Annals of Clinical Psychiatry, 18[3]:201–204, 2006

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230600801259

informa
healthcare

Neuroleptic Malignant Syndrome and Serotonin Syndrome in the Critical Care Setting: Case Analysis

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Background. *Serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) are medical emergencies associated with psychotropic administration. Differentiation and treatment can be complex, especially when features of both syndromes are present and the patient has taken both serotonergic and neuroleptic agents.*
Method. *Case analysis of a poly-drug overdose (venlafaxine, topiramate, divalproex sodium, risperidone, and carbamazepine) presenting with mixed SS/NMS features and whose clinical management suggests a practical algorithm for treatment of undifferentiated SS/NMS in critical care settings.*
Results. *The suggested algorithm includes: 1) Supportive care and withdrawal of all potentially offending agents; 2) Laboratory evaluation with prompt initiation of treatment for both disorders – cyproheptadine for SS and dantrolene for NMS; 3) Do not use bromocriptine (contraindicated in SS) or chlorpromazine (contraindicated in NMS) initially; 4) Add bromocriptine when clinical presentation becomes consistent with NMS (SS can be prolonged if serotonergic agent has long half-life).*
Conclusions. *Prompt and appropriate identification and intervention are essential for successful management of SS and NMS. The suggested treatment algorithm allows for specific treatment of both disorders and avoids potentially exacerbating either one. The algorithm derived from this case could serve as both a practical guideline and impetus for further investigation in light of increasing psychotropic co-administration.*

Keywords Neuroleptic malignant syndrome (NMS), Serotonin syndrome (SS), Cyproheptadine, Dantrolene, Bromocriptine, Mortality, CPK, Antidepressants, Antipsychotics, Venlafaxine, Topiramate, Risperidone, Divalproex sodium, Carbamazepine

INTRODUCTION

Psychotropic medications are associated with a variety of medical emergencies including overdose, serotonin syndrome (SS), and neuroleptic malignant syndrome (NMS). This case report involves all three.

SS has been defined as a potentially life-threatening medical complication resulting from treatment with one or more

Presented at the 27th Nordic Psychiatric Conference, Reykjavik, Iceland, August 13–16, 2003.

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serotonergic agents. Psychotropics implicated in causing SS include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), along with various other serotonergic agents (1–3). SS has been characterized in the literature by a classic triad consisting of mental status changes, autonomic dysfunction, and neuromuscular abnormalities (4). Sternbach has also suggested criteria that can be used in the diagnosis of SS (5). These criteria include: addition or increase in a serotonergic agent; absence of other possible etiologies (infectious, metabolic, substance induced, substance withdrawal) to explain clinical findings; and no recent addition or increase in the dose of a neuroleptic agent. In addition, at least three of the following clinical findings must be present: altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever (5). Reported mortality rates for SS range from 2–12% (1,6). The standard management of SS is withdrawal of the offending agent and supportive care with IV hydration and ventilator support, as clinically indicated. Symptoms typically resolve within 24 hours. Benzodiazepines have been utilized to treat myoclonus associated with SS (7). Further, non-selective serotonin antagonists, including cyproheptadine and chlorpromazine, have been utilized to provide symptomatic relief (8,9). It is important to recognize that in undifferentiated SS/NMS, chlorpromazine is contraindicated due to potential exacerbation of NMS (10).

NMS has been defined as a potentially life-threatening medical complication during treatment with neuroleptic agents. NMS is most often associated with high-potency neuroleptics; however, it has been reported with low-potency neuroleptics, atypical antipsychotics and other dopamine blocking agents (11,12). NMS has been characterized by the triad consisting of autonomic dysfunction (hyperthermia, blood pressure instability, tachycardia, and diaphoresis), encephalopathy, and skeletal muscle rigidity (11). Caroff outlined diagnostic criteria for NMS (13). These criteria include: treatment with neuroleptics within seven days of onset of symptoms; hyperthermia; muscle rigidity; and exclusion of other drug-induced, systemic, or neuropsychiatric illnesses. In addition, at least five of the following clinical findings must be present: altered mental status, tachycardia, tachypnea, diaphoresis, tremor, hypertension or hypotension, incontinence, elevated creatine phosphokinase (CPK), leukocytosis, and metabolic acidosis (13). Reported mortality rates for NMS range from 3–25% (14,15). Standard treatment for NMS involves immediate discontinuation of the antipsychotic and supportive care with IV hydration, cooling blankets and ventilator support. Recommended pharmacologic interventions include dantrolene (especially beneficial in the treatment of muscular rigidity (11)), bromocriptine, and amantadine which lower the mortality rate from 21% (supportive care) to 8.6%, 7.8%, and 5.9% respectively (15). The most frequent therapeutic combination utilized is dantrolene with bromocriptine. Since bromocriptine is reported to increase CNS serotonin, it is contraindicated in undifferentiated SS/NMS (10,16).

