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Atomoxetine: A New Alternative for the Treatment of Attention-Deficit/Hyperactivity Disorder

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Traditional therapy for the management of attention-deficit/hyperactivity disorder (ADHD) has consisted of stimulant medications, primarily methylphenidate and amphetamines. Among the disadvantages of the stimulants are their status as Class II controlled substances, which limits prescribing, and their adverse effect profile. Atomoxetine (Strattera®; Eli Lilly) is a new, non-stimulant alternative to these products. In November 2002, it was approved by the Food and Drug Administration for the treatment of ADHD in patients 6 years of age and older.[1,2] This issue of *Pediatric Pharmacotherapy* will review the studies available on atomoxetine in children and provide basic information on its use.

Mechanism of Action

Atomoxetine is a selective norepinephrine reuptake inhibitor. In a rat model, atomoxetine increased concentrations of norepinephrine in the prefrontal cortex three-fold, but did not alter serotonin levels. Atomoxetine also produced a three-fold increase in dopamine concentrations in the prefrontal cortex, but did not affect dopamine levels in the striatum or nucleus accumbens. Although the exact mechanism by which this activity results in improvement of ADHD symptoms is not known, the increase in catecholamine concentrations within the prefrontal cortex is similar to that seen with methylphenidate. The relative selectivity of atomoxetine, in contrast to the more widespread increases in catecholamines produced by methylphenidate, may also explain its relative lack of potential for abuse.[1-4]

Clinical Trials

In 1998, the first clinical trial with atomoxetine (then called tomoxetine) was conducted in a group of 22 adults with ADHD.[5] The study consisted of two 3 week treatment periods separated by a 1 week wash-out period. The patients were randomized to receive either placebo or atomoxetine titrated up to 40 mg/day by the end of week one, 40 mg twice daily by the end of week two, and maintained at 40 mg twice daily during week three, if tolerated. After wash-out, patients were crossed over to the remaining treatment arm. Atomoxetine significantly reduced scores on the ADHD Rating Scale (mean score decreased from 30 points to 21.5 by 3 weeks versus no change with placebo). Using a predetermined definition of improvement (30% reduction in symptoms), 11 of the 21 evaluable patients improved during treatment, versus only two patients during the placebo administration. Atomoxetine was well tolerated. One patient withdrew from the study because of anxiety. The other adverse effects reported were insomnia, appetite suppression, and increased heart rate.

Michelson and colleagues, publishing as the Atomoxetine ADHD study group, enrolled 297 children (8 to 18 years of age) with ADHD in a dose-ranging study.[6] Patients were randomized to placebo or atomoxetine at doses of 0.5, 1.2, or 1.8 mg/kg/day for 8 weeks. Both the 1.2 and 1.8 mg/kg/day groups had significantly greater improvement in ADHD symptoms than placebo. The two groups were not different from each other. The 0.5 mg/kg/day group showed moderate improvement, suggesting a graded dose-response relationship. Atomoxetine was also associated with improved social and family functioning, compared to placebo.

Spencer and colleagues studied atomoxetine in 30 children (7 to 14 years of age) with ADHD.[7] In this open-label, prospective, dose-ranging study, patients were given atomoxetine in doses of 10 to 20 mg/day, titrated up to 90 mg/day as needed over 11 weeks. In the 22 children completing the study, ADHD Rating Scale scores were significantly lower compared to baseline (mean reduction 38.6%). More than 75% of the children experienced at least a 25%

reduction in ADHD symptoms. The mean effective dose at 11 weeks was 1.9 mg/kg/day.
In 2002, Michelson and colleagues conducted another randomized, placebo-controlled study. One hundred and seventy-one children (6 to 16 years of age) were randomized to a 6 week trial of atomoxetine or placebo.[8] Atomoxetine was administered at a dose of 0.5 mg/kg/day for 3 days, followed by 0.75 mg/kg/day for 4 days, then 1 mg/kg/day. At 4 weeks, patients who were still symptomatic could have their dose increased to 1.5 mg/kg/day. All doses were given once daily. Symptom improvement was significantly greater in the atomoxetine-treated patients, whether evaluated by investigators, parents, or teachers. The average final dose was 1.3 mg/kg/day.

Also that year, Kratochvil and colleagues published the results of a 10 week randomized, open-label trial comparing atomoxetine to methylphenidate.[9] A total of 228 children (mean age 10.4 years) were enrolled. Atomoxetine was initiated at 0.2 mg/kg and titrated to 1 to 2 mg/kg, depending on metabolic function. Methylphenidate was started at 5 mg and titrated up to a maximum of 60 mg/day. No statistically significant differences between the drugs were noted in ADHD Rating Scale scores (mean reduction 19.4 points for atomoxetine and 17.8 points for methylphenidate) or in the general impressions of either investigators or parents. Tolerability and the frequency of medication discontinuation were also similar.

