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Mirtazapine: Potential advantages in adolescents with depression associated with chronic illness

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Many of the newer antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), have been used in the management of depression in children and adolescents. A subset of this population, children with depression associated with chronic illness, may require a different approach. Several studies have documented the prevalence of depression in these patients. While the majority of the papers published deal with the pediatric cancer population, there are also children with depression associated with other chronic, debilitating diseases, such as cystic fibrosis, sickle cell disease, and Crohn's disease. Some of these patients may benefit from the use of mirtazapine, a tetracyclic antidepressant with unique properties.

Mechanism of Action

The precise mechanism of action of mirtazapine is still uncertain. In general, the tetracyclic antidepressants, mirtazapine and maprotiline, act by increasing central noradrenergic and serotoneric (5-HT_1) neurotransmission. The methods by which they accomplish these results differ. Mirtazapine appears to act primarily as a potent antagonist at postsynaptic 5-HT_2 and 5-HT_3 (serotonergic) and central α_2-adrenergic (noradrenergic) receptors. Maprotiline does not possess this degree of receptor subtype specificity. These differences have led some investigators to refer to mirtazapine as the first noradrenergic and specific serotoneric antidepressant (NaSSA).[1,2]

Mirtazapine is also a potent antagonist at central and peripheral histamine (H_1) receptors, which may explain its sedative effects. Unlike maprotiline, mirtazapine has little activity at muscarinic or peripheral α_1-adrenergic receptors.[1-4]

Clinical Efficacy

Mirtazapine has been found in several large-scale clinical trials to be a safe and effective antidepressant. In a recent meta-analysis of eight clinical trials, mirtazapine was found to be significantly better than placebo and comparable to amitriptyline in the treatment of major depression in adults with symptoms of anxiety.[4] Other trials have shown mirtazapine to be equivalent to or better than trazodone, clomipramine, doxepin, imipramine, fluoxetine, and paroxetine in the treatment of moderate to severe depression.[1,5,6]

Potential Role in Adolescents

While currently only approved by the Food and Drug Administration for the treatment of depression in patients $\geq$ 18 years of age, mirtazapine may be very useful in selected adolescent patients. Although there are now many safe and effective antidepressants from which to chose, mirtazapine offers the additional advantage of stimulating appetite and promoting weight gain. Typically considered adverse effects in adults with depression, these effects may be very beneficial in adolescents with conditions such as Crohn's disease or cystic fibrosis where weight gain is often a challenge and in children who are receiving chemotherapy.

Although no data are currently available in children, in premarketing studies enrolling adults, 17% reported an increase in appetite and 12% reported weight gain. In some studies, up to 5-10% of patients reported a gain of > 7% body weight.[2] At this time, several patients at the Children's Medical Center have been treated with mirtazapine with positive results in terms of both weight gain and improvement in depressive symptoms.

Pharmacokinetics

The pharmacokinetic profile of mirtazapine has not been evaluated in children. In studies of adults, the drug is rapidly and completely absorbed after oral administration. Peak serum

concentrations are reached within 2 hours following a dose. Absolute bioavailability of mirtazapine is approximately 50% and is not affected by the presence of food. Mirtazapine is approximately 85% protein bound.[1,2]

Mirtazapine is metabolized primarily through demethylation by cytochrome P450 (CYP) 3A4 enzymes and hydroxylation by CYP2D6 and CYP1A2. The metabolites then undergo glucuronide conjugation prior to renal elimination. Before conjugation, some of the metabolites possess minor pharmacologic activity. The mean elimination half-life of mirtazapine in adults is 20 to 40 hours. Interestingly, female patients, regardless of age, tend to have a significantly longer half-life than males (an average of 37 hours for females versus 26 hours for males).[1-3]

Drug Interactions

Because of its metabolism through the cytochrome P450 enzyme system, there is the potential for significant drug interactions with mirtazapine. While mirtazapine itself does not appear to function as either an inducer or inhibitor of these enzymes, it could be affected by other drugs which alter enzyme function. To date, no clinically significant drug interactions with mirtazapine have been reported, but drugs metabolized through these pathways should be closely monitored.[2]

As with other antidepressants, patients who have been receiving monoamine oxidase inhibitors, phenelzine (Nardil®), tranylcypromine (Parnate®), or isocarboxazid (Marplan®), should be off therapy for at least a two week period prior to starting mirtazapine. Use of the two agents simultaneously or in rapid succession may result in hyperthermia, autonomic instability, seizures, or coma.[3]

