

PEDIATRIC PHARMACOTHERAPY



Volume 23 Number 8

August 2017

Extended-Release Methylphenidate Orally Disintegrating Tablets

Marcia L. Buck, PharmD, FCCP, FPPAG, BCPPS

The options for management of attention deficit/hyperactivity disorder (ADHD) continue to grow. Over the last five years, nearly a dozen extended-release formulations of methylphenidate and amphetamine salts have been introduced onto the market in the United States.¹ These products include traditional tablets and capsules, as well as liquids, chewable tablets, and more recently, orally disintegrating tablets (ODTs). In June 2016, Neos Therapeutics received approval from the Food and Drug Administration for their mixed amphetamine salts ODT (Adzenys XR-ODT™). Their extended-release ODT formulation of methylphenidate, Cotempla XR-ODT®, was approved on June 20, 2017 for the management of ADHD in children and adolescents from 6 to 17 years of age.²

As with other extended-release methylphenidate products, the ODT formulation provides 12 hours of symptom control, giving patients a once-daily dosing in a formulation that does not require swallowing a large tablet or capsule. Orally disintegrating tablets, introduced in the 1980s, have become a very popular dosage form worldwide.^{3,4} While first used for immediate-release medications such as antihistamines, new technologies have led to the ability to create extended-release products and widened the market for this dosage form.

Formulation

Extended-release methylphenidate orally disintegrating tablets are made using an ion-exchange resin technology. When methylphenidate is dissolved in the presence of the exchange resin, the positively charged mobile ion (sodium) which is bound to the sulfonate of polystyrenesulfonate particles is replaced with the positively charged methylphenidate. The prolonged release of drug into the systemic

circulation is achieved by coating the microparticles to delay their absorption and to mask their taste. Each tablet contains a mixture of approximately 25-30% immediate-release (uncoated) and 70-75% extended-release (coated) particles.⁵

Pharmacokinetics

The pharmacokinetic profile of extended-release methylphenidate ODT was evaluated in three premarketing studies conducted by the manufacturer.⁶⁻⁸ In the first study, the bioavailability and absorption of the ODT formulation was compared to a reference extended-release methylphenidate capsule (Metadate CD®).⁶ A total of 42 healthy adults (20-70 years of age) were enrolled in this phase 1 open-label cross-over study. A single dose of 51.8 mg of the ODT formulation or 60 mg of the extended-release capsule was given after a 10 hour fast. Both formulations provided 51.8 mg of methylphenidate base. Twenty-one plasma samples were collected over 36 hours following the dose. Thirty-nine patients completed the study. There were no significant differences in the pharmacokinetic data from the two groups. The mean maximum plasma methylphenidate concentrations (C_{max}) were 21.2 ± 5.48 ng/mL and 17.4 ± 5.77 ng/mL for the ODT and capsule formulations, respectively. Time to maximum concentration (T_{max}) was 4.96 ± 1.04 hours and 4.96 ± 1.05 hours. Area under the concentration-time curve (AUC) was also similar between the two formulations, with a mean AUC from time 0 to the last quantifiable concentration of 168.0 ± 57.40 ng•hr/mL for the ODT product and 164.5 ± 65.06 ng•hr/mL for the capsule. None of the differences in the parameters reached statistical significance.

A companion study compared extended-release methylphenidate ODT taken with food and in a fasting state.⁷ Forty-eight adults between 18 and 69 years of age, participated in this open-label, randomized cross-over study evaluating the bioavailability of the new formulation. As in the previous study, plasma samples were collected over a 36-hour period after a single dose. Maximum concentrations were 19.5 ± 6.48 ng/mL and 14.5 ± 4.21 ng/mL in the fasted and fed states, with median T_{\max} values of 5 hours and 4.5 hours, respectively. Values for AUC to the last quantifiable concentration were 163.8 ± 68.22 ng•hr/mL and 178.9 ± 66.62 ng•hr/mL, demonstrating no significant difference between taking the dose with food or without food.

The terminal elimination half-life of the extended-release methylphenidate ODT is approximately 4 to 5 hours.^{5,6} Methylphenidate is extensively metabolized through deesterification to inactive alpha-phenyl-piperidine acetic acid. Only 20% is excreted in the urine as unchanged drug. There have been no studies to evaluate the impact of renal or hepatic impairment on the pharmacokinetic profile of the drug.

