NEUROLEPTIC MALIGNANT SYNDROME: FOCUS ON ATYPICAL ANTIPSYCHOTICS

by Ghazal M. Palmer, PharmD, BCPS

Introduction

Neuroleptic malignant syndrome (NMS) is a serious, but uncommon side effect associated with antipsychotic use. The criteria for the syndrome include hyperthermia and muscle rigidity, plus two or more associated findings: change in level of consciousness, creatine kinase (CK) increase, diabetes, hypokalemia, leukocytosis, mutism, tachycardia, or tremor.1 Although NMS incidence is low, estimated to be 0.01-0.02%, among all patients receiving antipsychotics, the consequences are grave, with a mortality rate between 11% to 38%.2

The purpose of this paper is to review NMS cases associated with atypical antipsychotic use and to identify risk factors for the development of NMS for patients taking an atypical antipsychotic agent.

Pharmacology of Atypical Antipsychotics

Clozapine was the first atypical antipsychotic agent marketed in 1989. As a class, these agents are relatively new and exhibit less dopamine (D2) receptor antagonism in central nigrostriatal pathways compared to the “typical” antipsychotic agents. They are, therefore, less likely to produce extrapyramidal or parkinsonion side effects, including tardive dyskinesia.3

The exact pathophysiology of NMS is not known but is thought to be related to dopaminergic blockade. The exact trigger is not known but the syndrome involves a complex autonomic dysregulation involving multiple neuroendocrine and chemical pathways leading to a hypermetabolic state and altered thermoregulation.1 NMS has been reported with all of the atypical antipsychotics. The following cases illustrate these risk factors:

Starting a new regimen: A 16-year-old boy started on clozapine 12.5 mg daily developed symptoms of rigidity, hyperthermia, autonomic instability, and an elevated CK within eight hours of his first dose. Two children, ages 12 and 14 years old, developed NMS after only 2 days of treatment with aripiprazole 5-10 mg per day. The 12-year-old developed fever, rigidity, autonomic...

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>FDA Approval</th>
<th>Mechanism of Action</th>
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<td>Aripiprazole</td>
<td>Aricept®</td>
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<td>D₁ and 5-HT₁₆ receptor antagonist</td>
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<td>Clozapine</td>
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<td>D₂, 5-HT₁₆, H₁, cholinergic receptor antagonist</td>
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<td>Latuda®</td>
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<td>Olanzapine</td>
<td>Zypraxa®</td>
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<td>Ziprasidone</td>
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NMS with Antipsychotics

The frequency of NMS with atypical antipsychotic agents is not well known with evidence limited to case reports and case series. Risk factors for NMS include starting new drug regimens, dose increases, prolonged use, and previous adverse reactions to antipsychotics. The following cases illustrate these risk factors:

Starting a new regimen: A 16-year-old boy started on clozapine 12.5 mg daily developed symptoms of rigidity, hyperthermia, autonomic instability, and an elevated CK within eight hours of his first dose. Two children, ages 12 and 14 years old, developed NMS after only 2 days of treatment with aripiprazole 5-10 mg per day. The 12-year-old developed fever, rigidity, autonomic...

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NMS
dysfunction, and leukocytosis, while the
14-year-old experienced tremors, rigidity, gait
abnormalities and urinary incontinence.5

Dose increase: A 17-year-old man devel-
oped NMS symptoms after a 1 mg increase in
dose in his 4-month regimen history with the
drug. He developed fever, rigidity, leukocy-
tosis, and CK elevation only a few hours after
taking the increased dose.5

Prolonged use: A 15-year-old boy treated
with ziprasidone 80mg daily for eight weeks
developed NMS. He experienced fever,
tachycardia, rigidity, diaphoresis, inconti-
nence, disorientation, and leukocytosis.5

Previous reactions to antipsychotics: A
28-year-old man, previously treated with
haloperidol and fluphenazine for schizophre-
ia, was started on quetiapine 25 mg twice
daily after he developed extrapyramidal side
effects and diaphoresis on his original regi-
men. The quetiapine dose was increased to
400 mg twice daily over one week and shortly
thereafter he developed anorexia, inconti-
nence, muscle rigidity, fever, tachycardia,
leukocytosis, and CK elevation. A 16-year-
old boy who had a dystonic reaction when
treated with loxapine, developed NMS after
treatment initiation with clozapine months
later.5

