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New Treatment Options for Attention-Deficit/Hyperactivity Disorder (ADHD): Part I. Transdermal Methylphenidate and Lisdexamfetamine

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The treatment options for attention-deficit/hyperactivity disorder (ADHD) continue to expand. In the past 3 years, the Food and Drug Administration (FDA) has approved several new products. This issue of *Pediatric Pharmacotherapy* will provide a review of two new treatment options for children with ADHD: a transdermal methylphenidate delivery system, and lisdexamfetamine, an inactive dexamphetamine pro-drug.

Transdermal Methylphenidate

On April 6, 2006, the FDA approved the first methylphenidate transdermal system (MTS) for the management of ADHD in children 6 to 12 years of age. The patch contains methylphenidate dispersed in a multi-polymeric adhesive and is designed to provide consistent drug absorption over a 9-hour period. Unlike oral once-daily products, the duration of effect can be adjusted with the MTS patch by changing the duration of time worn. This may provide the opportunity for better individualization of treatment and greater day to day flexibility based on patient needs. In addition, the MTS patch may be of benefit in children unable to swallow tablets or capsules.¹⁻⁴

Clinical Studies in Children

In 2005, Pelham and colleagues reported the results of a multicenter, double-blind, randomized dose-ranging study of the MTS patch in 36 children with ADHD between 7 and 12 years of age.⁵ Patients received either a placebo or a 6.25 cm², 12.5 cm², or 25 cm² MTS patch each day, in random order. All patches were worn for a 12-hour period. Trained counselors documented behavior using daily report cards. The authors found significant dose-related improvement in ability to follow rules and fewer episodes of noncompliance, interruption, complaining, conduct problems, and negative verbalizations for both the 12.5 cm² and 25 cm²

patches. All measures except complaining and conduct problems were significantly improved in the 6.25 cm² group. The manufacturer subsequently decided not to pursue marketing of the 6.25 cm² patch.

The efficacy and safety of the MTS patch were assessed in a 2006 randomized, double-blind, placebo-controlled study conducted in a controlled laboratory classroom setting.⁶ A total of 93 children between 6 and 12 years of age were randomized to receive MTS or placebo patches over a 5 week dose-titration. The patient sample was 72% male and consisted of 13 children (17%) with inattentiveness, 4 (5%) with hyperactivity/impulsivity, and 62 (79%) with combined ADHD symptoms.

Children receiving the MTS patch performed significantly better on the Swanson, Kotkin Agler, M-Flynn, and Pelham (SKAMP) Teacher Ratings Scale and the Permanent Product Measure of Performance (PERMP) Derived Measures scores completed by the investigators from 2 to 12 hours after patch application, with a 9-hour wear-time. The least squares mean for the SKAMP-Department scores for the MTS group showed greater improvement than the placebo patch group, with significantly lower scores (3.2±0.58 compared to 8.0±0.58, p<0.0001). The least squares mean for the SKAMP-Attention scores showed similar improvement: 6.2±0.50 for the MTS group, compared to 9.9±0.50 for the controls (p<0.0001). Scores on the ADHD-Rating Scale-IV (ADHD-RS-IV) and the Conners' Parent Rating Scale-Revised Short Version, as well as the Clinical Global Impression (CGI) and Parent Global Assessment scales, demonstrated similar statistically significant differences compared to the placebo group.

Pharmacokinetics

In a pharmacokinetic study conducted by the manufacturer in children 6-12 years of age, the average peak serum concentration after 9 hours of MTS application was 39 ng/mL (range 0-114 ng/mL). Peak concentrations were inversely correlated to age, with an average of 25 ng/mL in 12 year olds and 53 ng/mL in 6 year olds. Methylphenidate undergoes hepatic metabolism to inactive byproducts, with an average elimination half-life of 3 to 4 hours.²

Drug Interactions

Methylphenidate should not be administered with monoamine oxidase inhibitors. Administration of methylphenidate may decrease the metabolism of warfarin, phenobarbital, phenytoin, and many antidepressants. Dosage adjustment may be necessary in patients requiring these drugs. Patients receiving concomitant alpha-2 agonists (clonidine or guanfacine) should be closely monitored for additive cardiovascular effects.^{1,2}

Contraindications/Precautions

In clinical trials, the MTS patch has been well tolerated. McGough and colleagues found no significant differences in adverse event reporting between the MTS and placebo patch groups.⁶ As with other methylphenidate preparations, the MTS patch is contraindicated in patients with glaucoma, marked anxiety, hypertension or other pre-existing cardiovascular conditions. It should be used with caution in patients with tics or Tourette syndrome.^{2,3}

