The Journal of Emergency Medicine, Vol. 43, No. 5, pp. 906–913, 2012

0736-4679/$ - see front matter

ELSEVIER

doi:10.1016/j.jemermed.2012.03.002

Clinical Reviews

TOXICOLOGY AND OVERDOSE OF ATYPICAL ANTIPSYCHOTICS

Alicia B. Minns, MD and Richard F. Clark, MD

Department of Emergency Medicine, Division of Medical Toxicology, University of California, San Diego, San Diego, California
Reprint Address: Alicia B. Minns, MD, Department of Emergency Medicine, Division of Medical Toxicology, University of California, San Diego, 200 West Arbor Drive, MC 8925, San Diego, CA 92103

☐ **Abstract—Background: Second-generation antipsychotic medications, or "atypical antipsychotics," are now first-line therapy in the treatment of schizophrenia and other psychotic disorders, and are additionally being used in a wide array of other psychiatric and non-psychiatric conditions in both adults and children. Overdose is frequently reported to poison control centers. Objectives: We review the toxicology and general management of poisonings involving the atypical antipsychotic medications. Discussion: The most serious toxicity involves the cardiovascular system and the central nervous system. All typical and atypical antipsychotics cause sedation, which is pronounced in overdose. The most common cardiovascular effects that occur after atypical antipsychotic overdose are tachycardia, mild hypotension, and prolongation of the QTc interval. Other clinical syndromes in overdose include neuroleptic malignant syndrome (NMS) and antimuscarinic delirium. Seizures may be observed. No antidotes exist for these poisonings, but they most often do well with supportive care. Conclusion: Antipsychotic overdose produces a gamut of manifestations that affect multiple organ systems. Treatment is primarily supportive. Specific therapies for NMS, hypotension, and seizures are discussed.** © **2012 Elsevier Inc.**

☐ **Keywords—atypical antipsychotic; overdose; ingestion; poisoning**

INTRODUCTION

In 1952, a French surgeon who was exploring strategies to reduce surgical shock noticed that an antihistamine he was using, chlorpromazine, had a powerful calming effect on mentation (1). A psychiatrist, Pierre Denker, heard about these results and decided to try chlorpromazine in some of his most difficult-to-manage patients. The results were remarkable, and chlorpromazine was approved by the U.S. Food and Drug Administration (FDA) in 1954 (1). By the mid 1960s, approximately 50 million people around the world had been treated with this medication, and several other phenothiazines were introduced, including fluphenazine and thioridazine (1). Before that time, patients suffering from most psychiatric disorders requiring medical therapy were treated with sedatives such as barbiturates. Those with severe psychiatric disease were housed in institutions for indefinite periods of time, and treatment was often unsuccessful. In the last half-century, multiple antipsychotic drugs have been marketed and have improved morbidity in many individuals. Second-generation antipsychotics, or "atypical antipsychotics," were introduced in 1989 and were anticipated to be equally effective for treatment of psychosis. They also had the advertised advantage of fewer extrapyramidal side effects such as dystonias, akathisia, parkinsonism, and tardive dyskinesia, at therapeutic dosing. These medications are now first-line therapy in the treatment of schizophrenia and are additionally being used in a wide array of conditions in both adults and children, including bipolar disorder, tic disorders, eating disorders, obsessive-compulsive disorder, and developmental disorders such as autism (2–4). We review the toxicology of the atypical antipsychotic medications.

RECEIVED: 14 September 2011; FINAL SUBMISSION RECEIVED: 27 February 2012;
ACCEPTED: 9 March 2012

DISCUSSION

Epidemiology

Overdose of antipsychotic medications is common. In 2009, there were over 43,000 calls to U.S. Poison Centers regarding atypical antipsychotics (5). In 2010, there were over 4000 calls to the California Poison Control System (CPCS) regarding both pediatric and adult antipsychotic exposures; two-thirds of these calls were regarding intentional ingestions. Ninety percent of 2010 CPCS exposures were to atypical antipsychotics; the remainder was to phenothiazine derivatives. Over 80% of these exposures were managed at a health care facility. There were 8 deaths reported (unpublished data).

