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Original Research

Relative Bioavailability of Methylphenidate Extended-release Chewable Tablets Chewed Versus Swallowed Whole

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ABSTRACT

Purpose: Methylphenidate hydrochloride extended-release chewable tablet (MPH ERCT) is approved for treatment of attention deficit hyperactivity disorder in patients aged 6 years and older. This article evaluates the pharmacokinetic parameters and relative bioavailability of MPH ERCT when chewed versus swallowed whole.

Methods: In this open-label, single-dose, 3-period, 3-treatment crossover study, 12 healthy adult volunteers were randomly assigned to treatment sequence. In each period, subjects received a single 40-mg dose of the assigned treatment (MPH ERCT chewed, MPH ERCT swallowed whole, or methylphenidate extended-release oral suspension [MEROS]). Blood samples for pharmacokinetic analysis were collected for 24 hours postdose. Key pharmacokinetic parameters included C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Findings: The geometric mean values for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were similar for MPH ERCT chewed, MPH ERCT swallowed whole, and MEROS. In all pairwise between-treatment comparisons, the 90% CIs of the geometric mean ratios for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were fully contained within the bioequivalence range of 80% to 125%. Early exposure over the first 4 hours after dosing (AUC_{0-4}) was similar for MPH ERCT chewed versus swallowed whole; AUC_{0-4} was approximately 15% lower for MPH ERCT, either chewed or swallowed, compared with MEROS. Each treatment was generally well tolerated.

Implications: There was no difference in overall rate or extent of exposure of methylphenidate when MPH ERCT was chewed versus swallowed whole by healthy volunteers. (*Clin Ther*. 2018;∎:∎∎∎–∎∎∎) © 2018 Published by Elsevier HS Journals, Inc.

Key words: attention deficit hyperactivity disorder, bioavailability, drug formulations, methylphenidate, pharmacokinetics.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents, with an estimated prevalence of 8.4% to 11% in the United States.[1,2] According to the *Diagnostic and Statistical Manual of Mental Disorders* (5th Edition), ADHD is characterized by a persistent pattern of inattention (eg, failure to give close attention or difficulty sustaining attention, failure to listen, lack of persistence, disorganization, distractibility, and forgetfulness), or hyperactivity with impulsivity (eg, excessive, inappropriate motor activity and talkativeness, inability to remain seated, discomfort with being still for an extended time, and difficulty waiting one's turn).[3] If untreated, ADHD symptoms can negatively affect an individual's overall quality of life, work or school performance, and social and family relationships, and increase future risk of accidental injury, substance abuse, and other

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psychiatric morbidity.[4,5] In an estimated 30% of patients diagnosed in childhood, ADHD persists during their adult years.[6]

Treatment guidelines recommend psychostimulant medication in combination with a psychological intervention, such as behavioral therapy, for children aged 6 years or older, adolescents, and adults with significant impairment due to ADHD.[7–9] The likelihood for treatment success depends on the preferences of the patient and his or her family, which is essential for deciding on a treatment plan.[8] Both methylphenidate and amphetamine psychostimulant medications are considered effective for treatment of patients with ADHD and are approved for such use in the United States.[10] The development of modified-release psychostimulant formulations has markedly improved treatment of ADHD. Psychostimulant formulations allowing once-daily dosing are associated with better treatment adherence compared with those requiring more frequent dosing.[11–13] In addition, modified-release, once-daily regimens have been associated with overall improvements in quality of life and have become the most frequently prescribed treatments for individuals with ADHD.[11,14,15]

Methylphenidate hydrochloride extended-release chewable tablet (MPH ERCT) is approved by the US Food and Drug Administration (FDA) for the treatment of patients with ADHD aged 6 years and older.[16] MPH ERCT is available in dosage strengths of 20, 30, and 40 mg that can be taken once daily in the morning, with or without food.[16] The 20-mg and 30-mg tablets are functionally scored, allowing them to be broken in half to provide dosages of 10 and 15 mg, respectively, for individualizing treatment.[16] This chewable formulation provides a treatment option for children and adults who have difficulty swallowing their medications. In the pivotal Phase III study in children with ADHD, treatment with MPH ERCT was found to have efficacy, safety profile, onset, and duration similar to those reported for other methylphenidate modified-release formulations.[16,17] In a randomized, single-dose, crossover trial in healthy adults, MPH ERCT 40 mg produced mean peak plasma concentrations and exposure similar to that of an immediate-release MPH chewable tablet, in which two 20-mg doses were given 6 hours apart.[16,18] Some patients, however, may prefer to, or might accidentally, swallow a chewable tablet, which has the potential to alter the pharmacokinetic profile of the active agent, based on how and where the tablet disintegrates in the gastrointestinal tract.[19,20]

The objective of the present study was to assess the pharmacokinetic profile and relative bioavailability of a single dose of MPH ERCT when chewed versus swallowed whole in healthy adult subjects. A single dose of MPH extended-release oral suspension (MEROS) was included for reference purposes.[21]

METHODS

Subjects

Healthy volunteers aged 18 years or older with a body mass index of 18 to 32 kg/m^2 were eligible if they were deemed by the investigator to be in good health based on medical history, physical examination, electrocardiogram, clinical laboratory testing, and general observation. Females of child-bearing potential were eligible if they used an acceptable contraceptive method. Subjects with a history or presence of cardiovascular disease, asthma, glaucoma, hypertension, depression, anxiety, or any other clinically significant disorder were excluded, as were those who used any over-the-counter medications within 7 days, or monoamine oxidase inhibitors or any other prescription medication or dietary or herbal supplements within 14 days of the first dose of study medication. Other exclusion criteria included positive screening results for hepatitis B, hepatitis C, or human immunodeficiency virus; evidence of suicidal tendencies based on the Columbia-Suicide Severity Rating Scale; a history of drug or alcohol addiction within the past 2 years; or recent blood donation.

Study Design

This was an open-label, single-dose, randomized, 3-period, 3-treatment crossover study of healthy subjects under fasting conditions. The study was conducted from February 12, 2011 through March 8, 2011 in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Council for Harmonisation Guidelines for Good Clinical Practice. The protocol and consent form were approved by an Institutional Review Board (IRB Services, Boca Raton, FL) before any subjects were enrolled. All subjects provided written informed consent.

The study consisted of 3 dosing periods separated by 7-day washout periods. Subjects were randomly