



UtoX Update

UPCC A PUBLICATION OF THE UTAH POISON CONTROL CENTER FOR HEALTH PROFESSIONALS

Atypical Antipsychotics

Overview

Antipsychotic medications have traditionally been used in the treatment of schizophrenia and schizoaffective disorders. They differ from the older “typical” antipsychotics (phenothiazines and butyrophenones) in that they have improved efficacy, especially in the treatment of negative symptoms, and reduced incidence of extrapyramidal reactions. The differences in activity at dopamine receptors and serotonin receptors contribute to their improved efficacy and side-effect profile. With reduced side effects, the newer atypical antipsychotics are also being used in the treatment of a variety of mood disorders. With the increased use of these agents, there also has been an increase in the number of exposures reported to the Utah Poison Control Center. Table 1 shows the number of exposures reported to the UPCC in 2001 and 2002. In the annual report from the American Association of Poison Control Center, 10 deaths reported to poison centers involved olanzapine, 6 involved quetiapine and 3 involved risperidone.¹

Table 1. 2001-02 Atypical antipsychotic exposures at the UPCC.

Generic Name	2001	2002
Aripiprazole	0	1
Olanzapine	78	94
Quetiapine	93	117
Risperidone	58	43
Ziprasidone	10	3
Clozapine	4	0
Sertindole	0	0
Total	243	258

The prototype atypical agent, clozapine (Clozaril®), was introduced in 1990. It was the first agent to display both serotonin and dopamine antagonism. Clozapine is associated with little to no incidence of extrapyramidal reactions (dystonia, akathisia, pseudoparkinsonism, tardive dyskinesia) or increased prolactin concentrations. It is more effective against the negative symptoms compared

to the conventional antipsychotics, making it very beneficial for patients who are refractory to conventional antipsychotics. However, its association with agranulocytosis led to the need for rigorous patient monitoring and the development and marketing of similar agents including risperidone (Risperdal®) in 1993, olanzapine (Zyprexa®) in 1996, quetiapine (Seroquel®) 1997, ziprasidone (Geodon®) in 2001 and aripiprazole (Abilify®) in 2002.

Pharmacology^{2,3}

The exact mechanism of action of these medications is unknown, but they antagonize several neurotransmitter receptors. The atypical antipsychotics have varying affinities for dopamine and serotonin receptors as well as alpha, histamine, and muscarinic receptors. The varying affinities for the receptors and subtypes influence the pharmacologic activity and adverse effect profile of this group of medications. Antipsychotic activity and extrapyramidal effects are related to antagonism at the dopamine type 2 (D₂) receptor. Antagonism at the serotonin type 2A (5HT_{2A}) receptor and muscarinic (M1) receptors is believed to be responsible for the reduced incidence of extrapyramidal effects of the atypical antipsychotic agents. In addition, antagonism at serotonin type 2C (5HT_{2C}) receptor is responsible for weight gain, alpha-1 receptor antagonism for sedation and hypotension, and histamine (H1) receptor antagonism for sedation and weight gain. Receptor interactions of each of the atypical antipsychotic agents are listed in Table 2.

The atypical antipsychotic agents are extensively metabolized in the liver by cytochrome P450 enzymes (CYP1A2, CYP2D6, CYP3A4). Clozapine, quetiapine, risperidone, and aripiprazole have active metabolites. Clinically significant drug interactions may be anticipated between the atypical antipsychotic agents and other drugs that are metabolized by cytochrome P450 enzymes.

Although these agents have similar therapeutic uses, their pharmacokinetic properties vary by agent. Table 3 is a summary of the pharmacokinetic properties for the available atypical antipsychotic agents.

Toxicity^{2,4-7}

In general, the toxic effects of the atypical antipsychotic agents are an exaggeration of their pharmacologic activity. The most commonly reported clinical effects include CNS depression, tachycardia, and hypotension. Toxic effects are more likely to occur in children and in adults who are not taking the agents therapeutically. Toxicity has occurred with the ingestion of one tablet of risperidone, olanzapine or clozapine in a child. Seizures are uncommon following an overdose of all of the atypical antipsychotic

Table 2. Receptor interactions of the atypical antipsychotic agents.

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
Extrapyramidal Side Effects (D2)	Minimal to None	Moderate	Low	Minimal	Low	Minimal
Sedation (alpha 1, H1)	High	Low	Moderate	High	Low	Moderate
Anticholinergic (M1)	High	Minimal to None	Moderate	Low	Minimal to None	Minimal to None
Orthostatic Hypotension (alpha 1)	High	Moderate	Moderate	Moderate	Moderate	Moderate
Weight Gain (5HT)	High	Low	Moderate	Moderate	Minimal to None	Moderate

agents except clozapine. Anticholinergic side effects are most commonly seen with clozapine and olanzapine.

