Gastrointestinal bleeding and massive liver damage in neuroleptic malignant syndrome

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Background: Neuroleptic malignant syndrome (NMS) is a rare side effect of antipsychotic therapy characterized by fever, muscular rigidity, altered mental status, increased level of serum creatinine phosphokinase, and increased number of white blood cells. The mortality rate of patients with NMS remains elevated.

Methods: We examined the clinical records of patients diagnosed with severe NMS admitted to the Clinical Toxicology Unit, Florence University Hospital, between 1990 and 2004.

Results: Eight patients presented with this neurological disorder. All were treated with supportive therapy, which included dantrolene, levodopa/benserazide, benzodiazepines, metamizole and/or paracetamol, and antibiotics. Five survived and three died. Of the three deceased, two had large hemorrhages in the gastrointestinal tract, and one had massive liver damage and diffuse hemorrhages throughout the body.

Conclusion: Our results suggest that gastrointestinal bleeding is a frequent cause of death in NMS patients. Bleeding may occur as a consequence of commonly accepted medical treatments (especially the use of cyclooxygenase inhibitors as antipyretic agents) and NMS-induced changes in blood coagulation status. To increase the survival rate of these patients, it is necessary to avoid using drugs that may facilitate gastrointestinal lesions and to utilize procedures known to decrease the risk of bleeding.

Keywords: neuroleptic malignant syndrome, fever, gastrointestinal bleeding

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, potentially fatal complication of antipsychotic therapy and may occur in patients treated with either typical or atypical neuroleptic agents (Shalev et al 1989; Robb et al 2000; Stanfield and Privette 2000). The syndrome is characterized by fever, muscular rigidity, altered mental status, increased level of serum creatinine phosphokinase, and increased number of white blood cells (Ebadi et al 1990; Pelonero et al 1998; Adnet et al 2000). It has also been described after the withdrawal of dopaminergic agents, such as L-dopa or inhibitors of catechol-o-methyl transferase, in patients affected by parkinsonian disorders (Friedman et al 1985; Iwuagwu et al 2000). These observations suggest that changes in dopamine receptor function may be largely responsible for the clinical findings present in these patients.

The proposed medical treatment of the syndrome is: (1) elimination of neuroleptic treatment; (2) supportive therapy; (3) administration of dopamine receptor agonists or agents able to increase the function of the dopaminergic system; (4) administration of dantrolene, a compound able to inhibit the release of Ca^{2+} from sarcoplasmic reticulum thus reducing muscle tone and heat production; and (5) administration of antipyretic agents to reduce body temperature (Ward et al 1986; Kaufmann and Wyatt 1987; Rosenberg and Green 1989; Tsutsumi et al 1998). It is widely accepted that lethal complications may occur in variable percentages (from 1% to 50%) of these

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Table 1 Criteria used for diagnosis of neuroleptic malignant syndrome

1. Chronic antipsychotic treatment
2. Fever (above 39 °C)
3. Altered mental status
4. Rigidity and tremors
5. Increased serum creatinine phosphokinase activity (>1000 U)
6. Leucocytosis (>10 000/mL)

patients and that the most common causes of death are deep venous thrombosis with pulmonary embolism, acute renal failure, pneumonia and other types of pulmonary failure (adult respiratory distress syndrome especially with rabdomyolysis), myocardial infarction, and sepsis (Kaufmann and Wyatt 1987; Shalev et al 1989).

In a retrospective evaluation of the cases admitted to the Clinical Toxicology Unit, Florence University Hospital, we found that gastrointestinal bleeding and massive liver failure with diffuse hemorrhages could result in death. Here we report our experience and suggest that careful control of gastrointestinal function and coagulation status may significantly reduce the mortality rate in NMS patients.

Methods

We examined the clinical records of patients admitted to the Toxicology Unit of Florence University Hospital between 1990 and 2004. This unit admits patients with drug dependence, drug side effects, poisoning, and those who have attempted suicide. Eight out of fifteen thousand patients presented a typical diagnosis of NMS with all the key features of the syndrome as reported in Table 1.

Results

The drug involved and the age and outcome of the eight NMS diagnosed patients are reported in Table 2. Five of these patients completely recovered, while three died. Among the latter three, two were under treatment with chlorpromazine, and one was treated with levomepromazine plus amitriptyline (see Table 2). Thus, all the patients with poor outcomes had been treated with agents able to antagonize not only dopamine but also muscarinic receptors (Costa et al 1978; Kwok and Mitchelson 1982). Finally, it is important to note that no history of gastrointestinal pathology was previously present in these patients.

