Pediatric Pharmacotherapy

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 2 Number10 October 1996

The Use of Selective Serotonin Reuptake Inhibitors in Children and Adolescents

In 1988, fluoxetine (Prozac®) was approved by the FDA for use in the United States.[1] With its introduction came a new era in the treatment of depression and obsessive-compulsive disorders. Compared to the non-specific receptor binding of the heterocyclic (tricyclic and tertiary) antidepressants previously available, fluoxetine offered fewer major adverse effects and relative safety after overdose.

Fluoxetine and its successors (Table 1) differ from the heterocyclic antidepressants in that they inhibit serotonin reuptake, with little or no effect on other receptor sites.[1,2] As a result of this specificity, these agents are referred to as selective serotonin reuptake inhibitors (SSRIs). Their clinical efficacy is believed to be the result of an initial increase in serotonin concentrations (inhibition of reuptake) in the synaptic cleft followed by desensitization of serotonin autoreceptors and increasing serotonin release. The latter effect is likely the most significant in treating symptoms of depression. Similar to the heterocyclic antidepressants, the full effect of SSRI therapy does not occur until two to three weeks after the initiation of treatment.[1,2]

Table 1. SSRIs Currently Available[a]
Fluoxetine HCl (Prozac®)[b]
Fluvoxamine maleate (Luvox®)
Paroxetine HCl (Paxil®)
Sertraline HCl (Zoloft®)
[a] all products are on formulary at UVA
[b] available in an oral liquid

Differences among the SSRIs consist primarily of relative receptor site specificity and pharmacokinetic characteristics. For example, paroxetine has the greatest affinity for serotonin receptors, but also shows mild binding at muscarinic receptors, resulting in its greater likelihood to cause anticholinergic adverse effects such as dry mouth.

Pharmacokinetic differences are reflected in bioavailability, protein binding, and elimination of parent compound and active metabolites. Bioavailability ranges from 44% with sertraline to 80-95 % with fluoxetine and fluvoxamine. With the exception of fluvoxamine, these agents are highly protein bound. All SSRIs undergo hepatic metabolism. Fluoxetine and sertraline have active metabolites with long elimination half-lives, resulting in prolonged effects even after the discontinuation of therapy. Genetic polymorphism resulting in the presence or absence of hepatic enzyme CYP2D6 greatly influences the rate of elimination of both fluoxetine and paroxetine.[1]

Use in Children and Adolescents

In children and adolescents, SSRIs have been used in the treatment of depression, obsessive-compulsive disorders (OCD), anxiety and panic disorders, eating disorders, attention deficit/hyperactivity disorder (ADHD), Tourette's syndrome, trichotillomania, mental retardation, Prader-Willi syndrome, Lesch-Nyhan syndrome, enuresis, and autism.[3-4] As might be expected from the relative infrequency of some of these conditions, there are few controlled clinical trials with SSRIs in children. Most published reports describe small open-label trials and case series.

Four trials involving SSRIs in children with depression have been conducted, including one controlled study, two unblinded trials, and one retrospective review.[3] Simeon and colleagues[5] conducted a placebo-controlled, double-blinded study in 32 children between the ages of 13 and 18 years. Half were given fluoxetine and the others received a placebo. Fluoxetine was initiated at a dosage of 20 mg per day and increased to 60 mg per day during the second week of treatment.

At the end of a two-month treatment period, symptoms had improved in the treated patients in

all areas of the rating scales except sleep disturbance. These differences, however, were not statistically significant. Adverse effects included headache, vomiting, insomnia, weight loss, and tremor, but were considered mild and transient. The authors concluded that approximately 2/3 of their sample population responded well to fluoxetine, but cautioned that most children still required significant assistance with psychosocial functioning.

Fluoxetine has also been studied in children with OCD, using dosages of 10 to 80 mg per day. Two trials, one open label and one placebo-controlled, have been published, as well as several case reports and a retrospective review.[3,6] In 1992, Riddle[7] and colleagues from the Yale Child Study Center conducted a placebo-controlled, double-blinded, cross-over study of fluoxetine in a group of 14 adolescents between 8 and 15 years of age. Patients were randomized to either placebo or a standard dosage of fluoxetine (20 mg per day) for a period of 8 weeks then were changed to the other treatment for a period of 12 weeks.