Pharmacology

Antipsychotics are most commonly classified as "typical" or "atypical." They can also be classified by their chemical structure. The "typical" antipsychotics, also called first-generation, include the commonly used butyrophenones (droperidol, haloperidol) and phenothiazines (chlorpromazine, promethazine, prochlorperazine, fluphenazine, thioridazine). These first-generation agents were also categorized based on their affinity for the dopamine D_2 receptor as low potency, such as chlorpromazine, or high potency, such as haloperidol. The "atypical," or second-generation agents, are defined clinically as having minimal or no extrapyramidal symptoms at clinically appropriate doses (6). There are now more than a dozen atypical antipsychotics in clinical use with a variety of differing chemical structures.

All dopamine receptors are coupled to G-proteins. Agonists binding to dopamine D_1 receptors stimulate adenylate cyclase and raise cAMP concentrations. D_2 receptor agonists inhibit adenylate cyclase and lower intracellular cAMP levels. Both first- and second-generation antipsychotics block dopamine D_2 receptors. Many of the first-generation phenothiazine agents block both D_1 and D_2 receptors. The atypical antipsychotics bind less avidly to the D_2 receptor, leading to fewer extrapyramidal effects (7). Atypical antipsychotics also antagonize serotonin receptors, mainly the $5HT_{2A}$ receptor, mitigating the "negative" symptoms of schizophrenia (3). The so-called negative symptoms of schizophrenia include avolition, anhedonia, social withdrawal, and others.

As a class, the atypical antipsychotics have a decreased propensity to cause adverse motor side effects and prolactin elevations as compared to the first-generation antipychotics. However, both the typical and atypical antipychotics have side effects that exist along a spectrum and are related to the unique receptor-binding profiles of each agent. For example, some atypical antipsychotics have α_1-adrenergic blockade (risperidone, olanzapine, quetiapine, and aripiprazole), which can cause orthostatic hypotension. Some antagonize central and peripheral muscarinic receptors (clozapine, olanzapine, quetiapine), which may result in sedation, sinus tachycardia, and urinary retention (4,8).

Clinical Effects

Antipsychotic overdose produces a gamut of manifestations that affect multiple organ systems (Table 1). The most serious toxicity involves the cardiovascular system and the central nervous system (CNS). All typical and atypical antipsychotics cause sedation due to CNS histamine H_1 receptor blockade in therapeutic dosing and is pronounced in overdose. Sedation is most prominent with clozapine and quetiapine (4). The most common cardiovascular effects that occur after atypical antipsychotic overdose are tachycardia, mild hypotension, and prolongation of the QT interval (9). Below we discuss the more serious clinical syndromes that may be observed with antipsychotic overdose and therapeutic misadventure, as well as some unique features of the more commonly used atypical agents.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal idiosyncratic reaction to antipsychotic drug treatment with an incidence of 0.01–0.02%. Although the precise pathophysiological mechanisms of NMS are uncertain, antipsychotic-induced dopamine receptor-blockade is thought to play the pivotal triggering role in the condition (10). Patients with refractory delirium and certain medical conditions such as dehydration are at an increased risk of developing NMS (11). Haloperidol, either alone or in combination with other medications, has been implicated in the majority of reported cases (12). Whether this is related to an increased propensity for haloperidol to cause NMS or simply that this agent is most frequently used in managing refractory delirium in critically ill patients is unknown. The incidence of NMS occurring from atypical agents is unknown, although it has been sporadically reported with most of the commonly prescribed medications (11). Many of the atypical antipsychotic-linked cases of NMS have occurred with clozapine, which is intriguing given that extrapyramidal symptoms occur so rarely with this drug. Additionally, clozapine binds only loosely to the D_2 receptor. Together, these characteristics suggest that low extrapyramidal inducing potential does not predict the occurrence of NMS, and D_2 receptor affinity is unlikely to be the sole mechanism responsible for NMS (13).

NMS is characterized by hyperthermia, autonomic instability, neuromuscular rigidity, and altered mental status. It is often difficult to distinguish from more