Case reports

Case 1

A 31-year-old female with a psychiatric diagnosis of bipolar disorder was treated with chlorpromazine (300 mg/day), haloperidol (12 mg/day), diazepam (20 mg/day), promazine (10 mg/day), and orfenadrine 100 mg/day.

She was found agitated and confused with increased muscular tone and diffuse tremors. Physical examination of the abdomen and thorax was negative. Her temperature was 39.3 °C, heart rate 120 beats per minute with regular rhythm, and blood pressure 140/80. Laboratory findings were: serum creatinine phosphokinase (CPK) 1895 U/L, lactate dehydrogenase 835 U/L, WBC 14 300/μL, hemoglobin 10.3 g/dL, hematocrit 31%, and platelets 181 000 mm^3. The patient's serum Na^+ level was 142, K^+ 4, and Cl^- 108 mEq/L. Blood urea nitrogen was 1.37 g/L and creatinine 6 mg/dL. The brain CT showed no signs of tumors or cerebral or subarachnoid hemorrhage. A lumbar puncture showed clear CSF with normal intracranial pressure and no signs of bacterial or viral infections.

Supportive therapy was started with the administration of fluids, electrolytes, and antibiotics. After formulation of the diagnosis, the patient received dantrolene (60 mg intravenously [IV] every 8 h) and bromocriptine (2.5 mg orally, every 12 h). For the next two weeks, the patient improved and was transferred to a psychiatric ward where she received chlordiazepoxide (100 mg/day). However, her general condition deteriorated and ten days later she returned to the Clinical Toxicology Unit unconscious. She had breathing difficulties, and her serum electrolytes were Na^+ 176, K^+ 6.5, Cl^- 153 mEq/L, and blood urea nitrogen was 3.17 g/L. She was treated with fluids, nutrients, diuretics, antibiotics, and cortisol (1 g IV). Within two days her general condition again transiently improved. Since the patient was agitated, the psychiatrist prescribed diazepam (20–40 mg/day) and chlorpromazine (50 mg/day intramusculary [IM]).

Table 2 Synopsis of the eight neuroleptic malignant syndrome reported cases

Poor outcome

	Age	Drugs involved	Outcome
1	31	Haloperidol, chlorpromazine, orphenadrine	Death (gastrointestinal bleeding)
2	43	Levomepromazine, amitryptyline	Death (massive liver necrosis)
3	60	Chlorpromazine, haloperidol, clopentixol	Death (ulcer bleeding, necrotizing enteritis)

Recovery

	Age	Sex	Drugs involved	Outcome
4	62	F	Haloperidol, clothiapine	Recovery
5	31	M	Clothiapine	Recovery
6	54	M	Thioridazine, bromperidol	Recovery
7	33	M	Pimozide, droperidol	Recovery
8	48	M	Clomipramine, thioriazine, olanzapine	Recovery

The fever returned, her blood pressure suddenly decreased, and blood hemoglobin content reached 6.5 g/dL with hematocrit at 19.6%. Partial thromboplastin time (PTT) time was 40 s. Ranitidine (200 mg IV three times a day) and packed red cells (5 units in three days) were promptly administered together with supportive therapy. In the next few days, the patient had repeated episodes of melena and emesis with the characteristic "coffee grounds" appearance. Supportive therapy and packed red cells were repeatedly administered but her general condition deteriorated and the patient died.

Case 2

A 43-year-old man who had been treated with benzodiazepine, levomepromazine, and tryciclic antidepressants for bipolar depression was admitted to the unit. His doctor reported that in the week before his admission the patient complained of repeated loss of equilibrium with falls.

On admission, he appeared unresponsive and in a stuporous state. His blood pressure was 120/80, pulse 100 beats/min with regular rhythm, muscular tone was rigid with tremor, and his body temperature was 39 °C. An abdominal examination was unremarkable for acute findings and no pathological or abnormal sounds were present during auscultation of the lungs. A few petechiae and ecchymoses were noticed throughout the body.