The pediatric pharmacokinetic profile of extended-release methylphenidate ODT was evaluated in an open-label, single-dose study of 32 children and adolescents with ADHD.⁸ The patients, ranging from 6-17 years of age were stratified into four groups; all patients received a single 51.8 mg dose (two 25.9 mg tablets). All patients had discontinued their usual methylphenidate preparation four days prior to the study. Maximum concentration were similar across the age groups: 38.1 ± 7.88 ng/mL in the children 6-7 years old, 30.7 ± 7.49 in children 8-9 years old, 30.7 ± 12.9 in children 10-12 years old, and 20.6 ± 5.97 in those 13-17 years old. Median T_{\max} was also similar, ranging from 3.5 to 5.5 hours. The mean AUC from time 0 extrapolated to infinity ranged from 378 ± 104 ng•hr/mL in the youngest patients to 190 ± 63 ng•hr/mL in the adolescents. Clearance increased with age, but was similar across the age groups when normalized for weight.

Clinical Trials

The safety and efficacy of extended-release methylphenidate ODT were evaluated in a randomized, multicenter, double-blind, placebo-controlled trial.⁹ A total of 87 children between 6 and 12 years of age with ADHD were enrolled. All patients met diagnostic criteria for ADHD and had been receiving a stable dose of methylphenidate for at least 1 month prior to enrollment. Extended-release methylphenidate ODT was initiated at a dose of 17.3 mg once daily

in the morning and titrated on a weekly basis over a 4-week period to optimize response. The maximum daily dose was 51.8 mg. Following the optimization period, the children were maintained on their optimal dose for 1 week before assessment. At the end of the week, the children were randomized to receive extended-release methylphenidate ODT or a placebo ODT for the 1-week blinded evaluation period. Efficacy was assessed in a simulated classroom setting using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Attention, Department, and Combined scores, as well as the Permanent Product Measure of Performance, attempted and corrected (PERMP-A and PERMP-C) tools.

The post-treatment SKAMP-Combined scores averaged over the classroom assessment day were significantly improved (lowered) compared to those receiving placebo. The least squares means and 95% confidence intervals in the two groups were 14.3 [12.2, 16.4] and 25.3 [23.0, 27.6], respectively, with a difference of -11.0 [$-3.9, -8.2$] ($p < 0.0001$). Differences in the SKAMP-Attention and SKAMP-Department scores were also significantly different in the two groups, with least square differences of -4.5 [$-5.9, -3.1$] and -6.1 [$-8.0, -4.3$], both $p < 0.0001$. The onset and duration of effect were evaluated in the methylphenidate group based on SKAMP-Combined scores at 1, 3, 5, 7, 10, 12, and 13 hours post-dose. Scores were significantly lower in the treatment group by 1 hour after medication administration. The difference remained significant through hour 12 ($p < 0.0001$ at 3, 5, and 7 hours; $p = 0.0024$ at 10 hours, and $p = 0.0262$ at 12 hours).

Average PERMP-A and PERMP-C scores also showed significantly greater improvement in the treatment group. The least squares means for PERMP-A were 111 [102, 119] in the treatment group and 79.3 [70.3, 88.2] in the placebo group. PERMP-C scores were 107 [98.9, 116] and 75.7 [67.0, 84.4], respectively ($p < 0.0001$). As with SKAMP scores, the onset of effect was demonstrated in the PERMP scores by 1 hour post-dose ($p < 0.0001$ in both groups) and continued through hour 12 ($p < 0.01$ in both groups).

Treatment-related adverse effects were evaluated in all patients during the 5-week dose optimization and stabilization phase as well as the blinded comparison phase. Of the 87 children participating in the study, 70 (80%) experienced at least one adverse effect. A total of 170 adverse effects were identified, with 126 considered to be related to methylphenidate. The most common adverse effects included decreased appetite (in

26.4% of children), stomach pain (21.8%), headache (19.5%), insomnia (12.6%), upper respiratory tract infection (11.5%), lability of affect (9.2%), irritability (6.9%), cough or vomiting (5.7%, each). The majority of the adverse effects were mild. The only moderate or severe adverse effects (pneumonia, upper respiratory tract infection, and elevated liver function tests) were not felt to be associated with the treatment. Two patients discontinued participation in the study as the result of an adverse effect; one for stomach pain and one case of severe influenza which developed during the double-blind assessment phase in one of the patients in the placebo group.

As a new formulation of an existing drug, the FDA did not require additional safety and efficacy studies because the bioequivalence had been established with a reference drug.⁶ This regulatory pathway allows the manufacturer to extrapolate information from previous studies done with the reference drug and avoids the need to conduct duplicative clinical trials in children.

Contraindications and Warnings

Extended-release methylphenidate ODT should not be administered to patients with a history of hypersensitivity to any form of methylphenidate.⁵ Angioedema and anaphylaxis have been reported in both pediatric and adult patients taking methylphenidate.