Critical care diagnostic and treatment issues exist when there is a confounding presentation wherein both SS and NMS features are present. This case report illustrates these issues in a patient who had overdosed on multiple psychotropics. A practical algorithm is suggested based on the clinical management of this case.

CASE REPORT

Ms. K. is a 23-year-old white female admitted following a mixed polydrug overdose. The patient has a significant history for bipolar I disorder including both manic episodes with psychotic features as well as depressive episodes as defined by DSM-IV criteria (17). The patient had two previous overdoses, and three previous psychiatric admissions. Further, alcoholism was a comorbid disorder. Prior to the current admission, the patient was maintained on the following psychotropic agents: venlafaxine, topiramate, divalproex sodium, risperidone and carbamazepine. For unknown reasons, the patient took a mixed overdose of all of the above-mentioned psychotropics.

Upon arrival to the emergency room, she was intubated for airway protection. The patient was arousable and responsive to verbal stimuli. She was afebrile with a pulse of 129 beats per minute (bpm) and blood pressure of 126/70. Admission labs were pertinent for the following abnormal values: white blood cell (WBC) count of 12,000/mm^3, CPK of 523 U/L, carbamazepine level of 39 μg/ml, valproic acid level of 122 μg/ml, and ammonia of 113 μmol/L. Liver function tests were within normal limits. Urine toxicology screen was negative. Electrocardiogram revealed sinus tachycardia. Chest radiograph and CT of the brain were both unremarkable.

On admission to the intensive care unit, all outpatient psychotropic medications were discontinued. She was sedated and maintained with a continuous intravenous infusion of lorazepam 0.5 to 1.0 mg/hr (infusion rate was dependent on vital signs and response to treatment). She was also started on L-carnitine 250 mg IV q8h to assist in the metabolism of valproic acid (18). On the second day of admission, she was extubated, but was later re-intubated that same day after developing hypoxia. On the third day of admission, she became febrile with a maximum temperature of 103.7°F, diaphoretic, and remained tachycardic with a pulse of 112 bpm. Physical examination was pertinent for 4+ reflexes with sustained clonus and increased upper and lower extremity rigidity in comparison to the previous day. Laboratory findings were significant for a WBC count increased to 17,400/mm^3 with a left shift consisting of seventy-eight neutrophils and nine bands and a continued elevated CPK level of 554 U/L. Cooling blankets were initiated at this time. Whereas the patient had been managed initially with supportive care, these laboratory and physical examination finding changes led to a clinical diagnostic and therapeutic debate between SS and NMS. Pharmacologic management was instituted for both syndromes avoiding any intervention that could exacerbate either syndrome: cyproheptadine 4 mg via nasogastric (NG) tube q8h to address SS and dantrolene 75 mg via NG tube q6h to address NMS.

CPK levels continued to rise to 928 U/L on the fifth day of admission and eventually peaked at 1033 U/L on day seven of admission. During this admission, the patient's urine myoglobin was measured on day five and found to be negative. The patient had one episode of atrial flutter and was given adenosine with spontaneous conversion to normal sinus rhythm. An echocardiogram and EEG were both unremarkable. With the continuing symptoms and rising CPK levels, it was ultimately felt that the patient had a picture more consistent with NMS. Bromocriptine 2.5 mg via NG tube q6h was initiated to address NMS and cyproheptadine was discontinued.

The patient began to clinically improve with resolution of hyperthermia and decreasing CPK levels. Physical examination revealed decreasing muscle rigidity and normoreflexia. The patient was extubated on day ten and gave a history of multiple drug overdose and depression and agreed to voluntary admission to an inpatient psychiatric facility. On the tenth day of admission, the patient mistakenly received one dose of olanzapine 2.5 mg. However, there was no rise in CPK, temperature, or WBC abnormalities. The patient was discharged on day 14 to an inpatient psychiatric facility.

DISCUSSION

Differentiation between SS and NMS may be difficult at the time of presentation to an ICU when the patient has elements of both syndromes or, as in this case, meets criteria for both syndromes (Table 1) (6). Though unlikely, it is important to remember that having one syndrome does not preclude having the other. In light of the severe morbidity and mortality associated with SS and NMS, aggressive management should be considered when the differential includes both syndromes as occurred in this case.

