Catastrophic Consequences Secondary to Psychotropic Drugs, Part 2

Norman L. Keltner, RN, EdD, CRNP

In Part 1 of this series, neuroleptic malignant syndrome was discussed as it relates to the potential serious consequences of the use of dopamine antagonists, including antipsychotic drugs. Serotonin syndrome, the development of a hyperserotonergic state, also was discussed because of recent reports of potentially fatal consequences from this syndrome following the administration of selective serotonin reuptake inhibitors, now often used in the treatment of depression.

Part 2 of this two-part series focuses on the development of agranulocytosis associated with the use of clozapine and the development of lithium toxicity during treatment for mania.

Agranulocytosis and Clozapine

Agranulocytosis, defined as a white blood cell (WBC) count of less than 1000 cells/cm or a sudden and severe drop in the number of WBCs, is a potentially fatal adverse effect of neuroleptics and is linked most notably to clozapine administration. Patients suffering with agranulocytosis often are as sick as patients undergoing chemotherapy (Gerson, 1994).

Fatalities typically are related to overwhelming infection. Although clozapine (Clozaril) was introduced in the United States in 1960, it was not approved for marketing to the general public for 30 years (Keltner & Folks, 1991). This delay was related to the seriousness of agranulocytosis.

The most deadly cases of agranulocytosis occurred in Finland in June and July of 1975, where the mortality rate reached about 50% (9 of 18 cases) (Idanpaan-Heikkila, Alhava, Olinuora, & Palva, 1975). Early research indicated an incidence rate of 1% to 2%, with approximately one third of those individuals persisting. From its U.S. introduction in February 1990 to June 1996, 728 cases of leukopenia (defined as a WBC count between 2000 and 3000 cells/cm or a granulocyte count of 1000 to 1500 cells/cm) and 464 cases of agranulocytosis have been attributed to clozapine (Feldman, 1996).

Current investigations suggest a slightly lower morbidity rate for agranulocytosis (0.8% after 1 year and 0.9% after 18 months) as well as a significantly lower mortality rate (Alvir & Lieberman, 1994). These positive declines in morbidity and mortality are largely the consequence of deliberate protocols first instituted by Sandoz, the manufacturer of Clozaril, and the subsequent development of local monitoring systems based on the Sandoz system. Since its approval in 1990, 13 clozapine-related deaths have been reported (Sandoz, Inc., personal communication). When deaths occur, they happen early in treatment (Alvir & Lieberman).

Pathogenesis

No one physiological mechanism convincingly explains how agranulocytosis develops, although both immunological and toxicity models have been proposed (Gerson, 1994).

Feldman (1996) has distilled three possible mechanisms of pathology from his study of clozapine-induced agranulocytosis:
- The clozapine metabolite, desmethylclozapine, may have a direct cytotoxic effect on marrow cells;
- Release of granulocyte-stimulating factor may be suppressed by clozapine, resulting in hematologic imbalance; and
- Clozapine may induce antibody formations that are toxic to peripheral blood neutrophils and their committed precursors.
Epidemiology

Epidemiologic evidence gathered by the manufacturer of Clozaril indicates that women are more prone to develop agranulocytosis than men (0.9% [women] vs. 0.4% [men]), blacks have a greater risk of death from agranulocytosis than whites (9% [blacks] vs. 4% [whites]), and Finnish people and Ashkenazi Jews are more susceptible to blood dyscrasia than other groups (Feldman, 1996).

Management

Treatment with clozapine should not begin if the WBC count is less than 3500 cell/cm. Once treatment begins, weekly monitoring of WBCs is required to administer this drug safely. For patients taking clozapine, a drop in the WBC count to below 3500 cells/cm requires close surveillance. Interruption of therapy is required if WBCs drop below 3000 cells/cm and the granulocyte count dips below 1500 cells/cm (leukopenia). At these low levels, infection is possible and should be assessed accordingly. If no signs of infection are noted, treatment can resume with careful monitoring.

If WBCs drop below 2000 cells/cm and the granulocyte count is less than 1000 cells/cm, therapy must be terminated and the patient should not be rechallenged with clozapine (Olin, 1995). If agranulocytosis is diagnosed, prompt and daily assessment of blood counts is imperative (Gerson, 1994). Antibiotics should be prescribed if infection is apparent. Reversal of the agranulocytic process has been achieved with granulocyte colony-stimulating factor (G-CSF) (Gerson; Gullion & Yeh, 1994). This treatment significantly shortens the duration of agranulocytosis.