During fluoxetine treatment, the patients showed a significant improvement over their baseline scores on rating scales of obsessive ideation and compulsive activities. Switching to placebo administration resulted in a return to near baseline values. Adverse effects included insomnia, fatigue, nausea, and worsening of tic severity. One patient experienced suicidal ideation while receiving fluoxetine. While serum fluoxetine concentrations did not correlate with degree of disease response, adverse effects were associated with higher concentrations. The authors concluded that fluoxetine is generally a safe and effective therapeutic alternative for the treatment of children and adolescents with OCD.

Although the majority of studies and case series have utilized fluoxetine in the pediatric population, there are open trials and case reports demonstrating the efficacy of fluvoxamine (100-300 mg/day) and sertraline (75 mg/day). In addition, some reports describe the use of combination therapy with an SSRI and clomipramine or buspirone in children with OCD, and with methylphenidate in children with ADHD. In the few comparison trials that have been conducted with heterocyclic antidepressants, SSRIs appear to be as efficacious as the older "standard" therapies.[3]

Adverse Effects

Compared with older heterocyclic antidepressants, SSRIs cause less sedation, weight gain, anticholinergic and cardiovascular adverse effects. Although the SSRIs are associated with a long list of adverse effects, in most patients they are mild and transient, rarely requiring discontinuation of therapy.

In adults, the most frequent adverse effects reported include: GI upset (nausea, vomiting, and diarrhea) reported in 10-30% of patients, CNS effects (insomnia, headache, and nervousness) reported in approximately 15% of patients, sexual dysfunction, diaphoresis, rash, and tremor (each occurring in up to 10% of patients). [1,2] Similar results have been reported in pediatric studies.[3,5-7] These effects are typically dose-related, and most patients respond to a lower dose without loss of clinical benefit.

Differences in adverse effects among SSRIs may be the result of receptor specificity. Sertraline and fluoxetine are more frequently associated with diarrhea due to their greater specificity for serotonin receptors, while paroxetine has a lower incidence because of its antimuscarinic effects. The highly selective agents are also more frequently associated with insomnia and agitation, while less selective agents may be more likely to cause somnolence.[1]

Numerous other adverse reactions have been reported in isolated cases. The development of extrapyramidal symptoms has been reported in patients receiving fluoxetine and paroxetine.[1,8] These symptoms, including dystonic reactions, akathisia, and motor tics, are likely to be the result of an indirect effect on dopaminergic receptors and typically resolve upon discontinuation of therapy.

In addition, suicidal ideation has been reported in both children and adults receiving SSRIs, although this is difficult to assess apart from the underlying illness. In a retrospective review of 42 children between the ages of 10 and 17 years treated with fluoxetine, King et al[9] found six children with self-injurious ideation and behavior. Four of the children had a positive history of this problem, but worsened on therapy. All patients responded to discontinuation of fluoxetine and management with other medications.

Death associated with overdose appears to be rare. Feierabend[10] described the case of a 4 year old child who ingested approximately 35 (20 mg) fluoxetine capsules. The patient exhibited signs of agitation followed by a period of unresponsiveness. A serum fluoxetine concentration taken on admission was 3,080 ng/ml (usual values in adults receiving treatment are 40-500 ng/ml). The patient's symptoms resolved without treatment. As in this case, most patients recover without sequelae. Other signs of toxicity include: agitation, drowsiness, vomiting, diarrhea, coma, hypotension, arrhythmias, and seizures. There is no antidote for SSRI overdose; therapy consists of supportive measures.[1,2]

Drug Interactions

The SSRIs have a number of significant pharmacokinetic drug interactions as a result of protein binding or induction of hepatic metabolism of other substances (Table 2). The degree of metabolism through the CYP2D6 pathway influences the degree of severity of many of these drug interactions.[2] Patients should be instructed not to take any medications, including over-the-counter preparations, until they have checked with their doctor or pharmacist for potential drug interactions.