Laboratory findings were: CPK 4843 U/L, WBC 16 800/μL, hemoglobin 13.6 g/dL, hematocrit 39%, and platelets 322 000 mm^3. The patient's serum Na^+ level was 154, K^+ 3.7, and Cl^- 106 mEq/L. Blood urea nitrogen was 0.61 g/L and creatinine 3.4 mg/dL. No alcohol or barbiturates were detected in his blood. Urine drug screening demonstrated the presence of benzodiazepines, phenothiazines, and tricyclic antidepressants.

The patient was immediately treated with an infusion of fluids and antibiotics (cephtriazone 2 g). A few hours later, when the diagnosis of NMS became clear, dantrolene (60 mg every 8 h) was administered IV and levodopa/carbidoba (250/25 mg every 12 h) was administered by nasogastric tube. Since body temperature increased to 40.6 °C, sodium metamizole (1 g IV) was also administered along with ice packing.

On the second day of admission, the patient's general condition deteriorated. Blood pressure slowly decreased to 60 mmHg, blood CPK levels reached 135 000 U/L, blood hemoglobin decreased to 6.9 g/dL, and platelets decreased to 100 000 mm^3. PTT time increased to 43 s and plasma fibrinogen content to 610 mg/dL. Standard resuscitation therapy with infusion of plasma-expanders, hydrocortisol 2 g IV, and slow infusion of dopamine was unsuccessfully attempted. The patient died 36 h after admission to the hospital. The main findings detected at autopsy were massive liver necrosis with petechiae diffused in most tissues including brain.

Case 3

A 60-year-old man suffering from paranoid schizophrenia had been treated, until a few days before admission, with chlorpromazine (100 mg/day), haloperidol (5 mg/day), zuclopentixol (50 mg/day), carbamazepine (800 mg/day), and chlordiazepoxide (50 mg/day). On the day of admission, he was rather confused, muscular tone was rigid with tremors, body temperature 40 °C, blood pressure 120/70, heart rate 100/min with a normal rhythm. The abdominal examination was unremarkable for acute findings but showed an appreciable increase in liver volume. The base of the right lung was dull with normal fremitus. Laboratory findings were: CPK 5400 U/L, WBC 14 300/μL, hemoglobin 17.8 g/dL, hematocrit 50%, and platelets 156 000 mm^3. Plasma fibrinogen content was 333 mg/dL and PTT 25.7 s. The patient's serum Na^+ level was 144, K^+ 3.35, and Cl^- 107 mEq/L. Blood urea nitrogen was 0.98 g/L and creatinine 2.4 mg/dL. Arterial blood gases were: PaO_2 70.1, $PaCO_2$ 37.7, pH 7.40. Supportive therapy was immediately started with infusion of fluids, electrolytes, and antibiotics (ceftazidime 2 g three times a day). Dantrolene (60 mg every 8 h IV) and levodopa/carbidoba (250/25 mg every 12 h through the nasogastric tubing) were administered as soon as the diagnosis of NMS was formulated. To reduce the high fever, metamizole (1 g IV) along with ice packing was repeatedly used.

In the next four days, fever remained elevated, muscular tone increased, and level of consciousness decreased. A progressive decrease in blood platelet content, together with an elevation of fibrin degradation products (D-dimer: 1144 ng/mL) suggested activation of fibrinolysis and possible disseminated intravascular coagulation. The abdomen of the patient was evaluated during a surgical consult but, because of the general increase in muscular tone, it was not possible to reach an acceptable diagnosis.

Seven days after admission, the patient had a massive hematemesis, his blood pressure decreased to 60 mmHg and, in spite of standard resuscitation therapy, he died. At autopsy, gastric and duodenal ulcers were found, together with an acute necrotizing enterocolitis and an acute purulent peritonitis. Pulmonary edema was the considered immediate cause of death.

Discussion

Our clinical observations show that bleeding is an important cause of death in patients with NMS and suggest that actions aimed at avoiding or reducing bleeding and gut damage could significantly improve the prognosis of this "malignant" disease. Previous reports have shown that death occurs because of cardiovascular collapse, pulmonary embolism, aspiration pneumonia, or renal failure due to rhabdomyolisis (Kaufmann and Wyatt 1987). Other serious complications in these patients are myocardial infarction, sepsis, and disseminated intravascular coagulation (Pelonero et al 1998). Case 2 had massive liver damage and signs of blood loss, possibly due to intravascular coagulation, while case 3 had clear laboratory signs of intravascular coagulation that probably contributed to the development of intestinal perforation and massive loss of blood.

