J Anesth (2004) 18:135–137
DOI 10.1007/s00540-003-0223-3

Journal of
Anesthesia

Successful management of a patient with neuroleptic malignant syndrome associated with marked elevation of serum creatine kinase

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Key words Dantrolene · Bromocriptine · Propofol · Dopamine receptor · Antipsychotic medication

Introduction

Neuroleptic malignant syndrome (NMS) is a severe complication that occurs during the administration of neuroleptics, antidepressants, and medications for the treatment of Parkinson's disease. The syndrome is characterized by the sudden appearance of fever, motor rigidity, autonomic dysfunction, and increases in liver enzymes and creatinine kinase (CK) [1–3]. We report the intact survival of a patient with NMS associated with markedly elevated CK levels, in whom purification therapy led to successful management.

Case report

A 60-year-old man, 76.3 kg in weight and 170 cm in height, had been diagnosed with schizophrenia at age 24 years. Since then, he had been in and out of mental hospitals repeatedly. He had been treated with bromperidol (9 mg/day) on an outpatient basis for the past 7 years. Although he had residual delusions and hallucinations, his mental status was relatively stable. His past history included diabetes mellitus and hypertension, which had been controlled by oral medications. He was found by neighbors in an unconscious state at his home, and was brought to our hospital, where he was immediately transferred to the intensive care unit (ICU). Arterial blood pressure was 220/120 mmHg, with a heart rate of 120 beats/min, and body temperature was over 38°C. His level of consciousness according to the Glasgow Coma Scale was E4V3M5. NMS was diagnosed, as blood examination revealed typical findings of NMS, i.e., elevated levels of GOT (2120 IU·l^{-1}), GPT (540 IU·l^{-1}), lactic dehydrogenase (LDH; 15 500 IU·l^{-1}), blood urea nitrogen (BUN; 69.8 mg·dl^{-1}), creatinine (Cr; 3.8 mg·dl^{-1}), WBC (15 400·mm$^{3-1}$), and markedly elevated serum CK, reaching 161 440 IU·l^{-1} (normal, $<$230 IU·l^{-1}) (Table 1). Blood gas analysis indicated metabolic acidosis (pH, 7.37; Pa_{O_2}, 73.6 mmHg; Pa_{CO_2}, 26.2 mmHg; HCO_3, 14.7 mEq/l; and base excess (BE), −8.7 mEq/l). The patient was intubated and sedated using propofol (300 mg·h^{-1}) for respiratory management. The patient was hydrated to prevent renal failure, and urine was alkalinized with bicarbonate infusion to inhibit the production of nephrotoxic metabolites of myoglobin.

Treatments and changes in laboratory findings after admission to the ICU are summarized in Fig. 1. Administration of dantrolene at 40 mg·day^{-1} and bromocriptine at 7.5 mg·day^{-1} was immediately initiated to treat NMS. Plasma exchange (PE) was performed to facilitate the excretion of myoglobin. Plasauto EZ (Asahi Medical, Tokyo, Japan) was used to maintain blood flow at 4.8 l·h^{-1}. A Plasmaflo filter (Asahi Medical) made of a 0.5 m^2 membrane area was used, allowing replacement of 30% of plasma with fresh frozen plasma (40 units, 3200 ml). Plasma exchange was performed three times. In addition, continuous hemodiafiltration (CHDF) was performed for 5 days. A JUN-500 (UBE Medical, Tokyo, Japan) was used to maintain blood flow at 4.8 l·h^{-1}. A Renaflo II hemofilter (Minnteck, Minneapolis, MN, USA), made of a 0.71 m^2 polysulfone membrane area was used. Fortunately, the patient responded well to these treatments, with his elevated myoglobin concentration (14 120 ng·ml^{-1}) on admission to the ICU normalizing within 1 week (see Fig. 1). CK and transaminase levels also gradually decreased within

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Received: November 14, 2003 / Accepted: December 17, 2003

Table 1. Laboratory findings on admission to the intensive care unit (ICU)

CRP	22.7 mg·dl^{-1}
WBC	15 400·mm$^{3-1}$
RBC	500 × 10^{4}·mm$^{3-1}$
Hb	15.3 g·dl^{-1}
Hct	42.0%
Plt	17.8 × 10^{4}·mm$^{3-1}$
TP	7.1 g·dl^{-1}
T. Bil	0.7 mg·dl^{-1}
GOT	2120 IU·l^{-1}
GPT	540 IU·l^{-1}
LDH	15 500 IU·l^{-1}
CPK	161 440 IU·l^{-1}
BUN	69.8 mg·dl^{-1}
Cr	3.8 mg·dl^{-1}
Na	137 mEq·l^{-1}
K	4.7 mEq·l^{-1}
Cl	96 mEq·l^{-1}

