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Methylphenidate: New Information and New Options

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The next three issues of *Pediatric Pharmacotherapy* will focus on new pharmacologic approaches to the treatment of attention-deficit/hyperactivity disorder (ADHD).[a] This issue will focus on the use of methylphenidate, the most commonly used stimulant medication for ADHD, and highlight findings from the recently published National Institute of Mental Health (NIMH) multimodal treatment study. In addition, the availability of new dosage formulations will be addressed.

Mechanism of Action

The mechanism of action for methylphenidate, like other stimulants used in ADHD, is not well understood. It is believed that methylphenidate activates the brain stem arousal system and cortex. Structurally, methylphenidate acts as a dopamine and norepinephrine reuptake inhibitor, resulting in a prolongation of dopamine receptor effects.[1-4]

Recent Clinical Findings

Since its introduction in 1955, the efficacy of methylphenidate in the treatment of ADHD has been well established.[5] This one drug accounts for more than 80% of the prescriptions written for stimulants in the United States. Over one hundred papers have been contributed to the medical literature demonstrating the efficacy of methylphenidate in improving concentration and attention to academic work.[1-3,5]

In the past two years, the results of the NIMH multimodal treatment study of ADHD (MTA) have added considerably to our understanding of methylphenidate.[6-8] This multicenter study, the largest and longest of its kind, was designed to address several issues, including the role of stimulant medication alone or in combination with behavioral management. The MTA project involved 579 children over a 14 month period.[6] Evaluation of the dosing titration method and patient response to methylphenidate, using the MTA database, confirmed the drug's relative efficacy rate (77% of children responded favorably), the optimal dosage range (10 to 50 mg/day), and the utility of stepwise titration to identify the best dose for an individual patient.[7,8]

Pharmacokinetics

Methylphenidate is well absorbed after oral administration. It is extensively metabolized, primarily by deesterification to phenyl-piperidine acetic acid, which has no clinically significant pharmacologic activity. Approximately 10 to 20% of a dose is excreted unchanged in the urine. In 1999, Shader and colleagues conducted a study of 273 children between the ages of 5 and 18 years receiving immediate release (IR) methylphenidate; the elimination half-life in this population was 4.5 hours (95% CI 3.1-8.1 hours). The duration of effect for IR products is approximately 3 to 6 hours.[3,9,10]

Extended Release Products

Traditionally, one of the most difficult aspects of managing children with ADHD is timing their stimulant therapy. Ideally, adequate serum concentrations would be maintained throughout the school day and into early evening, to coincide with the completion of homework or afterschool activities. The stimulant effect should then wane throughout the evening, allowing normal sleep patterns to be preserved. The difficulty in achieving this pattern with IR methylphenidate, given in two or three doses per day, and the growing concern over having to administer doses during the school day led to the development of the first extended release wax-matrix products in the mid-1980's.[11] These products, including Ritalin-SR®, have a duration of approximately 6 to 8 hours. Ideally, a morning dose of these products would last the entire school day; however, many children still require an additional mid-day dose to provide adequate coverage in the late afternoon and early evening.

Recently, two products have been developed to provide a longer duration of effect. On August 1, 2000, the Food and Drug Administration (FDA) approved Concerta®, a tablet formulation using

OROS® technology.[12] The tablet contains an osmotically active trilayer core surrounded by a semipermeable membrane with an outer drug overcoat. In the aqueous environment of the gastrointestinal (GI) tract, the outer drug overcoat dissolves within the first hour to provide an immediate effect. Fluid then penetrates into the osmotic core, causing a polymer to expand and push drug through an orifice drilled into the drug-layer end of the tablet. The membrane controls the rate of water penetration, and thus, drug delivery. Taken once daily, Concerta® provides effective serum methylphenidate concentrations over a 10 to 12-hour period, equivalent to an IR product given three times daily, but with less fluctuation.

In June 2001, Pelham and colleagues compared once daily Concerta® to three-times-daily IR methylphenidate and placebo.[13] The treatment was given over a one week period to 68 children (ages 6 to 12 years) in the setting of an outpatient summer treatment program. All patients had previously been receiving methylphenidate and were given comparable doses. Standardized test scores, as well as parent and teacher ratings, were used to determine efficacy. The two treatments were equally effective across all domains tested. As expected, both were superior to placebo.