Adverse Effects

The adverse effect profile of the MTS patch is similar to that of oral methylphenidate. In clinical trials, the most commonly reported adverse effects were: decreased appetite (26%), insomnia (13%), nausea (12%), vomiting (10%), decreased weight (9%), tics (7%), nasal congestion (6%) affect lability (6%), nasopharyngitis (5%), and anorexia (5%).²

Patients receiving methylphenidate should be regularly assessed for changes in mood, sleep patterns, heart rate or blood pressure, as well as growth parameters.^{1,2} In 2007, Farone and Giefer studied the effects of the MTS patch on growth in 127 children between 6 and 12 years of age.⁷ Patients were followed for up to 3 years. Use of the patch was associated with small, but statistically significant, delays in growth (height, weight, and body mass index) compared to age-matched norms. The effects on weight and body mass index were directly related to the dose. As in previous studies with other methylphenidate preparations, the effects were most evident

during the first year of treatment and became less pronounced by the end of the study.

Erythema is common at the site of patch placement and typically does not require patch removal or discontinuation of treatment. If accompanied by edema, papules, or vesicles, it may be a sign of contact sensitization. In a study conducted by the manufacturer, prolonged exposure at a single application site resulted in contact sensitization in adults. Severe dermatologic reactions appear to be rare, but have been reported.^{1,2}

Dosing Recommendations

The recommended method for dose titration consists of initiating therapy with the 10 mg (12.5 cm² or 1.1 mg/h) patch. If needed, the dose may be increased at weekly intervals, using the larger patch sizes: 15 (18.75 cm² or 1.65 mg/h), 20 mg (25 cm² or 2.2 mg/h), and 30 mg (37.5 cm² or 3.3 mg/h). Recommendations for converting patients from oral methylphenidate to the MTS patch are still under development. Arnold and colleagues have suggested that a 10 mg (12.5 cm²) patch will provide a similar response to 5 mg oral methylphenidate given 3 times daily or 18 mg of the methylphenidate osmotic release product (Concerta®), due to the lack of the first-pass effect with the transdermal route.⁴ At this time, however, the manufacturer still recommends that patients being converted from oral methylphenidate to the patch begin the titration with the lowest patch size, due to the differences in transdermal drug absorption.²

The MTS patch should be applied 2 hours before optimal symptom control is needed and removed 9 hours after application. Symptom control typically lasts for 2 to 3 hours after removal. The patch should be applied to a clean, dry spot on the hip. Application on the arm or leg may result in greater variation in drug absorption. The site should be rotated daily and inspected each day after patch removal. The patch should not be applied to inflamed skin. Any residual adhesive may be removed with a cotton ball dipped in vegetable or mineral oil, avoiding vigorous rubbing. Once removed, the patch may be folded onto itself and flushed down the toilet.^{2,3}

The patch may be worn when bathing or swimming. Use of any heat source, such as a heating pad or blanket, at the patch site should be avoided. Heat increases the extent of drug absorption. Redness or itching at the site is common, but parents should be instructed to contact their health care provider if swelling or blistering occurs.^{2,3}

Availability and Cost

The MTS patch (Daytrana™; Shire) is available in 10, 15, 20, and 30 mg sizes as described previously.^{2,3} The average wholesale price for a box of 30 patches, any size, is currently \$143.28.⁸ At this price, the patch is approximately the same monthly expense as the once-daily oral products.

Lisdexamfetamine

On February 23, 2007, the FDA approved lisdexamfetamine for the treatment of ADHD in children 6 to 12 years of age. Lisdexamfetamine is a prodrug of dextroamphetamine which requires conversion in the gastrointestinal (GI) tract to release active drug. This formulation is only effective when given orally; reducing the potential for abuse through injection or inhalation.^{9,10}

Clinical Studies in Children

The approval of lisdexamfetamine was based on the results of two clinical trials conducted in children.^{11,12} Both were multicenter, randomized, double-blind, controlled studies supported by the original manufacturer (New River Pharmaceuticals). In the phase II crossover study, Biederman and colleagues compared the effects of lisdexamfetamine to an extended-release preparation of mixed amphetamine salts (MAS; Adderall XR™) and placebo.¹¹ A total of 52 children between 6 and 12 years of age were enrolled; 50 children completed the study. After a 3-week open-label dose-titration with MAS, patients were randomized to receive either lisdexamfetamine, MAS, or placebo. Doses were based on the patient's optimal MAS dose or the equivalent lisdexamfetamine dose (i.e., 30 mg lisdexamfetamine for 10 mg MAS). Patients received each treatment for 1 week. Both lisdexamfetamine and MAS produced significant improvement in SKAMP, PERMP, and CGI scores compared to placebo. Treatment effects were seen for up to 12 hours (the last time point measured).