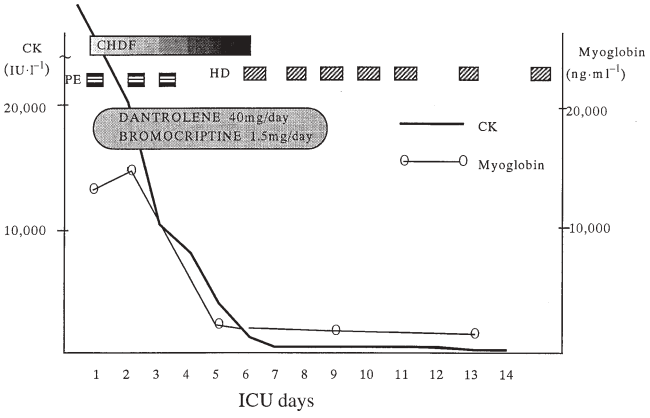

Fig. 1. Treatments and changes in laboratory findings are presented. Both creatinine kinase (*CK*) and myoglobin values were dramatically decreased after the initiation of plasma exchange (*PE*) and continuous hemodiafiltration (*CHDF*), followed by intermittent hemodialysis (*HD*). *ICU*, intensive care unit

a week. CHDF was terminated on day 6, and hemodialysis (HD) was performed instead, every 2 days. The patient was extubated on day 10 and his charged from the ICU 2 weeks after his admission. HD was required three times a week to treat renal dysfunction after his discharge from the ICU. Diuresis was noted on day 20, so HD was discontinued on day 45. Oral administration of quietiapine (50 mg·day^{-1}), a low-potency atypical antipsychotic agent, was started on day 45, with the dosage gradually increased to 400 mg·day^{-1}. His mental condition improved, and the patient was able to begin the rehabilitation process.

Discussion

Most neuroleptics are thought to be capable of inducing NMS, including the newer atypical antipsychotics [3]. Previous studies have reported NMS as a severe complication, with mortality rates of 15%–25% or higher [3–5]. In NMS patients with elevated CK, toxic intracellular substances such as myoglobin are thought to be released into the systemic circulation, leading to multiple organ failure (MOF) [6]. Treatments that prevent acute renal failure (ARF) and MOF are therefore particularly important to improve prognosis.

The clinical symptoms of NMS patients can be divided into two categories; those of central nervous system (CNS) origin, and those of muscular origin. Symptoms such as mental disorder, disturbed thermoregulation, and autonomic dysfunction result from the neuroleptic drug binding to dopamine receptors in the CNS. Dopamine agonists should thus be considered as first-choice agents to reverse the receptor blockade by neuroleptics. Intracellular Ca^{2+} metabolism is also disturbed in severe cases; these patients require dantrolene sodium to inhibit Ca^{2+} release from the sarcoplasmic reticulum [2,7]. In general, serum CK levels indicate the extent of muscle injury. Because the CK level was extremely elevated in our patient, reaching 161 440 IU·l^{-1} (normal, <230 IU·l^{-1}), dantrolene was administered in addition to bromocriptine mesilate, a central dopamine agonist. These two drugs were successfully used to treat this syndrome.

Myoglobin, a substance that can cause ARF, should be removed as soon as possible after it enters the circulation, as myoglobin-induced renal failure is one of the most serious complications in NMS. However, myoglobin cannot be eliminated by HD, due to its relatively high molecular weight (MW, 17 800). We therefore used PE prior to HD for our patient with markedly elevated CK. CHDF was then initiated instead of HD, because myoglobin was shown to be eliminated better by convection (ultrafiltration) than by dialysis (diffusion) [8–10]. The effectiveness of continuous renal replacement therapy (CRRT) remains controversial in terms of preventing renal failure [11]. To use CRRT more effectively, myoglobin should be removed prior to CHDF in patients with myoglobinemia. We could not show that myoglobin clearance was accelerated by the PE, compared to CHDF alone, because the PE was continued intermittently during CHDF, but we believe that the use of PE prior to CHDF was useful in this patient.

Acknowledgments. The authors thank Forte Science Communication Inc. (Tokyo, Japan) and Mr. S. Hardy-Yamada for English editing.

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