Central nervous system (CNS) stimulants may produce a mild increase in heart rate (mean increase 3-6 bpm) and blood pressure (mean increase 2-4 mm Hg).⁵ Use of these agents has been associated with sudden cardiac death, stroke, and myocardial infarctions in adults, and sudden cardiac death in children with structural cardiac abnormalities. A complete patient and family history should be obtained prior to starting methylphenidate to identify any risk factors.

Suppression of growth has been associated with long-term use of CNS stimulants.⁵ In naturalistic longitudinal studies, patients 10-13 years of age treated with methylphenidate experienced 2 cm less growth and 2.7 kg less weight gain over a 3-year period.

All CNS stimulants are Schedule II controlled substances and have a high potential for abuse and dependence. The risk for abuse should be evaluated prior to prescribing and reassessed regularly during treatment. Extended-release methylphenidate products, including the ODT formulation, pose a significant risk for abuse. Use of alcohol while taking an extended-release methylphenidate product may result in a more

rapid release of the drug, “dose dumping”, that can produce toxic plasma concentrations leading to excessive sympathomimetic effects, including arrhythmias, hypertension, and seizures.¹⁰ The effect of alcohol on extended-release methylphenidate ODT has not yet been evaluated, but researchers believe that it may be less than that associated with other extended-release dosage forms.¹¹ Additional studies on this effect is needed.

The risks of methylphenidate use should be reviewed with the patient and family prior to starting treatment. These discussions should include symptoms of abuse, as well as the symptoms and management of a methylphenidate overdose. Prior to having the prescription filled, the family should also have a plan established for appropriate storage of the tablets and disposal of any unused medication.

Adverse Effects

The most frequently reported adverse effects in cumulative clinical trials of methylphenidate include nausea, stomach upset or pain, decreased appetite, vomiting, dry mouth, insomnia, anxiety, nervousness or restlessness, changes in mood, dizziness or vertigo, tremor, blurred vision, tachycardia, increased blood pressure, hyperhidrosis, and pyrexia.⁵ Of the 42 adult patients participating in the first pharmacokinetic comparison study, 41 received the ODT product and 40 received the capsule.⁶ There were 17 treatment-emergent adverse events after administration of the ODT product and 20 following the capsule. The most commonly reported reactions in both groups were nausea and anxiety, occurring in approximately 18 to 20% of patients in both groups. The adverse effect profile of extended-release methylphenidate ODT in children was described in the *Clinical Trials* section.

Serious, but uncommon, adverse effects of CNS stimulants include exacerbation of underlying psychiatric illnesses, including bipolar or manic symptoms, and vasculopathies such as Raynaud’s phenomenon.⁵ Cases of priapism have been reported following methylphenidate use. Patients and families should be aware of the need to seek emergency medical attention for a prolonged erection.

Drug Interactions

The use of methylphenidate is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in those who have taken MAOIs within the previous 14 days. Common MAOIs include isocarboxazid, linezolid, methylene blue, phenylzine, selegiline, and tranylcypromine.⁵

Concomitant use with these drugs may result in hypertensive crisis. Medications that increase gastric pH (H₂ blockers, proton pump inhibitors, or sodium bicarbonate) may increase the rate of dissolution of the extended-release coated beads and decrease its effectiveness.

Availability and Dosing Recommendations

Extended-release methylphenidate ODT is available in 8.6 mg, 17.3 mg, and 25.9 mg grape-flavored tablets.⁵ These tablet strengths represent the amount of methylphenidate base and are equivalent to standard 10 mg, 20 mg, and 30 mg oral methylphenidate hydrochloride tablets or capsules. The tablets come in a package of 5 blister cards, each containing 6 tablets, with a reusable travel case. The blister packs should be stored at room temperature in the accompanying travel case until administration. Orally disintegrating tablets are fragile and must be used immediately after removal from the blister pack.

In patients not previously taking methylphenidate, therapy should be initiated with a 17.3 mg tablet taken in the morning, with or without food. The dose may be increased weekly by 8.6 mg or 17.3 mg increments until optimal symptom control is achieved. The recommended maximum daily dose is 51.8 mg.

Unused medication should be taken to a medication take-back program or returned to a collection source authorized by the Drug Enforcement Agency. If no program is available, methylphenidate may be mixed with an undesirable or unpalatable substance to make it unappealing to children or pets, placed into a sealed plastic bag, and discarded in household trash.⁵

Summary

Like other once-daily CNS stimulants, extended-release methylphenidate ODT is designed to improve adherence. While this preparation may be ideal for patients unable to take larger tablets or capsules, identifying the role for this dosage form in the treatment of ADHD requires further exploration.

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