Adverse Effects

In studies of patients 18 years of age and older, approximately 16% discontinued mirtazapine because of adverse effects. The most common adverse effects reported in these patients were somnolence (10.4%) and nausea (1.5%).[1-3]

When data from multiple clinical trials for depression in adults were pooled, the most frequent adverse effects reported with mirtazapine were somnolence (54%), dry mouth (25%), constipation (13%), and the previously mentioned increased appetite (17%) and weight gain (12%). Other reactions reported in more than 1% of patients include: asthenia (8%), elevations in serum triglyceride or nonfasting cholesterol levels (6-15%), central nervous system disturbances such as abnormal dreams, agitation, anxiety, confusion, or dizziness (1-7%), myalgias and flu-like symptoms (2-5%), urinary frequency (2%), edema (1-2%), tremor (2%), elevations in hepatic enzymes (2%), pruritus or rash (1%), and hypertension (1%).[2,3]

Rare, but significant, adverse effects observed with mirtazapine include agranulocytosis (2 out of 2,796 patients in premarketing trials), severe neutropenia (1 patient) and seizures (2 patients with a previous history of seizures). In these cases, the patients fully recovered after discontinuation of the drug.[1-3]

Patient Counseling and Monitoring

- Although agranulocytosis has only rarely been reported with mirtazapine, families of patients receiving the drug should be aware of the risk. Parents should understand the need to seek prompt medical attention for any sign of infection, including fever, chills, a sore throat, or flu-like symptoms.

- Because of the high incidence of sedation with mirtazapine, families of adolescents who are driving should be counseled about the need to determine the patient's degree of impairment prior to allowing the patient to operate a vehicle.

- Patients taking mirtazapine should be counseled that concomitant use of other central nervous system depressants, such as benzodiazepines or alcohol, will result in additive sedation and impairment of motor skills.

- In addition, patients and families should monitor the patient's degree of weight gain while on mirtazapine to ensure that it does not become excessive.

Management of Overdose

Another advantage of mirtazapine in the adolescent population is the minimal risk of toxicity with an overdose. Although there is still only limited experience with mirtazapine overdoses, all patients reported have experienced a full recovery. Signs and symptoms associated with overdosage include sedation, disorientation, and tachycardia. At this time, there are no reports of mirtazapine causing other arrhythmias,

seizures, or coma. Treatment is supportive. Patient management should include a careful history to identify a multiple-drug ingestion which might include a more toxic agent.

Dosing Recommendations

Mirtazapine is marketed as Remeron® by Organon. It is available in 15, 30, and 45 mg tablets. The 15 and 30 mg tablets are scored for dose titration. The recommended starting dose for adults is 15 mg per day in a single dose. This dose is usually given at bedtime to avoid excessive daytime sedation. In patients who fail to respond, dosage increases may be made every 1 to 2 weeks to a maximum of 45 mg per day.[2] Adolescents may start therapy with the adult dose, with adjustment based on individual patient response.

Although there are no specific guidelines for dosage adjustment in patients with moderate to severe renal or hepatic dysfunction, drug accumulation may occur. Conservative dose escalation and close monitoring for adverse effects is recommended.[3]

Summary

Mirtazapine may play a unique role in the management of adolescents with depression associated with chronic illness. In addition to its established role as an antidepressant, mirtazapine may be of use in stimulating the appetite and improving weight gain in children at risk for excessive weight loss. Research in this population is needed to better define the ideal dosing range, determine population pharmacokinetic parameters, and identify any differences in adverse effects.

References

1. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. Drugs 1999;57:607-31.
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5. van Moffaert M, de Wilde J, Veerecken A, et al. Mirtazapine is more effective than trazodone: a double-blind controlled study in hospitalized patients with major depression. Int Clin Psychopharmacol 1995;10:3-9.
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Literature Review

Anaphylaxis to Muromonab-CD3

Muromonab-CD3 (also known as OKT3) is used in the induction of immunosuppression following organ transplantation and in the management of steroid-resistant graft rejection. Anaphylactic and anaphylactoid reactions to muromonab-CD3 are not uncommon. Anaphylactoid reactions typically present with cytokine release syndrome, hypotension, and a shock-like response. In this report, a 15 year old girl who developed an anaphylactoid reaction following her first dose of muromonab-CD3 for a renal transplant is presented. Within 10 minutes of receiving a 10 mg IV dose, she complained of shortness of breath and paresthesias. She became profoundly hypotensive and developed laryngeal stridor requiring intubation and inotropic support. Her condition stabilized during the next 24 hours, but the transplanted kidney was lost because of acute infarction. As expected, there were no anti-OKT3 antibodies found in serum collected prior to, during, or up to 3 months following the episode. Berkowitz RJ, Possidente CJ, McPherson BR, et al. Anaphylactoid reaction to muromonab-CD3 in a pediatric renal transplant patient. **Pharmacotherapy 2000;20:100-4.**