A phase III study conducted in 290 children at 40 institutions provided similar results.¹² Patients (all between 6 and 12 years of age) received lisdexamfetamine at fixed doses of 30 mg, 50 mg, or 70 mg, or placebo daily for 4 weeks. Response was assessed by scores on the ADHD-RS—IV, CGI scale, and the Conners' Parent Rating Scale (CPRS). All doses of lisdexamfetamine produced significant improvement in ADHD-RS-IV, CGI, and CPRS scores compared to placebo (p<0.001). Symptom improvement was observed for up to 12 hours. Lisdexamfetamine was well tolerated. The primary reason for discontinuation was lack

of efficacy (reported in 1% of the 30 mg and 70 mg lisdexamfetamine groups and 17% of the placebo patients).

Pharmacokinetics

After oral administration, lisdexamfetamine is rapidly absorbed in the GI tract and converted to dextroamphetamine and L-lysine through both a first-pass effect and hepatic metabolism. In a pharmacokinetic study conducted in 18 children, the time to maximum serum dextroamphetamine concentration was approximately 3.5 hours after a dose. Administration with food, particularly a high fat meal, prolongs the time to maximum concentration by an hour, but does not affect the extent of absorption. Approximately 42% of a dose is eliminated as dextroamphetamine, with 25% eliminated as hippuric acid and 2% as intact lisdexamfetamine. Pharmacokinetic studies conducted in adolescents and adults have provided similar results to the pediatric data.¹⁰

Drug Interactions

Lisdexamfetamine should not be administered to patients taking monoamine oxidase inhibitors because of the potential for precipitating hypertensive crisis. Lisdexamfetamine may increase the effects of meperidine, norepinephrine, phenytoin, and tricyclic antidepressants. It may inhibit or reduce the response to adrenergic blockers, antihistamines, antihypertensives, and ethosuximide. When given concurrently, furazolidone and propoxyphene may increase the effects of lisdexamfetamine, while chlorpromazine, haloperidol, lithium, and urinary acidifying agents may decrease its effects.^{9,10}

Contraindications/Precautions

As with other dextroamphetamine products, lisdexamfetamine is contraindicated in patients with known cardiovascular disease, hypertension, hyperthyroidism, glaucoma, or anxiety. It should be used with caution in patients with tics or Tourette syndrome.^{9,10}

Adverse Effects

In the phase III placebo-controlled lisdexamfetamine study described earlier, the following adverse effects occurred in 5% or more of the children receiving lisdexamfetamine: decreased appetite (39%), insomnia (19%), abdominal pain (12%), headache (12%), irritability (10%), vomiting (9%), decreased weight (9%), nausea (6%), dry mouth (5%). Children taking lisdexamfetamine should be monitored for changes in heart rate, blood pressure, sleep patterns, and growth parameters.¹² The long-term effects of lisdexamfetamine on growth are not yet known.

Dosing Recommendations

The recommended initial dose for lisdexamfetamine is 30 mg taken once daily in the morning. If needed, the dose may be increased by 20 mg/day increments at weekly intervals. The maximum recommended dose is 70 mg/day. Lisdexamfetamine may be taken with or without food. In children unable to swallow the capsules, the capsule contents may be mixed in a glass of water. Once dissolved, the solution should be taken immediately and not stored for future use.^{9,10}

Availability and Cost

Lisdexamfetamine (Vyvanse™; Shire) is available in 20, 30, 40, 50, 60, and 70 mg capsules. The average wholesale price for 100 capsules of any strength is \$426.68, making the monthly cost approximately \$130.⁸

Summary

These new treatment options offer patients with ADHD more alternatives to standard therapies. Although both of the products discussed are based on traditional therapies, they provide unique advantages, such as titration of effect duration or a longer-acting once-daily product. As with all newly approved products, however, prescribers should use caution when titrating the dose of these new products or evaluating patients for adverse effects, as rare events may not have been detected during premarketing clinical trials.

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Pharmacology Literature Review

Indomethacin pharmacokinetics and outcomes

The authors of this study developed a population pharmacokinetic model for oral and intravenous indomethacin for the treatment of patent ductus arteriosus in preterm infants. The model was created from 227 serum concentrations from 90 infants given 0.01 mg/kg doses each day for 6 days. The mean estimate for clearance was 18.9 mL/hr/kg, with an estimated mean volume of distribution of 0.5 L/kg and half-life of 20 hours. Ductus closure occurred in 67% of patients. The authors reported no dose-response relationship between indomethacin plasma concentrations and ductus closure. Al Za'abi M, Donovan T, Tudehope D, et al. Orogastric and intravenous indomethacin administration to very premature neonates with patent ductus arteriosus: population pharmacokinetics, absolute bioavailability, and treatment outcome. *Ther Drug Monit* 2007;29:807-14.

Formulary Update

The Pharmacy and Therapeutics Committee did not meet during February. The next meeting will be March 14, 2008.

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