All atypical antipsychotic agents have the potential to affect repolarization of the myocardium and therefore prolong the QT interval. In animal studies, QT prolongation was documented with clozapine, olanzapine and risperidone. Ziprasidone was noted to have a high prevalence of QT prolongation in preclinical trials. Although reported rarely, QT prolongation has been noted following overdose with clozapine, quetiapine and risperidone. There are no reports of torsade de pointes occurring with these agents to date.

Compared to the traditional antipsychotic agents, the incidence of extrapyramidal effects is expected to be much lower following an overdose with the atypical antipsychotic agents. Although lower in frequency, the extrapyramidal side effects that do occur tend to be dose related and have been noted following overdose with clozapine, olanzapine, quetiapine and risperidone.

The moderate antagonist activity of olanzapine on muscarinic receptors is likely enhanced in an overdose. Olanzapine overdose may resemble opiate intoxication due to the occurrence of miotic pupils and CNS depression. This has been unresponsive to naloxone in case reports of overdose. Both mydriasis and miosis have been reported following an overdose of the atypical antipsychotic agents. Like the typical antipsychotic agents, miosis appears to occur more frequently than mydriasis despite the muscarinic blocking activity of some of the agents. Miosis was reported in 38% of patients who overdosed on olanzapine.

Due to the structural similarity of quetiapine to tricyclic antidepressants (TCAs), the metabolites of quetiapine have been found to cross react with some TCA immunoassays. False positive urine toxicology screens for TCA are frequently observed with quetiapine overdose.

Treatment

Initial treatment of an atypical antipsychotic overdose should include airway, circulation, and breathing support. Serum concentrations are not routinely available and are not useful in guiding treatment of overdose. An ECG should be obtained and continuous cardiac monitoring instituted with particular attention to the possibility of a prolonged QTc interval. Drugs that are known to prolong the QT interval should be avoided (i.e. quinidine, droperidol, erythromycin, sotalol) Patients should also be monitored for seizure activity and extrapyramidal reactions.

Ipecac-induced emesis is not recommended in the atypical antipsychotic overdose due to the potential for CNS depression and seizures. Activated charcoal is most effective if administered within one hour of ingestion, but delayed administration may be warranted with olanzapine and ziprasidone due to longer time to peak concentrations in therapeutic doses. Gastric lavage may be considered after a potentially life threatening ingestion if it can be performed in a timely manner. However, in the majority of situations, activated charcoal alone is likely to be sufficient for GI decontamination.

Hemodialysis and multiple-dose activated charcoal are unlikely to be effective to enhance the elimination of these drugs due to their large volumes of distribution and high protein binding.



Nationwide Toll-Free Number

The UPCC participates in a new nationwide toll-free number. This new nationwide number was made possible through a grant from the Centers for Disease Control and Prevention to the American Association of Poison Control Centers and the Poison Center Enhancement and Awareness Act of (PL 106-174.) When you dial 1-800-222-1222 from anywhere in the United States or territories you will reach the poison control center that covers that area. This has made a tremendous impact on our ability to provide outreach public education. Patients only have to remember one number! Feel free to call us on our new number. But don't worry, our old phone number will continue to work.

Summary

There is no specific antidote for the atypical antipsychotics. Treatment is symptomatic and supportive. Patients should be monitored for CNS depression, cardiac toxicity, including hypotension and ECG abnormalities, and the possibility of seizures. In general, patients should be observed for 4-6 hours after overdose. Ideally, observation time should be based on the individual pharmacokinetic parameters of each individual agent (Table 3). Consideration should always be given to the possibility of co-ingestants in the overdose setting.

Camille Davis, Pharm.D. Student

References

1. Litovitz TL, Klein-Swartz W, Rodgers GC, et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002;20:391-452.
2. Burns MJ. The Pharmacology and Toxicology of Atypical Antipsychotic Agents. *Clin Toxicol* 2001;39:1-14.
3. Stahl SM. Selecting an Atypical Antipsychotic by Combining Clinical Experience with Guidelines from Clinical Trials. *Journal of Clinical Psychiatry* 1999; 60 (suppl 10) 31-41.
4. Aciri AA, Henretig FM. Effects of Risperidone in Overdose. *American Journal of Emergency Medicine* 1998; 16: 498-501.
5. Pollak PT, Zbuk K. Quetiapine fumarate overdose: Clinical and pharmacokinetic lessons from extreme conditions. *Clinical Pharmacology and Therapeutics* 2000; 68: 92-97.
6. Glassman AH, Bigger JT. Antipsychotic Drugs: Prolonged QTC Interval, Torsades de Pointes, and Sudden Death. *American Journal of Psychiatry* 2001; 158: 1774-1782.
7. Al-Mateen CS, Wolf CE. Falsely elevated imipramine levels in a patient taking quetiapine. *J Am Acad Child Adolesc Psychiatry* 2002; 41:5-6.