Clonidine for ADHD

Clonidine has been used for the management of children with attention deficit/hyperactivity disorder (ADHD) for approximately ten years. While the exact mechanism of action is unknown, clonidine, a centrally acting alpha-adrenergic agonist, is believed to reduce neuronal firing in the locus coeruleus, decreasing excessive central nervous system stimulation. This brief report covers the basic pharmacology of clonidine, including toxicologic information, and the studies conducted in children with ADHD to date. The authors present a well-balanced discussion of the data, including the value of transdermal clonidine in children who wish to avoid having to take oral medications during the school day. Chafin CC, Hovinga CA, Phelps SJ. Clonidine in the treatment of attention-deficit hyperactivity disorder. **J Pediatr Pharm Pract 1999;4:308-15.**

Cytochrome P450 3A review

The cytochrome P450 enzyme system is responsible for the metabolism of numerous drugs and is the site of many drug interactions. The 3A subfamily is now recognized as being one of the largest groups within the P450 superfamily. This in-depth article begins with a

review of the CYP450 system, including aspects of genetic variation and the significance of extrahepatic sites. While the role of CYP3A4 is now fairly well defined and is given the most detail, the authors also present some interesting findings about CYP3A5 and CYP3A7. The remainder of the article is focused on the developmental aspects of 3A function and how these factors affect drug elimination and drug interactions in children. The article is well written and extensively referenced, making it an invaluable resource for those interested in pediatric pharmacology. de Wildt SN, Kearns GL, Leeder JS et al. Cytochrome P450 3A: Ontogeny and drug disposition. **Clin Pharmacokinet 1999;37:485-505.**

Methylphenidate pharmacokinetics

During the past decade, there have been a number of studies published describing the pharmacokinetic profile of methylphenidate. The authors of this review provide an overview of these studies, with special attention to the significant variations in individual response and the problems inherent in our current practice of administering methylphenidate as a racemic mixture of the more potent d-threo-methylphenidate and less potent l-isomer. Kimko HC, Cross JT, Abernethy DR. Pharmacokinetics and clinical effectiveness of methylphenidate. **Clin Pharmacokinet 1999;37:457-70.**

RSV immune globulin and palivizumab review

This brief review covers the major studies conducted to date with therapies to prevent respiratory syncytial virus (RSV). The studies are presented sequentially, with the first section devoted to early work with RSV immune globulin. The majority of the review focuses on palivizumab, the monoclonal antibody which has become the drug of choice for RSV prophylaxis. The guidelines developed by the American Academy of Pediatrics are included, as well as a discussion of cost. This is a very nice review for students and those not already using these agents in practice. Robinson RF, Nahata MC. Respiratory syncytial virus (RSV) immune globulin and palivizumab for prevention of RSV infection. **Am J Health-Syst Pharm 2000;57:259-67.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 1/28/00:

1. An injectable preparation of caffeine citrate without preservatives (Cafcit®; Roxane) was added to the Formulary. This product is indicated for the treatment of apnea of prematurity in infants. Therapy should be initiated with a loading dose of 20 mg/kg given intravenously over 30 minutes, followed by a maintenance dose of 5 mg/kg given over 10 minutes every 24 hours.

2. Sodium ferric gluconate (Ferrlecit®; Schein) was added to the Formulary, restricted to use in patients receiving hemodialysis. This product is a parenteral iron complex used with erythropoietin to increase red cell production. Sodium ferric gluconate has been used successfully in some patients who experienced severe reactions to iron dextran, although there is still a significant risk for reactions with this preparation. Pediatric dosing has not been established.

3. Rofecoxib, a cyclooxygenase-2 (COX-2) inhibitor, was added to the Formulary with restriction to patients with a previous history of a gastrointestinal bleed or intolerance of non-specific non-steroidal anti-inflammatory drugs (NSAIDs), patients on anticoagulants or high-dose steroid therapy, or in patients with thrombocytopenia or clotting disorders.

4. The 1999 annual report of the Adverse Drug Reaction Reporting Program was also presented. For more information about this report, please contact Dr. Anne Hendrick, Director of Drug Information Services at 4-8034.

If you have any comments or suggestions for future issues, please contact us at Box 274-11, UVA Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mlb3u@virginia.edu.