate of absorption. Conclusion: Data collected from this study demonstrate that Medikinet retard capsules can be opened and the content sprinkled on a tablespoon of applesauce without influencing the rate and extent of bioavailability.

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Introduction

Medikinet retard 10 mg and 20 mg capsules have been approved for marketing in Germany and will be available in other countries soon. Medikinet retard, an extended-release formulation of Medikinet, is indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

Stimulant medications remain the first-line ADHD therapies and provide robust improvement in ADHD symptoms in both minors and adults [MTA Cooperative Group 2004, Taylor et al. 2004]. Methylphenidate (MPH), the active ingredient of Medikinet retard, is the leading stimulant for the treatment of ADHD, with years of proven efficacy and safety.

The conventional formulation of methylphenidate is short-acting and must be given at least twice a day. This often means that children with ADHD have to receive additional doses. The need to administer multiple doses to children at school throughout the day may become problematic with regard to compliance, security and privacy issues, and is a good reason to switch to an extended-release formulation for children with ADHD who respond to methylphenidate [NIH 2000].

Current prescribing practices, therefore, favor extended-release preparations due to increased convenience, compliance and tolerability with once-daily dosing.

Medikinet retard combines the advantages of both immediate-release (IR) and extended-release (ER) formulations of MPH, i.e. rapid onset and prolonged duration of action, in a single dose intended for once-daily administration [Döpfner et al. 2004].

This was accomplished by developing a formulation containing both IR and ER beads such that 50% of the dose is provided by the IR component and 50% of the dose is provided

by the ER component. The 10 mg and 20 mg capsules utilize the same formulation and ratio of immediate- and extended-release beads. The principle of release extension of Medikinet retard is an enteric coating of the ER beads, the capsule itself is not responsible for the extended release [Döpfner et al. 2003].

Since many children are not able or do not like to swallow intact capsules [EMEA 2005], it would be advantageous for compliance if the content could be sprinkled on applesauce and administered without the capsule cover.

The present study was conducted to demonstrate bioequivalence (lack of food interaction) of methylphenidate hydrochloride after administration of the content of a 20 mg capsule sprinkled on applesauce compared to the intact capsule after single-dose oral administration of 20 mg methylphenidate hydrochloride in the fed state in female and male volunteers.

Materials and methods

Materials

Medikinet retard 20 mg capsules were obtained from Medice (Iserlohn, Germany). Medikinet retard 10 mg and 20 mg capsules are expected to be marketed in other countries as Medikinet XL.

Subjects and study design

The clinical part of this study was conducted at IKP Bobenheim, Prof. Dr. Lücker GmbH (Mannheim, Germany), and bioanalysis was performed at University Childrens Hospital, BPA (Graz, Austria). The biostatistical evaluation was carried out by BEBAC (Vienna, Austria). The study was sponsored by Medice (Iserlohn, Germany).

A sample size of 12 volunteers was chosen according to published studies and previous experience of the sponsor with Medikinet retard. This sample size was expected to be sufficient to demonstrate bioequivalence with statistical power of at least 80%.

Study protocol and subject informed consent forms were approved by the Ethics Committee of the Landesärztekammer Baden-Württemberg and the German regulatory authority (BfArM) prior to inclusion of any subject into the study. The 12 subjects enrolled were healthy Caucasian men and women, from 18 – 45 years, and with a body mass index from 18 – 29 kg/m^2.

All subjects were in general good physical health determined by medical history, physical examination (including a 12-lead electrocardiogram at screening), vital signs and clinical laboratory tests (hematology, blood chemistries, urinalysis, HIV and HbsAg antibody screen, serum at screening and urine at each treatment period, pregnancy tests and a screen for alcohol and drugs of abuse). Subjects must have been free of any MPH for 30 days prior to dosing and throughout the study, must have agreed to abstain from alcohol- and caffeine-containing beverages and food during the study, and had to be non- or only moderate smokers.

After a fasting period of at least 10 hours, the subjects consumed a standardized breakfast (approximately at 8:00 a.m.). A single dose of 20 mg oral MPH hydrochloride was administered 5 minutes after end of breakfast as follows:

- Treatment b1: capsule contents sprinkled over 1 tablespoon (15 ml) applesauce, intake together with 150 ml water (test).
- Treatment b2: intact capsule administered together with 150 ml water (reference).