Later that year, Wolraich and colleagues published a double-blind randomized multicenter study of 282 children with ADHD (ages 6 to 12 years), comparing the safety and efficacy of Concerta® with IR methylphenidate or placebo for 28 days.[14] Using similar methodology to the earlier study, Concerta® was given once daily, while the IR methylphenidate was given three times daily, with doses determined by titration or previous treatment. Children in both treatment groups showed greater reductions in core ADHD symptoms than the children given placebo. Teacher and parent Conners' ratings did not differ between the two treatments. Adverse effects were also similar between the treatment groups. Based on these results, the authors concluded that once daily administration of Concerta® was equivalent to standard IR dosing.

On April 3, 2001, a second once-daily dosage formulation was introduced.[15] Metadate CD® is a capsule formulation, containing a mixture of 30% immediate release and 70% extended release coated beads. This preparation provides a biphasic drug release, with the first peak in serum concentrations occurring at 1.5 hours and a second at 4.5 hours. Taken once daily, Metadate CD® produces effective serum concentrations over an 8 hour period, similar to IR methylphenidate dosed twice daily.

The safety and efficacy of Metadate CD® was established in a double-blind, parallel group, placebo-controlled study of 321 children (ages 6 to 15 years) with ADHD. Patients were given a single morning dose of Metadate CD® (20 to 60 mg) or placebo for up to 3 weeks. Change from baseline using the teachers' data from the Conners' Global Index Scale was used for comparison. Metadate CD® showed clear benefit over placebo, whether the children were evaluated in the morning or afternoon.[15]

While no comparison studies with Concerta® and Metadate CD® have been performed, Concerta® may provide a longer duration of effect for children needing symptom control into the evening. It has been suggested that the slightly shorter duration of action with Metadate CD® may be useful in children who experience loss of appetite in the evening or insomnia with Concerta®.[16]

Drug Interactions

Methylphenidate may increase the serum concentrations of anticoagulants, anticonvulsants (phenytoin, phenobarbital, and primidone), tricyclic antidepressants, and the selective serotonin reuptake inhibitors (SSRIs). The clinical significance of these interactions has been debated in the literature. At this time, there is insufficient evidence to consider simultaneous use of these drugs contraindicated. Patients receiving these therapies concurrently, however, should be closely monitored during dosage adjustments for increased adverse effects.

Methylphenidate decreases the antihypertensive effects of guanethidine in a dose-dependent manner. Alternative antihypertensives should be used in patients requiring treatment. Monoamine oxidase inhibitors (MAOIs) may increase the effects of methylphenidate, resulting in headaches, gastrointestinal discomfort, or hypertension. These agents should not be used concurrently, and patients previously receiving MAOIs should wait for two weeks before starting methylphenidate therapy. Serious adverse effects have also been reported in patients taking methylphenidate and clonidine, although a causal relationship has not been established. This combination should be used with caution.[3,4]

Adverse Effects

The most commonly reported adverse effects with methylphenidate include headache (12-14%), loss of appetite (4-9%), insomnia (4-5%), abdominal pain (4-7%), and dizziness (2%) or somnolence (1%). It is important to note that the frequency of headaches actually declines in many children after starting methylphenidate.[10,12,15,17-20]

Approximately 1 to 4% of patients require discontinuation of therapy because of these adverse effects or the precipitation or worsening of agitation or tic disorders. In patients with insomnia, symptoms can often be reduced by reducing or omitting the afternoon dose in twice or three times daily dosing regimens. Rare adverse effects with methylphenidate include changes in blood pressure or tachycardia, vision disturbances, increases in hepatic transaminases, rash, anemia, or leukopenia. Patients should have periodic complete blood counts performed throughout treatment.

It has been suggested that children receiving methylphenidate for prolonged periods may experience an overall reduction in growth. A causal effect, however, has not been established. If a decrease in growth velocity does occur, it appears to be transient, with compensatory "catch-up" growth occurring after discontinuation of treatment. Normal adult height ranges have been demonstrated in several longitudinal studies. In some children, methylphenidate will cause enough appetite suppression or nausea to adversely affect weight gain over time. Because of the potential for impaired growth, children receiving methylphenidate should be monitored for appropriate height and weight gain.[21]

Methylphenidate may lower the seizure threshold This effect is known to occur in patients with a history of seizures or abnormal electro-encephalogram (EEG) studies, but may also occur in patients without a prior history. If seizures develop, methylphenidate should be immediately discontinued.[10,12,15,17]

Chronic abuse of methylphenidate has been reported to cause tolerance and psychiatric dependence. While there does not appear to be a correlation between the use of methylphenidate and substance abuse in children with ADHD, the potential for abuse does exist. Methylphenidate is a schedule II controlled substance.

