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New Treatment Options for Attention-Deficit/Hyperactivity Disorder (ADHD): Part II. Guanfacine

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Clonidine and guanfacine, alpha-2A adrenergic agonists, have been used off-label in the management of children with attention-deficit/hyperactivity disorder (ADHD) for more than a decade. Guanfacine is preferred by many health care providers for its longer duration of action.[1,2] A new extended-release formulation of guanfacine is currently under review by the Food and Drug Administration (FDA) specifically for the treatment of ADHD in children between 6 and 17 years of age.[3] This issue of *Pediatric Pharmacotherapy* will provide a basic review of guanfacine and highlight recent studies of both the immediate-release and the new extended-release product.

Mechanism of Action

Guanfacine, like clonidine, is a centrally acting selective alpha-2 adrenergic agonist. Stimulation of alpha-2 adrenergic receptors in the prefrontal cortex results in enhanced executive functioning, increased attentiveness, and improvements in working memory. In patients with ADHD, improved neurotransmission in this region increases the ability to control or inhibit inappropriate behaviors and increase focus. Guanfacine preferentially binds alpha-2A receptors, compared to the more general affinity of clonidine for alpha-2A, B, and C and imidazoline receptors.[1,2]

Clinical Studies in Children

Immediate-release Guanfacine

The first studies of guanfacine in children with ADHD were published in 1995.[4-6] These three small open-label studies demonstrated the efficacy of immediate-release guanfacine in improving ADHD symptoms and served as a foundation for further research. The first placebo-controlled guanfacine trial was published by Scahill and colleagues in 2001.[7] A total of 34 children (mean age 10.4 years) with ADHD and a tic disorder were randomized to receive either guanfacine, beginning with 0.5 mg and titrated as needed, or placebo for 8 weeks. The effective dose of guanfacine ranged from 1.5 to 3 mg/day. Guanfacine produced a significantly greater improvement in ADHD Rating Scale scores (37% versus 8% in the controls, $p<0.001$). Clinical Global Improvement (CGI) scale scores were rated as much improved or very much improved in 9 of the 17 guanfacine patients, while none of the placebo patients achieved these scores ($p<0.001$). In addition, tic severity decreased by 31% in the guanfacine group, with no improvement in the placebo group using the Yale Global Tic Severity Scale ($p=0.05$). There was no significant difference between the groups in mean parent-rated hyperactivity index scores, with a 27% improvement in the guanfacine group and a 21% improvement in the placebo group.

In 2001, Taylor and Russo conducted a comparison study of guanfacine and dextroamphetamine in adults with ADHD.[8] Seventeen adults were enrolled into this randomized, double-blind, placebo-controlled crossover study. The subjects received each treatment (0.25 mg guanfacine, 2.5 mg dextroamphetamine, or placebo) for a 2 week period separated by 4 day wash-outs. Doses were titrated to achieve symptom control, up to a maximum of 2 mg guanfacine or 20 mg dextroamphetamine. The average final daily doses were 1.1 mg guanfacine and 10.2 mg dextroamphetamine.

Both drugs significantly reduced ADHD symptoms compared to baseline, using the ADHD Behavior Checklist for Adults ($p<0.05$). The only significant difference between the results achieved with the two drugs was in the

Color-Word subscale of the Controlled Oral Word Association Test, where guanfacine produced a greater degree of improvement ($p<0.01$).[8]

Two additional studies have evaluated the effects of guanfacine in children with pervasive developmental disorders (PDD) and ADHD or hyperactivity.[9,10] In 2004, Posey and colleagues conducted a retrospective study in 80 children (3-18 years of age) who received guanfacine.[9] The authors found a response rate of 23.8% (19/80), using an average dose of 2.6±1.7 mg/day. The children most likely to respond to guanfacine were those with PDD alone or in combination with Asperger's. Patients with co-morbid autism or mental retardation were less likely to benefit from treatment.

Scahill and colleagues conducted a prospective open-label study of guanfacine in 25 children with PDD-associated hyperactivity.[10] After 8 weeks of treatment, there was significant improvement in parent-rated hyperactivity using the Aberrant Behavior Checklist, a decline from 31.1±8.89 at baseline to 18.9±10.37 at study completion ($p<0.001$). The teacher-rated scores also declined, from 29.9±9.12 at baseline to 22.3±9.44 ($p<0.01$). Forty-eight percent of the children achieved a rating of much improved or very much improved on their CGI scores. The average final dose in this study ranged from 1 to 3 mg/day.