The washout period between each administration was at least 6 days. The total dose for this study was 40 mg MPH hydrochloride and both treatments were swallowed unchewed. A single oral dose of 20 mg MPH hydrochloride is within to the usual recommended therapeutical daily dose range for treatment of attention deficit hyperactivity disorder in children [Medice 2005].

An administration of the investigational medicinal product after a normal breakfast is recommended, as administration after a meal ensures that the medication remains sufficiently long enough in the stomach. Gastrointestinal disturbances are alleviated, and the anorectic effect of methylphenidate is diminished. Furthermore, in the daily routine of a busy household with children, the application after breakfast is considered to be easier to remember [Midha et al. 2001].

On study Day 1 of treatment b1 and b2 (20 mg MPH hydrochloride) a standardized breakfast suitable for children was given, as close as possible to 8:00 a.m., consisting of:

- 100 g whole-wheat granola with nuts (Nestlé),
- 150 ml full-cream milk (3.5% fat),
- 250 ml apple juice.

Subjects consumed the meal within 20 minutes after start. Treatments were administered within 5 minutes after end of this breakfast. 6 hours after administration, a standardized lunch was served and, 12 hours after administration, a standardized dinner.

From 1 hour before until 1 hour after administration, no intake of fluids except those together with breakfast and for administration were allowed. The consumption of xanthine-containing or alcoholic food and beverages as well as grapefruit juice was prohibited starting 24 hours prior to dosing until discharge.

No further dietary restrictions were given.

The study performance was not blinded. The responsible staff of the bioanalytical site was blinded for treatment.

During the study, concomitant medication/therapy was generally not allowed. A symptomatic treatment of adverse events (e.g. treatment of headache by 500 mg paracetamol = 100% recommended daily allowance) was allowed by the discretion of the investigator. Women taking hormonal contraceptives should have continued intake.

Starting on study Day 1 of the respective period, blood samples were taken for bioanalysis of methylphenidate plasma concentrations at the following time points: predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 16 and 24 hours after administration; per subject, the total number of samples per period was 16. Per sample, 10 ml of blood were collected in polypropylene tubes, stabilized with citrate and cooled immediately after collection. The samples were centrifuged within 45 minutes at about 4 C at 1,500 g for 15 minutes. The plasma was then transferred into 2 polypropylene tubes and stored below –20 C until transport to the bioanalytical laboratory. Sample collection and transfer processes were monitored by a barcode system. The samples were shipped temperature-controlled to University Childrens Hospital, Division of Biochemical Analysis and Mass Spectrometry, Graz, Austria, where bioanalysis were performed. The total blood loss for pharmacokinetic measurements was 320 ml.

For analysis of MPH (free base) in plasma, a validated gas chromatography/mass spectrometry method with [$^{18}O_2$] MPH stable isotope internal standardization was used [Leis et al. 2000]. The sample preparation included a liquid-liquid extraction step and subsequent derivatization with HFBA (heptafluorobutyric anhydride). The mass spectrometer was operated in NICI (negative ion chemical ionization) mode using single ion monitoring.

The lower limit of quantification (LLOQ) was 0.072 ng/ml, linear range of the method was 0.072 – 18.25 ng/ml. Inter-day precision of the method (calculated from low/intermediate/high quality control samples on 5 consecutive days) was < 4.4% with a maximum inaccuracy of 6.5%. Inter-day precision at the LLOQ is 6.3%. All analytical data were subjected to a blinded plausibility review prior to statistical analysis.

Pharmacokinetic analysis

The maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) were determined directly from plasma concentration-time data. At time points in the lag-time between time zero and the first concentration equal or above the lower limit quantification (LLOQ), concentrations below LLOQ were calculated as zero. Trailing concentrations below LLOQ were not to be used in calculations. Pharmacokinetic parameters were calculated by noncompartmental analysis from actual time points (if deviating from scheduled ones). The $AUC_{0\text{-}tz}$ was calculated according to the linear trapezoidal rule from the time of administration to the time point of the last quantifiable concentration. The apparent terminal elimination rate constant $_z$ was estimated by semilogarithmic regression of concentration-time data. Only data points that described the terminal decline were used in regression, and a minimum of three data points was used. Estimates of $t_{1/2}$ were calculated as ln(2)/ $_z$ for each subject in each treatment. The estimated last concentration $\hat{C}_z$ was used in ex-

trapolating AUC to infinite time ($AUC_{0-\ }$) as: $AUC_{0-\ } = AUC_{0-tz} + \hat{C}_z / \ _z$.