There are also a number of pharmacological reasons that could explain why gastrointestinal bleeding was frequent in our patient series. The most obvious is probably the use of nonsteriodal antiinflammatory drugs (NSAIDs) to reduce body temperature. This is a commonly accepted procedure for the treatment of elevated fever (Kaufmann and Wyatt 1987) in spite of the fact that NSAIDs inhibit prostaglandin synthesis, thus decreasing epithelial mucus formation and mucosal resistance to injury. NSAIDs may cause lesions not only in the stomach, but in the duodenum, ileum, and colon (Wolfe et al 1999). In our clinical records, NSAID administration was associated with that of the H_2 receptor antagonist ranitidine, a procedure that was obviously not sufficient to prevent tissue damage and bleeding. NSAIDs inhibit both cyclooxygenase (COX) 1 a constitutive enzyme present in most of the cells, including platelets, and COX 2, an inducible enzyme particularly abundant in neutrophils and in macrophages (Vane et al 1998). Inhibition of platelet function could certainly have facilitated bleeding in NMS patients (Patrono et al 1985).

Dantrolene was another drug administered to NMS patients. It has been previously observed that patients treated with this drug may suffer a number of side effects including gastric irritation, abdominal cramps, and constipation (Patrono et al 1985). These side effects are not surprising since dantrolene inhibits calcium flux across the sarcoplasmic reticulum and may inhibit the depolarization-induced contraction of smooth muscles thus changing gastrointestinal and colon motility (Ward et al 1986). Dantrolene administration may also cause important liver damage (Utili et al 1977; Donegan et al 1978), and its use may certainly be involved in causing the massive liver necrosis of case 2.

All the patients also received agents able to stimulate dopamine receptors. Case 1 was treated with bromocriptine while cases 2 and 3 with L-dopa/benserazide. Dopamine receptor agonists were administered on the assumption that they could facilitate recovery. It is indeed widely accepted that when dopamine is locally injected in the pre-optic anterior hypothalamus it reduces body temperature (Cox et al 1978), while neuroleptic injected into the basal ganglia may cause muscular rigidity and generate heat (Adnet et al 2000). Dopamine interacts with at least 5 receptor subtypes (Emilien et al 1999) and it is not clear which of them is involved in human thermoregulation. It is known, however, that dopamine receptor agonists (including dopamine, bromocriptine, and apomorphine) affect gastric and intestinal secretion and motility often leading to emesis (Morris 1978; Parkes 1981). Thus it is reasonable to assume that systemic administration of dopamine agents could increase secretion of the gastrointestinal tract, cause alteration of the peristalsis and contribute to the fatal outcome of cases 1 and 3.

Finally, all the patients with fatal outcome had been treated for prolonged periods (years) and were under treatment, at the appearance of NMS symptoms, with drugs able to antagonize muscarinic receptors. Case 1 had received chlorpromazine together with orfenadrine, case 2 received levomepromazine and amitryptiline, and case 3 had received chlorpromazine, zuclopenthixol, and carbamazepine. All these agents have a significant affinity for muscarinic receptors (Costa et al 1978; Kwok and Mitchelson 1982). It is widely accepted that these receptors play a key role in the control of gastrointestinal motility and secretion (Stockbrugger 1988; Nelson et al 1996; Ehlert et al 1999), and that a prolonged treatment with muscarinic receptor antagonists causes supersensitivity of these receptors. This supersensitivity may be easily observed as an abstinence syndrome in patients treated for prolonged periods with antidepressants. Vomiting and diarrhea together with perspiration are the main signs of this pathology (Dilsaver and Greden 1984). It is therefore reasonable to assume that withdrawal of muscarinic antagonists contributed to an increase in gastrointestinal motility and secretion in cases 1 and 3 who died with gastrointestinal bleeding.

The three fatal cases described suggest that the mortality rate is still elevated in patients with severe NMS. They also suggest that in the management of these patients it may be useful to: (1) avoid the use of NSAIDs; (2) carefully monitor

blood coagulation status to rapidly detect and possibly correct signs of intravascular coagulation; and (3) use agents able to minimize the risk of mucosal damage in the gastrointestinal tract (proton pump inhibitors and/or prostaglandin agonists). Finally, the elevated mortality rate in our patient series in which all the patients received dantrolene and dopamine receptor agonists suggest that further clinical studies are necessary before assuming that the administration of these agents is a useful therapeutic procedure.

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