Treatment of NMS
The primary treat-
ment is symptom-
atric and supportive.
Non-pharmacological
treatment includes
aggressive cooling
measures for hy-
perthermia, such as
evaporative cooling with water and fans, cool-
ing blankets, and ice water baths if necessary.
Fluid resuscitation is important to correct
hypotension, replace insensible losses, and to
ensure adequate renal blood flow, especially in
the case of elevated serum CK. Intravenous
benzodiazepines are the treatment of choice
for agitation, insomnia, muscle rigidity and
catatonia.6

Hyperthermia caused by NMS is unre-
sponsive to antipyretics because the underly-
ing cause of the fever is not from pyrogens.

Dantrolene can be considered in patients
with extreme temperature elevation and muscle
rigidity. By inhibiting calcium release from
the sarcoplasmic reticulum of skeletal muscle
cells, dantrolene inhibits muscle hyperactivity,
thereby controlling hyperthermia.7 Dant-
rolene is given for NMS in a dose of 1-2 mg/
kg IV up to every 6 hours. There are mixed
reports on the effectiveness of dantrolene. In
some reports, dantrolene was found to de-
crease NMS symptom duration and decrease
mortality.6 However, in an analysis of 271
case reports, the effectiveness of dantrolene
was reduced when it was given with other
medications but the mortality rate was higher
in the reports where dantrolene was given
alone.7 Dantrolene is not FDA approved
for the treatment of NMS and carries a black
box warning for possible hepatotoxicity and
a warning not to use it for conditions other
than recommended.

Bromocriptine is a dopamine agonist and
may be useful to treat Parkinson-like effects
associated with NMS. It is only available
orally, which limits usefulness in critically ill
patients. The initial adult dose of bromocrip-
tine is 2.5 mg, administered 3-4 times/day

(continuation from pg. 1)
ECG CHANGES IN TOXICOLOGY

by Jessica Holly, MD
Emergency Medicine Resident

In the obtunded patient with a suspected ingestion, recognizing drug-induced ECG changes can give clues about the possible ingestion.

Tricyclic Antidepressants- TCAs block fast Na+ channels, thus slowing the action potential and depolarization of the myocardium. Conduction delays include AV block, right axis deviation, right bundle branch block, and prolonged PR, QRS and QT intervals. Wide complex tachycardias are common in TCA toxicity, and include sinus tachycardia with aberrant conduction, ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Digitalis- Digitalis acts by inhibiting the Na/K-ATPase pump. At therapeutic levels, ECG changes can be observed, known as the “digitalis effect”. This effect includes scooping.

Lithium- Lithium causes subtle ECG changes; dangerous arrhythmias are rare. Common findings include T wave flattening or inversion, prolonged QTc interval, and bradycardia. SA node arrest and other malignant arrhythmias are rarely observed.

Prolonged QT interval- A prolonged QT interval increases the period that the heart is vulnerable to ventricular arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Numerous medications can cause prolongation of the QT interval, including Class IA and III antidysrhythmics, psychotropics, antihypertensives, antimicrobials, antifungals, antihistamines, among others. A patient with a history of prolonged QT should be prescribed these medications with extreme caution.

IRRITANT GASES

by Mark Goodman, MD
Emergency Medicine Resident

Mixing of household chemicals can lead to exposure of irritant gases. Environmental and industrial exposures can also release irritant gases leading to exposure. The water solubility of the gas effects the clinical presentation. Highly soluble gases present primarily with upper respiratory tract and mucosal irritation. Ammonia, sulfur dioxide, hydrogen fluoride and formaldehyde are highly soluble gases. Less soluble gases such as phosgene, nitrogen dioxide, nitric oxide and ozone can have delayed presentation of toxicity including pulmonary edema and lower respiratory tract symptoms. Chlorine and chloramine gas are considered intermediate solubility and can cause both upper and lower respiratory tract symptoms. Chloramine gas is most often encountered by the mixing of ammonia and hypochlorite cleaning solutions. Bronchodilators, humidified oxygen and respiratory support are the mainstays of treatment. Nebulized bicarbonate, nebulized lidocaine and steroids may have a role in treatment but are not well studied.