Statistical analysis

All measured variables and derived pharmacokinetic parameters were listed individually and, if appropriate, tabulated by descriptive statistics.

For descriptive statistics, summary tables were provided giving sample size, absolute and relative frequency of categorical variables and sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), median, minimum and maximum of continuous variables.

For descriptive statistics of pharmacokinetic parameters and concentrations, additionally geometric mean, geometric standard deviation (SD) were given. The harmonic mean was given for $t_{1/2}$. Comparative statistics were calculated using EquivTest software (version 2.0, Statistical Solutions Inc., Crosse's Green, Cork, Ireland).

The ln-transformed values of the primary pharmacokinetic characteristics AUC_{0-tz}, $AUC_{0-\ }$ and C_{max} were subjected to an analysis of variance (ANOVA). The effects considered in the ANOVA model were: treatment, sequence, subjects within sequence and study period. The error variance of the model had to be taken as test variance for all effects except the sequence effect. The latter had to be tested using the variance "subject-within sequence" as an error term.

For AUC_{0-tz}, $AUC_{0-\ }$ and C_{max}, the parametric point estimates for the treatment ratios test/reference and 90% confidence intervals were calculated using the adjusted means (least squares means) from the ANOVA of ln-transformed data with subsequent exponential transformation. Point estimates and 90% confidence intervals were given in %.

The test treatment was considered bioequivalent to the reference treatment if the 90% CI for the AUC_{0-tz} treatment ratio lies within a range of 80 – 125%. The acceptance range for C_{max} was set to 75 – 133% [Blume et al. 2005]. The extended acceptance range for C_{max} appeared clinically acceptable due to the therapeutic window and previous studies on Medikinet retard.

Differences in t_{max} were evaluated by a nonparametric method [Hauschke et al. 1990].

Safety parameters

A medical history was taken from each subject at screening and a physical examination was performed at screening and at final check. Vital signs, clinical chemistry, hematology, coagulation and urinalysis were performed at screening and at final check. A 12-lead ECG, drug screen, virus antibody test and a pregnancy test in females was performed at screening. Adverse events, if present, were coded based on MedDRA. All subjects were included in the safety analysis.

Results

Subjects

12 healthy volunteers (8 female and 4 male) were included in the study.

All of them were dosed, and finished both study periods of the study. Subjects aged 35 ± 8 years (20 – 44) with a body weight of 71 ± 13 kg (52 – 92), a body height of 173 ± 11 cm (160 – 195), a body mass index of 24 ± 2 kg/m^2 (20 – 27), and a low alcohol consumption of 35 g/d. 7 (58%) of them were nonsmokers and 5 (42%) moderate smokers (10 cigarettes/day).

Pharmacokinetics

Comparative plasma concentration-time profiles for methylphenidate following a single oral dose of Medikinet retard 20 mg are presented in Figures 1 and 2. The data indicate that plasma MPH concentration over the 24-hour sampling interval were similar for the 2 treatments. Both treatments exhibited the expected biphasic characteristics for most subjects; the first peak occurring approximately at 2 hours and the second one around 6 hours after administration. Review of individual plots reveal that the trough between the 2 plasma peaks is less pronounced after the test treatment.

Residual areas < 7% were seen in all cases, thus, sampling was carried out long

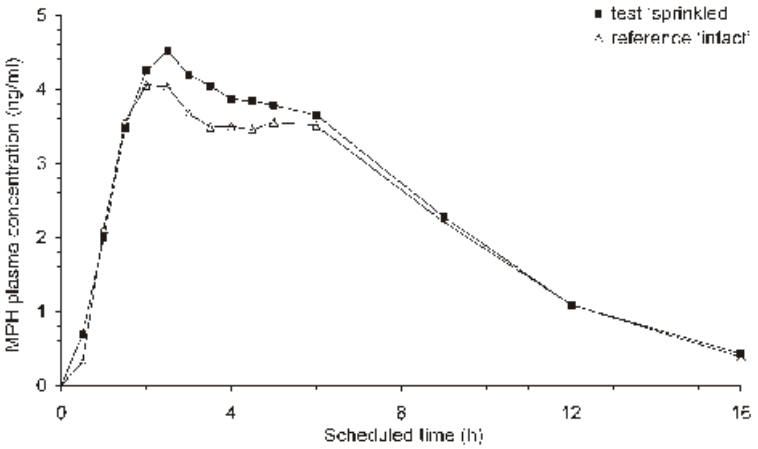

Figure 1. Arithmetic mean MPH concentration-time profiles in 12 healthy male and female subjects after single-dose administration of Medikinet retard 20 mg, content of capsule sprinked on 15 ml applesauce (solid squares) or intact (open triangles).