Gillman outlined criteria to differentiate between the two syndromes when there is a diagnostic quandary (10). Utilizing Gillman's criteria, clinical features in this case that favored SS were use of a serotonergic agent, clonus, and hyperreflexia; those features favoring NMS were use of a neuroleptic agent, slow onset of symptoms, and muscle rigidity; however, non-specific features present that were consistent with both syndromes included hyperthermia, tachycardia, confusion, diaphoresis, and elevated CPK levels levels. As there is much overlap between SS and NMS, differentiation is even more complicated in the setting of acute overdose with multiple psychotropics.

Mills compared the two syndromes after a review of case reports in the medical literature (6). In this comparison of SS and NMS, it was found that hyperthermia, mental status changes, muscle rigidity, leukocytosis, and increased CPK levels were more commonly reported in NMS. However, these features can be found in patients with SS. Furthermore, laboratory findings are not very useful in differentiating between the two syndromes. While Hermesh reported that CPK levels are typically much higher in NMS, no minimal cutoff CPK level relevant to NMS has been explicitly defined (19).

Although there is much overlap between SS and NMS, one feature that differentiates the two syndromes involves the duration of symptoms. SS usually has a shorter course with symptoms resolving or improving in less than twenty-four hours from initiation of symptoms (6). Nonetheless, consideration must be given to the possibility of prolonged SS secondary to long elimination half-lives or active metabolites (20). On the other hand, NMS has a much longer duration of symptoms, typically resolving after an average of nine days (6). Of course, this does not provide any practicality during initial management if both diagnoses are being considered. However, this does change management after 48 hours if a patient's symptoms have not resolved or improved. At this point, NMS would be more likely and treatment options should be changed to address this more closely.

Treatment strategies utilized in this case suggest a practical algorithm for the management of an undifferentiated presentation of SS/NMS (Table 2). Initial interventions should include intubation for airway protection, IV hydration, benzodiazepines, and monitoring for vital signs and laboratory values. Aggressive treatment for both syndromes should be started early in a patient's management with combined cyproheptadine and dantrolene. Bromocriptine and chlorpromazine should not be utilized in undifferentiated SS/NMS. As symptoms persist

Table 1 Signs and Symptoms Observed in Undifferentiated Case of SS/NMS

	Serotonin Syndrome	Neuroleptic Malignant Syndrome
Duration	24–72 Hours	Up to 2 Weeks
Altered mental status	+	+
Diaphoresis	+	+
Hyperthermia	+	+
Tachycardia	+	+
CPK elevated	+	+ (>1000)
Leukocytosis	+	+
Fever	+	+
Myoclonus	+	
Hyperreflexia	+	
Muscle rigidity		+

Table 2 Algorithm for Treatment of Undifferentiated SS/NMS

Intubation for airway protection
IV hydration
Monitoring of vital signs
Withdrawal of potential offending agents
Cooling blankets
↓
Laboratory evaluation (serial CPKs)
Aggressive treatment for both:
Cyproheptadine (for SS) and Dantrolene (for NMS)
↓
Do NOT use bromocriptine initially (Contraindicated in SS)
Do NOT use chlorpromazine initially (Contraindicated in NMS)
↓
Add bromocriptine as duration extends beyond 48 hours with picture more consistent with NMS

beyond 48 hours without significant improvement with continued elevation of CPK levels (usually greater than 1000 U/L), the probability of the diagnosis being NMS increases and bromocriptine should then be added to the treatment regimen.

It is important to recognize that our case study involved an overdose of psychotropic medications and not the appearance of SS/NMS during standard therapeutic dosing. While NMS is classically understood to arise idiosyncratically, independent of dosage, SS typically is considered a toxic effect associated with excessive serotonergic agonism (11,20). Nevertheless, the treatment algorithm presented has been directly extrapolated from established treatment protocols for each syndrome. SS and NMS are medical emergencies that require prompt and effective treatment protocols. Thus the algorithm proposed can be viewed as a guideline for acute intervention when both SS and NMS are not well differentiated.

This case reveals both the complexities in the differentiation of SS/NMS as well as the need for aggressive intervention. Further, this case has led to a practical treatment algorithm when features of both syndromes are present. A definite need exists for carefully designed and controlled investigations of the efficacy of different treatment modalities for acute intervention when SS/NMS is undifferentiated. It is hoped that the algorithm derived from this case will serve as both a practical guideline and impetus for further investigation in light of increasing co-administration of antidepressant and antipsychotic medications.

NOTE

Additional information can be found by calling the Neuroleptic Malignant Syndrome Information Service (NMSIS) Hotline 888-NMS-TEMP (888-667-8367), or on the web at www.nmsis.org

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