M-44 Sodium Cyanide Device

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The device is tubular and is placed in the ground with 1.5 inches sticking out of the ground baited with meat. This device is used in specific situations to control coyotes, redfox, gray fox and wild dogs. The purpose of the device is to protect livestock, poultry, and endangered species and to prevent the spread of disease. Although this device is primarily used on private lands, it may also be used on federal land in any county in the state. Areas where it is used are marked with signs. While human exposure to this device would be extremely unlikely, it is important to know that this device contains 91% sodium cyanide. Please report any exposure to this device to the Utah Poison Control Center at (801) 581-7504 or (800) 222-1222. We thank you in advance for your assistance.

Table 3. Pharmacokinetic properties of atypical antipsychotic agents.

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
Absorption	Well Absorbed	Well Absorbed	Well Absorbed	Increased by Food	Increased by Food	Well Absorbed
Volume of Distribution	2-5 L/kg	1-1.5 L/kg	10-20 L/kg	10 L/kg	2 L/kg	4.9 L/kg
Time of Peak	1-4 Hours	1-1.5 L/kg	5-6 Hours	1-2 Hours	5 Hours	3-5 Hours
Protein Binding	92-95%	90%	93%	83%	>99%	99%
Terminal Half-Life	10-105 Hours	3-24 Hours	20-7- Hours	4-10 Hours	4-10 Hours	75-146 Hours



Meet the UPCC Staff

Heather Hunter

Heather moved to Utah from Oregon in 1985. She has been the outreach education provider for Utah Poison Control Center for two years. She has a master's degree in health education from the University of Utah, and is a Certified Health Education Specialist, CHES. Heather also teaches Healthy Lifestyles for Weber State University. Previously, she designed and managed the Community Health Information Center at McKay-Dee Hospital for eight years and was the tobacco specialist for Weber-Morgan Health Department for two years. Favorite Poison Education Topic: Look-a-Like products. Hobbies: running, hiking, movies and being at the beck and call of her five children.

Poison Prevention Week

Utah Poison Control Center Reminds Parents of Dangers to Children

"Children Act Fast, So Do Poisons," the general theme for National Poison Prevention Week March 16-22, is a familiar one for staff at the Utah Poison Control center (UPCC). Last year, the center received almost 38,000 reports of poison exposures, 62 percent involving children less than six years of age.

In 2002, the staff of the UPCC was able to safely and effectively manage 90 percent of the emergency calls for children at their homes. During this important week, we remind parents to keep household chemicals and medicines stored away from children at all times.

Please call the UPCC at 581-7504 for educational brochures, telephone stickers and magnets to distribute to your patients.

Beside Toxicology Consultation

The UPCC can provide beside consultations to a limited number of hospitals for patients with severe poisoning, envenomation or unusual toxicologic problems. This service can currently be provided at University Hospital, Primary Children's Medical Center, Salt Lake Regional Medical Center, LDS Hospital and the VA Medical Center. Please contact the center at 1-800-222-1222 to provide patient information and to request a consult.

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*CSPI denotes Certified Specialist in Poison Information.

Journal Donation Request!

The UPCC would like your help in completing our resource library.

We are missing assorted issues between the years 1983 and 2000 of **THE AMERICAN JOURNAL OF EMERGENCY MEDICINE**. We are also in need of various issues between the years 1982 and 2002 of the **ANNALS OF EMERGENCY MEDICINE**. Please contact Renate at 801-581-7504 to make arrangements for pickup or delivery.

New Employees

The Utah Poison Control Center is pleased to welcome Heather Bennett, MPA as Assistant Director. Heather has recently completed a Masters in Public Administration with an emphasis in Health Care from the University of Utah.

Employment Opportunities

The UPCC has one position available. The UPCC is looking for a Specialist in Poison Information to work primarily the night shift (seven on, seven off). You can find out more about this position on our website at <http://uuhs.c.utah.edu/poison/employment>.

The Utah Poison Control Center expresses its sincere thanks to
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