Products and Dosing Recommendations

Methylphenidate is available in the following forms:

- Ritalin® (Novartis), Methylin® (Mallinckrodt), or generic
  5, 10, 20 mg IR tablets
- Ritalin-SR® or generic
  20 mg sustained release tablets
- Methylin ER® or Metadate ER® (Celltech)
  10, 20 mg extended release tablets
- Metadate CD® (Celltech)
  20 mg extended release capsules
- Concerta® (Alza/McNeil)
  18, 36, and 54 mg extended release tablets

Methylphenidate may be initiated with IR tablets at a dose of 5 mg twice daily, usually given before breakfast and lunch. Gradual dose escalation, based on clinical response, may be made at weekly intervals, using increments of 5 to 10 mg. If necessary, a third dose of 5 to 10 mg may be added in the afternoon (typically 8 AM, noon, and 4 PM) Daily doses above 60 mg do not appear to add any benefit and may be associated with an increase in adverse effects. Once an appropriate dose has been established, patients may be changed over to a sustained or extended release product, if desired.[3,10]

In children starting therapy with Concerta®, the lowest strength (18 mg) should be used. The dose should be administered once daily, in the morning. Dose adjustment may be done at weekly intervals, to a maximum of 54 mg once daily. Patients already receiving methylphenidate may be switched to Concerta® using a conversion chart provided by the manufacturer (Table 1).[3,12]

Table 1. Conversion Chart for Concerta®

Previous methylphenidate dose	**Daily Concerta® dose**
5 mg immediate release BID or TID or 20 mg sustained release	18 mg QD
10 mg immediate release BID or TID or 40 mg sustained release	36 mg QD
15 mg immediate release BID or TID or 60 mg sustained release	54 mg QD

The ability of the patient to swallow the tablet whole should be considered at the time of prescribing. Because of their size, Concerta® tablets should not be used in children with GI narrowing or obstruction. Patients and family members should be informed that the outer shell of the Concerta® tablet remains whole in the GI tract and is passed in the stool.

Metadate CD® is initiated as a single 20 mg dose once daily. The dose may be adjusted at weekly intervals to optimal effect. Doses above 60 mg are not recommended. In patients previously taking methylphenidate twice or three times daily, Metadate CD® may be started at an equivalent total daily dose.[3,15]

Cost

There is considerable variation in the cost of methylphenidate (Table 2). As expected, the

newer once-daily products are considerably more expensive than the generic or older products.

Table 2. Methylphenidate Cost Comparison

Product	Typical Dose	Cost*
IR generic	10 mg TID	$42.86
Ritalin®	10 mg TID	53.48
Ritalin SR®	40 mg QD	83.05
Concerta®	36 mg QD	73.13
Metadate CD®	40 mg QD	69.36

* reflects cost for a 30-day supply, based on average wholesale price (AWP)- 2001 Drug Topics Red Book

Summary

Methylphenidate remains the most widely used therapy in the management of children with ADHD. Data from the NIMH MTA trial confirms its place as a safe and effective treatment. New dosage formulations allowing once daily dosing are making methylphenidate easier to use and may improve compliance. Other products are still in development, including a new refined formulation of Ritalin® which is expected to offer greater flexibility in dose titration.

[a]These reviews have been developed for a workshop on therapies for behavioral illnesses in children to be given at the 22nd Annual University of Virginia McLemore Birdsong Pediatric Conference from May 17th through 19th. For more information, please contact Shirley P. Newman, Conference Coordinator at 434-924-2554.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/25/02:

1. Preservative-free clonidine (Duraclon®) was added to the Formulary for epidural postoperative analgesia.
2. Tinzaparin (Innohep®) was added as a less expensive alternative to enoxaparin for outpatient use.
3. Metoprolol XR®, Prempro®, and Cathflo® (alteplase for catheter clearance) were added as line extensions.

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