Table 2. SSRI Drug Interactions

Precipitant	**Object**	**Result**
MAO Inhib.	all SSRIs	neuroleptic malignant syndrome
L-tryptophan	all SSRIs	CNS toxicity
cimetidine	paroxetine	incr. conc.[a]
phenobarbital, phenytoin	paroxetine	decr. conc.[a]
cypro-heptadine	fluoxetine	decr. response
dextro-methorphan	fluoxetine	hallucinations
smoking	fluvoxamine	decr. conc.[a]
fluoxetine	buspirone	decr. response
fluoxetine, fluvoxamine	carbam-azepine	incr. conc.[a]
paroxetine	digoxin	incr. conc.[a]
fluoxetine, sertraline	lithium	inc. conc.[a]
paroxetine	procycline	inc. conc.[a]
all SSRIs	warfarin	incr. bleeding
fluvoxamine	astemizole	incr. conc.[a]
	benzodiazep. beta blockers clozapine diltiazem methadone terfenadine theophylline	

[a] change in serum concentration of object drug

In summary, SSRIs offer the advantages of fewer significant adverse effects and safety in overdose compared to older antidepressants. Their role in the treatment of psychiatric conditions in children and adolescents is just beginning to be explored. Selection of a specific agent should incorporate differences in receptor specificity, pharmacokinetic characteristics, and adverse effect profiles, in order to optimize therapy for the individual patient.

References

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Pharmacology Literature Review

Carbamazepine Drug Interactions

As the use of carbamazepine as a first-line anticonvulsant increases, the need for clinicians to be aware of its many drug interactions

becomes more important. This review is organized by the underlying mechanism of the drug interaction, making it a useful reference for students, residents, and new practitioners. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine: An update. **Clin Pharmacokinet 1996;31:198-214.**

Frequency of Pediatric Adverse Drug Reactions

The authors of this study evaluated pediatric hospital admissions in Valencia, Spain resulting from drug reactions over a 6-month period. It was estimated that 21 out of 512 (4%) admissions were related to adverse reactions, mostly considered to be of moderate severity and requiring patient observation. The most common effects were seizures, dizziness, and vomiting. No deaths occurred. The most common medications cited were antihistamines and cold preparations, fenoterol, phenylephrine, acetaminophen, and vaccines (DTP and polio). Martinez-Mir I, Garcia-Lopez MG, Palop V et al. A prospective study of adverse drug reactions as a cause of admission to a p(a)ediatric hospital. **Br J Clin Pharmacol 1996;42:319-24.**

Idiosyncratic Drug Reactions

This brief article describes a current theory suggesting that many non-dose related adverse effects are the result of activation of toxic intermediate metabolites. This process has been suggested as the underlying mechanism for acetaminophen toxicity, but may also be involved with the reactions observed with tacrine, clozapine, cotrimoxazole (trimethoprim-sulfamethoxazole), halothane, dapsone, flutamide, and carbamazepine. Pirmohamed M, Madden S, Park BK. Idiosyncratic drug reactions: Metabolic bioactivation as a pathogenic mechanism. **Clin Pharmacokinet 1996;31:215-30.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/27/96:

1. Dalteparin (Fragmin®) and fosphenytoin (Cerebyx®) were accepted pending the development of usage guidelines. Dalteparin is the second low molecular weight heparin to be marketed in the U.S. and is approved for prophylaxis against deep vein thrombosis. The usual adult dosage is 2,500 IU SC for 5-10 days postoperatively. There are currently no dosage studies in children.

Fosphenytoin is a phosphate ester prodrug of phenytoin which is freely soluble in aqueous solutions. As a result, it is associated with fewer local adverse effects and is expected to have fewer IV drug incompatibilities. However, fosphenytoin is much more expensive than generic IV phenytoin.

2. Upon the recommendation of the Infectious Diseases Subcommittee, meropenem (Merrem®) and nevirapine (Viramune®) were added. Meropenem is a wide-spectrum antibiotic similar in spectrum to imipenem. The pharmacokinetics of meropenem have been studied in children (Antimicrob Agent Chemother 1995;39:1721-5). A dosage of 20 mg/kg every 8 hours is recommended for intra-abdominal infections and 40 mg/kg every 8 hours for meningitis.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor used as part of combination therapy in patients with HIV infection. At this time, two tolerability studies have been conducted in children, with few adverse effects reported other than rash. One pediatric patient developed Stevens-Johnson syndrome after taking nevirapine. No dosing-ranging studies have been conducted in children.

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