DID YOU KNOW?

Research has shown that energy drink use predicts subsequent nonmedical use of prescription stimulants and analgescics.

- CESAR FAX Nov. 1, 2010

References

Pregnancy and Lactation
There is a potential risk for NMS among pregnant patients treated with antipsychotics. All of the atypical antipsychotics are pregnancy category C, with the exception of clozapine (category B). Bromocriptine and dantrolene are pregnancy categories B and C, respectively. Both drugs may be used in NMS as the risk to the fetus does not outweigh the risk to the mother.

Bromocriptine suppresses lactation and is not recommended in nursing mothers due to cessation of milk supply. Dantrolene is excreted in breast milk so nursing is not recommended during therapy and for two days after therapy ends.

Conclusions
Evidence shows that recent medication initiation, dose increase, prolonged use, or previous adverse reactions to any antipsychotic may place a patient at an increased risk for developing NMS. Due to the grave consequences of NMS, it is vital to appropriately identify the syndrome and aggressively treat the symptoms in order to prevent NMS.

Pediatric NMS
The potential for NMS in children is harder to determine. Atypical antipsychotics have not been conclusively studied in pediatric patients. Of the atypical antipsychotics, only clozapine (category B) has been used in children. Bromocriptine and dantrolene are pregnancy categories B and C, respectively. Both drugs may be used in NMS as the risk to the fetus does not outweigh the risk to the mother.

References
TOXICITY TODAY

THANK YOU

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.

ANGELA GREEN is a second year doctor of pharmacy student at the University of Utah who joined the UPCC as a Poison Information Provider in April. Angela graduated from BYU in 2010 with a BS in Neuroscience. The day she dissected sheep brains in a neuroscience class reminded her why she chose NOT to be a brain surgeon and reinforced her excellent decision to attend pharmacy school. Angela has a deep fascination for math and science and currently tutors students in chemistry and calculus. When Angela is not studying or working, she is dancing. Angela danced on the BYU contemporary dance team for three years and performed throughout the United States, Jamaica, Dominican Republic, and Puerto Rico. She currently teaches dance and performs with a local dance company in Salt Lake City. Angela enjoys assisting callers with poison emergencies and applying what she learns in pharmacy school to real-life cases at the Utah Poison Control Center.

KAMI ROAKE joined the Utah Poison Control Center as a Poison Information Provider in April of 2011. She is currently a doctor of pharmacy student at the University of Utah and will graduate in May 2013. She graduated from the University of Utah with a BS in Exercise and Sport Science in 2008. Following graduation, Kami hopes to find a pharmacy residency where she has the opportunity to continue learning in an area of interest. When she is not focusing on school some of her favorite past times include scrapbooking, snowboarding, volunteering, and spending time with family and friends. Her favorite cases are ones that are unique, so that she can learn about new toxins and their potential effects.

TOXINS IN THE NEWS

- **Linezolid**, an antibacterial agent, is also a reversible monoamine oxidase inhibitor (MAOI). Reactions consistent with serotonin syndrome have been reported when it’s administered to patients taking serotonergic drugs. It should generally not be given to patients taking serotonergic drugs, however, there are some conditions that may be life-threatening or require urgent treatment with linezolid.
- Newborns are at risk of extrapyramidal signs or withdrawal (e.g., agitation, abnormal muscle tone, tremor, difficulty breathing) from antipsychotic medications taken by the mother during the third trimester of pregnancy. Patients should not stop taking these medications if they become pregnant without talking to their healthcare professional.
- **Street cocaine** has been found to be adulterated with levamisole, which can cause vasculopathy and pancytopenia. It has been found nationwide, including Colorado, New Mexico, and Utah.

MEET THE UPCC STAFF

**Angela Green**

**Kami Roake**

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