Extended-release Guanfacine

In the January 2008 issue of *Pediatrics*, Biederman and colleagues published the results of a randomized, double-blind, placebo-controlled trial of extended-release guanfacine in children with ADHD.[11] A total of 345 children between 6 and 17 years of age were enrolled in this multicenter study. Patients were randomized to receive extended-release guanfacine (at a dose of 2 mg, 3 mg, or 4 mg) or placebo once daily. There was significant improvement in ADHD Rating Scale total scores in each of the three treatment groups, with a mean reduction at endpoint of -16.7 compared to -8.9 for the placebo group ($p < 0.0001$). Significant improvement in CGI scores was demonstrated in 55.95% of the 2 mg group, 50% of the 3 mg group, and 55.56% of the 4 mg group, compared to only 25.64% of the placebo group.

Pharmacokinetics

Immediate-release guanfacine is well absorbed, with an oral bioavailability of approximately 80%. Peak concentrations occur 1-4 hours after an oral dose. It has a large volume of distribution, 6.3 L/kg, reflecting extensive distribution throughout the body. Guanfacine is metabolized via hepatic conjugation. The parent compound and metabolites are excreted in the urine. The elimination half-life of immediate-release guanfacine is approximately 10 to 17 hours in adults.[2]

In 2007, Swearingen and colleagues conducted a Phase I open-label single-dose pharmacokinetic study of extended-release guanfacine in 52 adults.[12] The maximum serum concentrations (C_{max}) ranged from 0.98±0.26 ng/mL with a 1 mg dose to 3.58±1.39 ng/mL with the 4 mg dose. Area under the concentration-time curve ($AUC_{0-\infty}$) ranged from 32.4±8.78 ng/mL·h^{-1} for the 1 mg dose to 124.1±45.1 ng/mL·h^{-1} for the 4 mg dose. The average elimination half-life ranged from 16.6±3.8 to 17.5±3.8 hours.

The pharmacokinetic profile of extended-release guanfacine was also recently studied in a group of 14 children (6-12 years of age) and 14 adolescents (12-17 years of age).[13] All subjects received a single 2 mg dose on the first day of the study, followed by a wash-out period, then sequential doses of 2 mg, 3 mg, and 4 mg each for a week. After the 2 mg dose, the younger children achieved a higher $AUC_{0-\infty}$, with an average of 62.5±23.9 ng·hr/mL compared to 47.3±13.7 ng·hr/mL in the adolescents. Time to maximum plasma concentration was approximately 5 hours for both age groups. The C_{max} increased proportionally to the dose, with the 2 mg dose producing C_{max} values of 4.39±1.66 ng/mL and 2.86±0.77 ng/mL in the younger and older groups, respectively. For comparison, a week of treatment with the 4 mg dose produced C_{max} values of 10.1±7.09 ng/L and 7.01±1.53 ng/mL. The average elimination half-life was 14.4±2.39 hours in younger children and 17.9±5.77 hours in adolescents.

Drug Interactions

Administration of guanfacine with other central nervous system depressants may result in excessive sedation.[1,2]

Contraindications/Precautions

Abrupt discontinuation of guanfacine may result in increased levels of serum catecholamines. In comparison to clonidine, guanfacine produces less of an effect on blood pressure because of its weaker binding affinity for imidazoline receptors. In patients taking guanfacine for hypertension, abrupt discontinuation has resulted in mild rebound hypertension, anxiety, and irritability. It is recommended that guanfacine doses be slowly tapered over a period of several weeks to avoid these effects.[1,2]

The incidence of rebound hypertension with guanfacine discontinuation in patients with ADHD appears to be low. Kisicki and colleagues compared abrupt discontinuation of extended-release guanfacine to a taper in 45 healthy young adults (ages 19-24 years).[14] All subjects received a standardized dose-escalation, starting with 1 mg extended-release guanfacine followed by a 1 mg increase every 4 days. Following the dose escalation, the abrupt cessation group received placebo for the remainder of the 32-day study, while the taper group received a 1 mg decrease in dose every 4 days. There were no clinically significant differences in blood pressure or tolerability between the two groups. The mean systolic blood pressure decrease from baseline was -8.84 mm Hg in the abrupt cessation group, compared to -9.69 mm Hg in the taper group. Statistically significant differences in blood pressure were observed on the first day of discontinuation and the next to last day of the study, but the overall mean blood pressures were no different.

Adverse Effects

Guanfacine is generally well tolerated. The most frequently observed adverse effect in children is sedation, although it occurs less commonly with guanfacine than with clonidine. This difference may be due to the greater specificity of guanfacine for the alpha-2A receptor subtype. The sedation observed with these agents typically lessens over the first few weeks of treatment.[1]

In the clinical trial of extended-release guanfacine conducted by Biederman and colleagues, the most common adverse effects observed were somnolence (in 24-38% of patients, depending on dose received), fatigue (15-20%), upper abdominal pain (10-16%), and sedation (9-16%).[11] The incidence of adverse effects increased with increasing dose. In the majority of patients, these effects were mild to moderate in intensity and did not require drug discontinuation. A total of 12.5% of the study participants dropped out because of adverse effects.