Spencer and colleagues conducted two identical 12 week efficacy trials of atomoxetine.[10] A total of 291 children (7 to 13 years of age) were randomized to receive placebo, atomoxetine (up to 2 mg/kg/day or 90 mg), or methylphenidate (up to 1.5 mg/kg/day or 60 mg). Compared with placebo, atomoxetine produced significantly greater improvement in ADHD Rating Scale scores, as well as Clinical Global Impressions-ADHD Severity scores and Conners' Parent Rating Scale scores. The authors did not include the results of the methylphenidate-treated patients and did not compare their results to those of the atomoxetine-treated group.

To assess the influence of gender on response, Biederman and colleagues performed a subset analysis of atomoxetine in girls with ADHD who were enrolled into one of two different clinical trials.[11] A total of 51 girls (7 to 13 years of age) were studied. Doses of atomoxetine were titrated up to a maximum of 2 mg/kg/day or a total of 90 mg. Atomoxetine was found to be superior to placebo in ADHD Rating Scale scores, Conners' Parent Rating Scale scores, and Clinical Global Impression of Severity of ADHD scores. No significant adverse effects were reported. The authors concluded that atomoxetine was safe and effective in school-aged girls.

Earlier this year, Michelson and colleagues published an additional paper describing two 10 week, randomized, double-blind, placebo-controlled studies of atomoxetine in 536 adults with ADHD.[12] Patients receiving atomoxetine started therapy at 60 mg/day and were titrated up to a maximum dose of 120 mg/day by week 4, if needed. In both studies, atomoxetine was significantly better than placebo in improving scores on the Conners' Adult ADHD Rating Scale (total scores, scores for inattentive symptoms, and scores for hyperactive/impulsive symptoms). Patient self-assessment also showed significant benefit from treatment.

Pharmacokinetics

The pharmacokinetic profile of atomoxetine has been extensively studied in children, adolescents, and adults. When doses have been normalized by weight, pharmacokinetic parameters have been similar in all age groups. Atomoxetine is well absorbed after oral administration. The extent of absorption is not affected by the presence of food. Maximum serum concentrations are reached 1 to 2 hours after dosing. The volume of distribution of atomoxetine at steady state is 0.85 L/kg. The drug is highly bound to serum proteins (98%), primarily to albumin. Atomoxetine is eliminated by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. The major metabolite, 4-hydroxyatomoxetine, is pharmacologically active, but exists only in minimal concentrations. A minor metabolite, N-desmethylatomoxetine, is not active. The 4-hydroxy metabolite undergoes subsequent glucuronidation prior to renal excretion.

The elimination half-life of atomoxetine in clinical trials was 5.2 hours, with a clearance of 0.35 L/kg/hr. In patients who are poor metabolizers (7% of Caucasians and 2% of African-Americans), elimination half-life was prolonged (mean 21.6 hours), with an elimination rate of 0.03 L/kg/hr.[2,13,14] No specific evaluation of metabolic status or dosing adjustment for poor metabolizers is recommended; however, clinicians should be aware of the potential for slower drug elimination in some patients. The dose of atomoxetine should be adjusted in patients with hepatic dysfunction (see Dosing Recommendations). Renal impairment does not require dosage adjustment.[2]

Adverse Effects

In the accumulated data from clinical trials of children and adolescents, the most common reasons for discontinuing therapy with atomoxetine included: aggression, irritability, somnolence, and vomiting (each reported in approximately 0.5% of patients). The most frequently observed adverse effects in patients not requiring discontinuation were: decreased appetite (14% of patients), vomiting (11%), dizziness (6%), fatigue (4%), nausea and dyspepsia (4%), and mood swings (2%). In trials enrolling adults, similar adverse effects were reported. In addition, adults experienced dry mouth (21%), insomnia (16%), constipation (10%), urinary retention (3-8%), and sexual dysfunction (2-7%). Most of these adverse effects diminished over the first months of treatment.[1,2] In clinical trials, atomoxetine has also been associated with mydriasis and, as a result, should not be used in patients with narrow angle glaucoma. Hypersensitivity reactions have been reported, but appear to be rare.[2]

Although atomoxetine is often associated with a brief period of anorexia and weight loss upon initiation, these effects appear to abate with continued treatment. In short-term trials ($\leq$ 10 weeks), children treated with atomoxetine had a significant decrease in weight compared to children given placebo (mean change –0.4 kg versus +1.5 kg). Height increased in the treated patients an average of 0.9 cm versus 1.1 cm in the controls. Uncontrolled data from open-label extension studies of up to 18 months duration suggest minimal effects on weight and height over time. Controlled long-term studies are not yet available to confirm these findings.[2]

Because atomoxetine increases endogenous catecholamine concentrations, its ability to increase heart rate and blood pressure in children has also been of concern. The manufacturer recommends that atomoxetine not be used in patients with a history of cardiovascular or cerebrovascular disease and that pulse and blood pressure be assessed prior to starting therapy and periodically thereafter. The cardiovascular effects of atomoxetine were evaluated in 550 pediatric patients enrolled into the manufacturer's clinical trials.[1,15] Although there were statistically significant increases in both heart rate (mean +7.8 bpm) and blood pressure (+2.1 mm Hg) in the atomoxetine-treated patients, these differences were not felt to be clinically significant. No effect on the QT interval was observed. All values returned to baseline after discontinuation, and no patients reported adverse cardiovascular symptoms.

