Bioequivalence of Methylphenidate Immediate-Release Tablets Using a Replicated Study Design to Characterize Intrasubject Variability

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Purpose. To determine the relative bioavailability of two marketed, immediate-release methylphenidate tablets. The study used a replicated study design to characterize intrasubject variability, and determine bioequivalence using both average and individual bioequivalence criteria.

Methods. A replicated crossover design was employed using 20 subjects. Each subject received a single 20 mg dose of the reference tablet or test tablet on two occasions and two doses of the test tablet on two occasions. Blood samples were obtained for 10 hr after dosing, and plasma was assayed for methylphenidate by GC/MS.

Results. The test product was more rapidly dissolved in vitro and more rapidly absorbed in vivo than the reference product. The mean Cmax and AUC(0 – ∞) differed by 11% and 9%, respectively. Using an average bioequivalence criterion, the 90% confidence limits for the Ln-transformed Cmax and AUC(0 – ∞), comparing the two replicates of the test to the reference product, fell within the acceptable range of 80–125%. Using an individual bioequivalence criterion the test product failed to demonstrate equivalence in Cmax to the reference product.

Conclusions. The test and reference tablets were bioequivalent using an average bioequivalence criterion. The intrasubject variability of the generic product was greater and the subject-by-formulation interaction variance was borderline high. For these reasons, the test tablets were not individually bioequivalent to the reference tablets.

KEY WORDS: methylphenidate; average bioequivalence; individual bioequivalence; human; pharmacokinetics; replicated design.

INTRODUCTION

When the first generic methylphenidate tablet was approved by the U.S. Food and Drug Administration (FDA), an in vivo bioequivalence study was not required because of the AA coding in the “Orange Book” (1), and a determination of bioequivalence was based on in vitro dissolution testing alone. The dissolution properties of the generic product were subsequently re-examined because of reports that the generic and innovator products were not therapeutically equivalent in patients. An in vivo bioequivalence study was also initiated to compare the generic and innovator tablets and to explore if differences in the in vitro dissolution of the two formulations were predictive of possible differences in the in vivo bioavailability of the two dosage forms.

EXPERIMENTAL

Dissolution Testing

The dissolution of both tablet formulations was determined using the USP basket method, at 100 rpm, with 900 ml of water as the dissolution media (2). Six tablets of each formulation were studied.

In Vivo Study Design

A four-way single dose, replicated crossover bioequivalence study was conducted in 20 healthy male volunteers between the age of 20 and 33 years. The research followed the 1964 Declaration of Helsinki and was approved by both the Institutional Review Board of the University of Tennessee and the Risk Involving Human Subject Committee of the FDA. All subjects were evaluated with a medical history and tests for clinical chemistry (SMA 18/90), CBC, urinalysis and ECG prior to entering the study. The 20 subjects were divided into four groups. Each group received the two products in a different sequence: Group 1—Products 1, 1, 2 and 2; Group 2—Products 1, 2, 2 and 1; Group 3—Products 2, 2, 1 and 1; and Group 4—Products 2, 1, 1 and 2. One week elapsed between doses. On each of the four dosing days, the subjects reported to the clinical laboratory in the morning after an overnight fast and received 180 ml of water to hydrate the subjects and facilitate catheter placement. One hour later each subject received a 20 mg methylphenidate tablet with 180 ml of room temperature water. No food was permitted until a standard lunch was served four hours after dosing.

Ten milliliter blood samples were obtained before dosing and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 8 and 10 hours after dosing. Samples were collected by venipuncture or indwelling catheter into heparinized evacuated tubes. Plasma was removed by centrifugation at 4°C. and the plasma was stored in glass vials at −70°C until analysis.

Analysis of Methylphenidate in Plasma

A previously described (3–5) gas chromatographic/mass spectrometry method was used to determine the methylphenidate plasma concentrations. The method used deuterated methylphenidate as an internal standard. Standard curves were
prepared each day that subject samples were assayed, using methylphenidate fortified human plasma at concentrations of 1, 2, 3.9, 7.8, 11.7 and 14.6 ng/ml. Quality control samples were also prepared at methylphenidate concentrations of 2.1, 7.0 and 12.3 ng/ml in human plasma. All samples from a given subject were assayed together, along with standards and controls.

Pharmacokinetic and Statistical Analysis

The maximum plasma concentration (Cmax) and time to reach the maximum concentration (Tmax) were determined by inspection of the data. The area under the plasma concentration-time curve to 10 hours [AUC(0–10)] and the AUC to infinite time [AUC(0–∞)] were calculated using standard methods (6).

To determine average bioequivalence, the statistical analysis was performed using the GLM procedure from the SAS statistical package on a VAX 8000 computer. The statistical significance (p value) for differences between mean values for Cmax, Tmax and AUC(0–∞) were determined from the analysis of variance for both replicates. The two, one-sided tests (7) were carried out by computing 90% confidence intervals for Cmax and AUC(0–∞) using Ln-transformed data for the individual replicate sets, as well as the means of both sets of replicates.

To determine individual bioequivalence, the statistical analysis was carried out using the criterion described in the FDA’s draft guidance (8). The variance terms, i.e., intrasubject variability and subject-by-formulation interaction, were estimated by a method of moments, using a saturated model for efficient estimates (9,10). The means were estimated by ordinary least squares estimates using equal weighting across sequences since there were an equal number of subjects in each sequence. For two-treatment designs, this estimator is the best linear unbiased estimator of the mean treatment effect (11). The 95% upper confidence bound was computed using a non-bootstrap procedure (12–13). Both constant-scaled and reference-scaled methods were used. Individual bioequivalence is established for a Ln-transformed bioavailability measure if the 95% upper confidence bound is ≤0, the individual bioequivalence limit specified in the draft guidance.

RESULTS AND DISCUSSION

The test formulation was more rapidly dissolved than the reference formulation although both tablet formulations met