Similar results were demonstrated in the pediatric extended-release guanfacine pharmacokinetic study described previously.[14] The most common adverse effects reported were somnolence (in 89% of children), insomnia (14%), headache (7%), blurred vision (7%), and altered mood (7%). None of the children in the study experienced significant changes in electrocardiographic parameters, vital signs, or laboratory results.

In 1999, Horrigan and Barnhill published a case series of five children who developed symptoms of mania after being treated with guanfacine.[15] Symptoms began 1 to 3 days after starting therapy and resolved with discontinuation of therapy. All of the children had developmental disorders in addition to ADHD and several had risk factors for bipolar disorder, which may have placed them at higher risk for this adverse effect. While this adverse effect has not been reported by others, it should be considered as a potential risk in children with complex developmental disorders.

Dosing Recommendations

Immediate-release guanfacine is typically initiated at a dose of 0.5 mg at bedtime, with the addition of a second dose in the morning after 4-7 days. If needed, a third dose may be added after school. This schedule allows the patient time to accommodate to the sedating effects of the drug without producing excessive daytime sedation. If symptom control has not been achieved, the dose may then be increased by 0.5 mg increments.[1] The recommended dose of extended-release guanfacine is 1 to 4 mg per day, given as a single daily dose.[3]

Availability and Cost

Immediate-release guanfacine (Tenex®; Reddy Pharmaceuticals) is available in 1 mg and 2 mg tablets. The average retail price for 30 tablets is approximately $60 for the 1 mg strength and $90 for the 2 mg strength. Extended-release guanfacine (Intuniv™; Shire Pharmaceuticals) is not yet available, but is expected to be marketed in 1 mg, 2 mg, 3 mg, and 4 mg capsules.

Summary

The alpha-2 adrenergic agonists, guanfacine and clonidine, are effective alternatives to stimulant medications in the treatment of children with ADHD. Although clonidine has been more widely studied, guanfacine offers several advantages, including a longer elimination half-life, less sedation, and a reduced risk for adverse cardiovascular effects. The availability of a once-daily extended-release guanfacine product will offer a new option for ADHD patients who fail to respond to or are intolerant of traditional therapies.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/14/08:

1. Iloprost (Ventavis®), a synthetic analogue of prostacyclin I_2, was added to the Inpatient Formulary for the treatment of patients with pulmonary arterial hypertension. Iloprost is administered in a 2.5 to 5 mcg dose inhaled 6-9 times daily. The drug will not be routinely stocked in the pharmacy; patients will be allowed to bring in their home supply.

2. Etravirine (Intelence®), a non-nucleotide reverse transcriptase inhibitor, was added to the Inpatient and Outpatient Formularies for the treatment of HIV-1 infection. It is a category A antimicrobial.

3. The restriction on the use of inhaled nitric oxide (INOMax®) was amended to include testing for vasodilator response during right-sided cardiac catheterization in patients with pulmonary hypertension.

4. The restriction on natalizumab (Tysabri®) was amended to include use by Gastroenterology/Hepatology for patients with Crohn's disease who have not responded to tumor necrosis factor alpha blocking agents.

5. Carbapenem antibiotics (ertapenem and meropenem) have been reclassified as category A antimicrobials and require the approval of the Antibiotic Surveillance Team prior to use in adults.

6. The restriction on recombinant factor VIIa (NovoSeven®) has been amended to include use in surgical patients. A Hematology consult is required for patients needing more than 2 doses.

7. Immediate release niacin 500 mg and ribavirin lyophilized powder (Virazole®) were removed from the Formulary.

8. Maraviroc (Selzentry™), an oral selective chemokine receptor CCR5 antagonist, was added to the Outpatient Formulary for the treatment of patients with HIV-1 infection.

9. Multidose vials of enoxaparin (300 mg/3 mL) are now available in the Outpatient pharmacy.

10. The guidelines for the prophylaxis and treatment of nausea and vomiting were revised to make IV promethazine a second-line agent, to limit the dose of promethazine to no more than 25 mg, and to require dilution to a minimum of 10 mL.

11. Standard **adult** IV doses for intermittent replacement of magnesium sulfate and potassium chloride were approved. Potassium chloride will be available in 10 mEq/ 100 mL (central or peripheral line) and 20 mEq/ 50 mL (central line only) options. Magnesium sulfate will be available in a 2 g/ 50 mL option.

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