Lithium Toxicity

Lithium, a naturally occurring element, was discovered in 1817 by the Swedish chemist August Arfwedson (Schou, 1980), and was used over the ensuing years for a variety of disorders. In 1947, lithium was discovered to be an effective therapy for mania by the Australian physician Cade. In that same year, it was banned from use in the United States, but finally was approved for treatment of bipolar disorder in 1970 (Ayd, 1991).

The precise mechanism for lithium’s therapeutic action is not known but may be related to “incomplete ion substitution for other extracellular and intracellular cations and to interference with cAMP-mediated processes that are regulated by polypeptide hormones” (Groleau, 1994). Because lithium is excreted unchanged by the kidney, drugs or other factors that interfere with renal elimination contribute to lithium buildup and the potential for lithium toxicity.

Drugs most likely to promote this are the nonsteroidal antiinflammatory agents (NSAIDs) and many diuretics (Keltner & Folks, 1997). Other factors leading to increased serum lithium levels include renal disease or insufficiency, sodium and fluid depletion resulting in increased sodium and lithium reabsorption, and lithium’s inhibition of its own excretion once a certain serum threshold has been reached. This last factor partially explains the rapid progression of toxicity once it begins (Groleau, 1994).

The following discussion of lithium toxicity outlines complicating variables:

- Early lithium toxicity presents with some of the same symptoms found in routine lithium maintenance therapy. For example, a fine tremor is both a routine side effect and an early symptom of mild lithium toxicity. Nausea, vomiting, and diarrhea not only are common side effects, but occur across the spectrum of mild to severe lithium toxicity;
- Most clinicians divide lithium toxicity into three categories: mild, moderate, and severe. Although severe toxicity may be life threatening, mild lithium toxicity is not, and further, the majority of long-term lithium patients experience some level of toxicity during their treatment (Amadsen, 1988); and
- Although serum lithium levels are important objective data to aid the clinician, limitations exist.

First, some patients can be toxic at “therapeutic” levels. Second, as the movement of lithium from extracellular to intracellular space is a slow process, serum levels are more accurate for patients toxic from chronic administration than from acute ingestion.

For example, acute lithium ingestion, in the form of a suicide attempt, may result in high serum levels without expected toxic symptoms. The potential for more severe toxicity later on, should this patient not be treated, is a real possibility (Groleau, 1994).
**T A B L E**

**Treatment for Lithium Toxicity**  
1. Discontinue lithium.  
2. Consider inducing emesis.  
3. Consider gastric lavage.  
5. Administer intravenous fluids (NaCl if hypotonic) to increase lithium excretion.  
6. Monitor serum lithium levels frequently.  
7. If patient is toxic and serum level is over 2.5 mEq/L, consider hemodialysis.  
8. If patient has serum level over 4.0 mEq/L, consider hemodialysis.

Adapted from Morton, Sonne, & Lydiard (1993).

**Management**  
Although no antidote for lithium poisoning exists, two interventions include enhancing lithium elimination and providing supportive care as needed (Groleau, 1994). Forced diuresis (e.g., administration of mannitol) or giving acetazolamide (Diamox), one of the few diuretics that do not impede lithium excretion, are useful means for enhancing lithium excretion. If supportive nursing and medical care is available, discontinuing lithium and other contributing drugs (most diuretics, NSAIDs) may be all that is needed to reverse toxicity (Keltner & Folks, 1997).

In treatment of acute poisoning, gastric lavage has been successful. One to two liters of parenteral normal saline given over 6 hours may provide sufficient volume to prevent hypovolemia and restore blood pressure. The sodium in this solution can enhance renal clearance of lithium when serum levels are below 2.5 (Keltner & Folks, 1997). As noted, as serum toxicity levels rise, lithium excretion declines further.

In cases of severe toxicity, hemodialysis has proven invaluable and is the cornerstone of treatment for acute lithium poisoning (Okusa & Crystal, 1994). Hemodialysis should be considered if toxicity is severe and the serum level is over 2.5 mEq/L. Hemodialysis should be considered in any patient with a serum level above 4.0 mEq/L (Morton, Sonne, & Lydiard, 1993). The Table outlines the management strategies for lithium toxicity.

**References**  


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**Column Editor**  
Bruce Mericle, RN, MS  
Surveyor, Health Care  
Financing Administration  
U.S. Department of Health and Human Services  
Baltimore, MD