Drug Interactions

Although atomoxetine does not induce or inhibit the CYP2D6 pathway, it serves as a substrate for this enzyme and may be affected by other drugs that alter 2D6 function. Drugs that inhibit the activity of CYP2D6, such as fluoxetine, paroxetine, and quinidine, have been shown to prolong the elimination of atomoxetine. Dosage adjustment may be necessary in patients requiring these therapies.[2]

The interaction between atomoxetine and paroxetine, a selective serotonin reuptake inhibitor which may also be used for ADHD, has been studied in depth. Belle and colleagues at Lilly conducted an evaluation of this interaction in 22 healthy adult volunteers.[14] During period 1, the subjects were given 20 mg atomoxetine every 12 hours for nine doses. In period 2, they received 20 mg paroxetine once daily for 11 days, followed by administration of both drugs for another 6 days. Serum concentrations of atomoxetine and N-desmethylatomoxetine were significantly increased during concurrent paroxetine administration. The elimination half-life for atomoxetine increased from a mean of 3.92 hours to 10.02 hours. Time to achieve maximum serum atomoxetine concentrations was also significantly prolonged. Paroxetine pharmacokinetics were unaffected by co-administration of atomoxetine. The study subjects tolerated the combination without adverse effects, although tachycardia related to postural changes was noted in some patients who were known to be slow metabolizers.

Concurrent administration of albuterol and atomoxetine may result in an additive increase in heart rate and/or blood pressure. In addition, atomoxetine should not be administered with monoamine oxidase inhibitors or within two weeks of administration of these agents because of the risk for precipitating neuroleptic malignant syndrome or a hypertensive crisis.[2]

Dosing Recommendations

Atomoxetine is available in 10, 18, 25, 40, and 60 mg capsules. In children and adolescents weighing < 70 kg, the recommended starting dose is 0.5 mg/kg/day. This dose may be increased after 3 days to a total of 1.2 mg/kg/day. It may be administered once daily or divided and given as a morning and an afternoon dose. The maximum recommended daily dose is 1.4 mg/kg/day or 100 mg, whichever is less.

In adolescents and adults weighing > 70 kg, atomoxetine may be initiated at a dose of 40 mg given once daily. This dose may be increased

after 3 days to a total of 80 mg (administered once daily or in divided doses). After 2 to 4 weeks, an additional dosage increase to 100 mg may be made if symptom control has not been achieved.

In patients with hepatic impairment, the dose of atomoxetine should be reduced. It is recommended that for patients with moderate hepatic dysfunction (Child-Pugh Class B), the dose be reduced by 50%. For patients with severe impairment (Child-Pugh Class C), the dose should be reduced by 75%. In patients receiving concurrent therapy with an agent which inhibits CYP2D6, atomoxetine may be initiated with standard doses, but further dose increases should be made with caution.

It has been noted by some clinicians that the onset of symptom control with atomoxetine is delayed compared to the stimulants. A trial period of at least two weeks is recommended to determine the efficacy of therapy. Atomoxetine can be discontinued without tapering.[2]

Cost

The average patient cost for a one month supply of atomoxetine is approximately $90. This is slightly more expensive than the average cost of the newer once-daily stimulant preparations: methylphenidate products such as Concerta® ($75) and Metadate CD® ($77), or amphetamine products such as Adderall XR® ($73).[16] There are considerable pricing differences, however, among retail pharmacies.

Summary

Atomoxetine provides a useful new alternative to traditional ADHD therapy with stimulants. Whether atomoxetine will become a first-line therapy, or considered an option for patients intolerant of or unresponsive to stimulants remains to be determined. More clinical experience and additional comparison trials with the stimulants are needed to better define the role of atomoxetine in the treatment of ADHD.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/28/03:

1. The etonorgestrel/ethinyl estradiol vaginal ring (NuvaRing®) and the norelgestromin/ethinyl estradiol transdermal system (Ortho Evra®) were rejected.
2. Ezetimibe (Zetia®) was added to the Outpatient Formulary for the management of hypercholesterolemia in patients intolerant of or with an inadequate response to HMG-CoA reductase inhibitors.

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