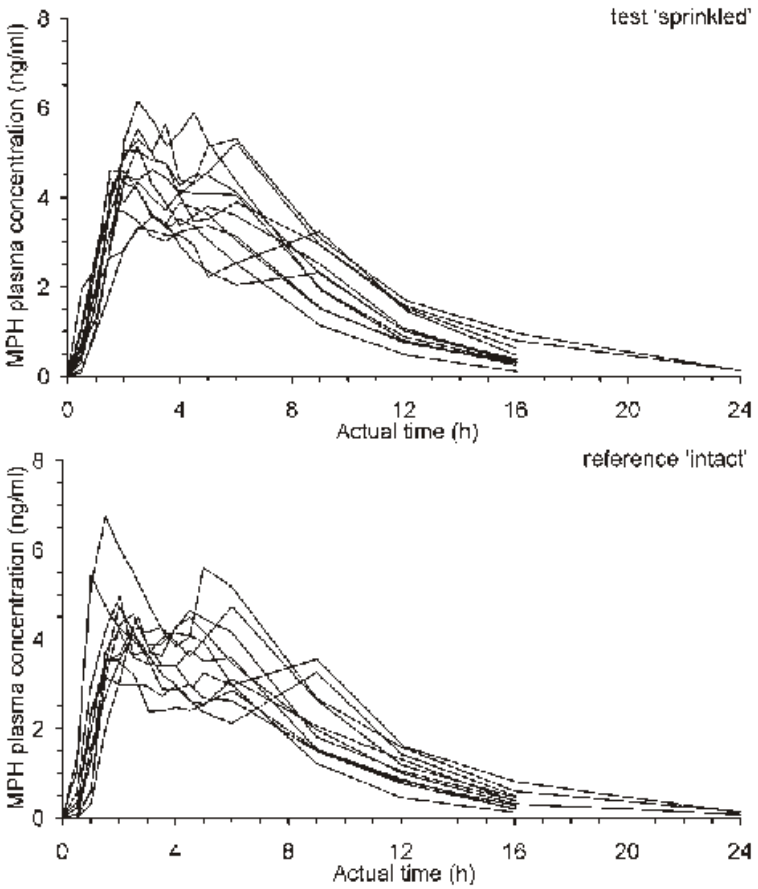

Figure 2. Individual MPH concentration-time profiles in 12 healthy male and female subjects after single-dose administration of Medikinet retard 20 mg, content of capsule sprinked on 15 ml applesauce (top) or intact (bottom).

enough to get reliable estimates of AUC_{0-} . LOQ was sufficiently low, since the last observed concentration was 4.5% of the peak plasma concentration for the test (median, range 2.2 – 9.4%), and 4.1% (2.4 – 7.6%) for the reference.

A summary of MPH pharmacokinetic parameters and analysis for bioequivalence is provided in Table 1.

Bioequivalence confirmed with the inclusion of the 90% confidence interval for AUC_{0-tz}, AUC_{0-} and C_{max} within 80 – 125%; t_{max} showed a neglectible difference of –0.02 hours.

The intersubject variability in pharmacokinetic parameters was 19.1% for AUC_{0-tz}, 14.8% for C_{max} and 18.8% for AUC_{0-} . The intrasubject coefficient of variation was 7.00% for AUC_{0-tz}, 8.89% for C_{max} and 6.73% for AUC_{0-} .

Elimination half-lives were almost identical after both treatments (test: 2.73 h, reference 2.77 h).

Safety

Both treatments, the opened capsule and the intact capsule were well tolerated in the study. There were no changes in physical examination findings in any subject between screening and final check. In summary, 7 subjects reported adverse events during the study (9 with the test treatment and 6 with the reference). The adverse events included headache (test: n = 4, reference: n = 4) and head pressure (test: n = 1, reference: n = 1). Dizziness, nausea, sensitivity to light and tiredness were reported in the test group only (each n = 1) and abdominal pain in the reference group only (n = 1).

None of the adverse events was serious, and no significant adverse events occurred. All adverse events were resolved at the end of the study without any action being taken and without sequelae.

Discussion and conclusions

Single oral doses of 20 mg methylphenidate hydrochloride were safe and well tolerated in healthy female and male subjects. Adverse events observed, mainly nervous

Table 1. Summary of MPH pharmacokinetic parameters and bioequivalence analysis (n = 12).

Parameter	Summary statistics	"sprinkled"	"intact"	PE[a]	90% CI
AUC_{0-tz} (ng × h/ml)	Geometric Mean ± SD	36.98 ± 7.71	35.05 ± 6.75	105.5	100.2, 111.1
	CV%	20.8%	19.2%	–	–
	Median	36.57	35.80	–	–
	Min, Max	27.81, 52.41	27.03, 53.07	–	–
C_{max} (ng/ml)	Geometric Mean ± SD	4.65 ± 0.91	4.52 ± 0.88	103.0	96.5, 110.0
	CV%	19.5%	19.6%	–	–
	Median	4.82	4.60	–	–
	Min, Max	3.33, 6.15	3.16, 6.75	–	–
t_{max} (h)	Median	2.50	2.02	–0.02	–1.49, +0.52
	Min, Max	1.50, 6.0	1.00, 6.0	–	–
AUC_{0-} (ng × h/ml)	Geometric Mean ± SD	38.23 ± 7.89	36.20 ± 6.71	105.5	100.5, 111.0
	CV%	20.6%	18.5%	–	–
	Median	37.73	37.39	–	–
	Min, Max	28.84, 53.16	28.28, 53.67	–	–
$t_{1/2}$ (h)	Harmonic Mean ± SD	2.73 ± 0.39	2.77 ± 0.42	–	–
	CV%	14.3%	15.0%	–	–
	Median	2.76	2.96	–	–
	Min, Max	2.22, 3.42	2.14, 3.35	–	–

[a]Point estimates were calculated based on the minimum variance unbiased estimator from ANOVA for ratios, and the Hodges-Lehmann estimator from the nonparametric method for differences

system disorders (headache), were all mild-to-moderate in intensity and resolved without any action taken. The adverse event profile was consistent with the currently applicable SmPC (Summary of Product Characteristics) for Medikinet retard 10 mg/20 mg [Medice 2005].

90% geometric confidence intervals for AUC_{0-tz} and C_{max} data were well within accepted bioequivalence limits.

Average AUC was 36.0 ng .h. ml^{-1}; C_{max} was 4.58 ng/ml, which is in good agreement with previous studies of the same formulation (sponsor's data on file, where values of 48.9 ng h ml^{-1} or 41.9 ng h ml^{-1} (AUC), and 6.42 ng/ml or 5.29 ng/ml (C_{max}) were reported.

Estimated elimination half-life of 2.75 hours is slightly higher than the previously reported 2 hours [Patrick et al. 1987], but is in good agreement with sponsor's previous studies, where 3.23 hours and 2.67 hours were found.

Observed intrasubject variability was lower than expected both for AUC (7.00%) and C_{max} (8.89%).

Because of the relative short half-life of MPH of approximately 2 hours [Patrick et al. 1987], a b.i.d. dosing of an immediate-release product (IR) is usually required to maintain therapeutic concentrations throughout the normal school day. The pharmacokinetics of methylphenidate from another MPH product administered as a single dose either as intact capsule or sprinkled over applesauce were not influenced in adult volunteers [Pentikis et al. 2002].

This study has shown that either mode of administration has almost the same pattern of absorption and elimination following single-dose administration in the fed state.

Medikinet retard 20 mg lacks food interaction if the content is sprinkled on apple-

sauce compared to the reference treatment (intact capsule) in terms of extent and rate of absorption and, thus, may be used interchangeably. Especially in children compliance plays an important role for the efficacy of a treatment and compliance is improved remarkably by once a day dosing at breakfast. In order to assist administration, maintenance of the galenic principle of a registered modified release formulation (fast release of half of the content, delayed release of the other half) after dispersion of the content of the capsule on food could be demonstrated.

The option to sprinkle the beads on applesauce will facilitate therapy of ADHD patients, who have problems in swallowing tablets or capsules.

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Funding for this study was provided by Medice, Iserlohn, Germany. The clinical part of this study was conducted at IKP Bobenheim (Mannheim, Germany) and bioanalysis was performed at University Childrens Hospital, BPA (Graz, Austria). The biostatistical evaluation was carried out by BEBAC (Vienna, Austria).

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