Neuroleptic malignant syndrome following cardiac surgery: successful treatment with dantrolene

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Abstract

Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction to neuroleptic drugs, which is potentially fatal. It has been occasionally reported that NMS occurs subsequently after surgery. We report a case of a 53-year-old male patient who developed NMS following cardiac surgery due to the resumption of zotepine. The patient was attacked with hyperthermia, sweating, significant shivering, trembling of the fingers, disturbed consciousness and extreme muscle rigidity after the resumption of zotepine. Furthermore, laboratory measurements revealed increased levels of serum blood urea nitrogen, creatinine and creatine phosphokinase. In addition, elevation in white blood cell counts and myoglobinemia were also observed. After a diagnosis of NMS was established, administration of zotepine was stopped and treatments with administration of dantrolene and a large amount of fluid infusion intravenously were started. Following these treatments, the clinical symptoms subsided and the laboratory findings improved without need for hemodialysis. Dantrolene, which is able to effectively impede the abnormal flow of calcium from the sarcoplasmic reticulum into the muscle cytoplasm, was beneficial to reduce the clinical symptoms of NMS. We hereby present a patient with NMS following cardiac surgery, and discuss its subsequent management.

Keywords: Neuroleptic malignant syndrome; Neuroleptics; Cardiac surgery; Dantrolene

1. Introduction

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction to neuroleptics, which is characterized by hyperthermia, muscular rigidity, severe autonomic dysregulation and disturbed consciousness. The frequency of NMS in the patients given neuroleptics is only 0.3%, but the incidence of NMS is potentially fatal [1,2]. Subsequent incidences of NMS following surgery have been occasionally reported [3]. We now describe a case of NMS following cardiac surgery and discuss its management.

2. Case report

A 53-year-old man was admitted to our hospital with a residual atrial septal defect (ASD). He had been prescribed zotepine (100 mg/day) for schizophrenia since the age of 40. The patient had undergone direct closure of an ASD at 18 years of age, without any complications during or after surgery. There was no history of disorders associated with anesthesia in the family, or among close relatives. Preoperative laboratory measurements were within normal limits.

After admission, the patient underwent pericardial patch repair for ASD with the aid of cardiopulmonary bypass (CPB) and induced ventricular fibrillation. He was sedated with intravenously administered midazolam. Anesthesia was induced and maintained with sodium thiamylal (140 mg), midazolam (50 mg), fentanyl citrate (1.2 mg) and vecuronium bromide (42 mg). The surgery was performed without any complications, although it took a long time to dissect adhesions for the previous surgery. The total CPB time was 104 min, the time for ventricular fibrillation was 38 min and the total operation time was 5 h 30 min. Postoperative serum creatine phosphokinase (CPK) and creatine kinase myocardial band levels were peaked at 1046 and 21 U/l, respectively, on postoperative day (POD) 2.

The postoperative course is shown in Fig. 1. On the day of the operation, the patient was awake and was weaned...
from ventilation. He commenced oral intake of food and drink on POD2 and started to take zotepine again on POD4. On POD5, white blood cell (WBC) counts increased again; hyperthermia (body temperature over 40 °C), sweating, significant shivering, trembling of the fingers, disturbed consciousness and extreme muscle rigidity were observed. Laboratory measurements revealed that WBC counts increased again to 15620/μl and serum levels of creatinine and BUN elevated to 2.85 and 68 mg/dl on POD6, respectively. At this point, the diagnosis of NMS was made by a psychiatrist and zotepine was stopped. Subsequently, treatments with intravenous administration of dantrolene 40 mg $\times$ 3/day and 3500 ml/day of continuous fluid infusion were started. WBC counts are still in excess of 10 000/μl and the serum CPK levels peaked at 1465 U/l on POD8. Myoglobinuria (120 ng/ml) was also observed. Following the treatments, the symptoms subsided; in addition WBC counts, serum CPK, creatinine and BUN levels decreased gradually to normal range. Finally, he recovered completely from NMS with no sequelae of NMS.

3. Discussion

NMS is a rare, but potentially fatal idiosyncratic reaction to neuroleptics. NMS presents with hyperthermia, severe autonomic dysregulation, muscular rigidity and disturbed consciousness [1,2]. Pertinent laboratory findings in this syndrome include leukocytosis, elevated serum CPK levels released from skeletal muscle and myoglobinuria. NMS is similar to malignant hyperthermia (MH) in physiopathologic and symptomatologic terms; therapeutic approaches to its treatment are also similar. In both NMS and MH, there are rapid leakages of calcium from the sarcoplasmic reticulum of skeletal muscle into the muscle cytoplasm; this sets off a chain of events that result in massive muscular contractions, increased levels of CPK, hyperthermia and myoglobinuria [4,5]. MH is an autosomal inherited myopathy that is usually triggered by volatile anesthetic agents and depolarizing muscle relaxants [6]. Functional changes in the ryanodine receptor, which is the calcium release channel of skeletal muscle sarcoplasmic reticulum, results in high myoplasmic calcium concentrations in skeletal muscle cells and subsequent muscle contractures and hypermetabolism. This abnormal calcium metabolism within the skeletal muscle fiber is the leading cause of MH. On the other hand, the contribution of genetic causes to NMS still remains obscure. In the present case, there was neither an inherited tendency, nor occurrence of events suggesting MH, during surgery. Furthermore, the present case was in accordance with the diagnostic criteria for NMS.

Since the 1980s, the combination of a direct dopamine
receptor agonist bromocriptine, and a muscle relaxant drug, dantrolene have been found to be effective in treatment of NMS. The therapeutic use of dantrolene, in particular, is considered to have contributed to the reduction in mortality from 25% before 1984 to 11.6% since 1984 [1,2]. Although the precise mechanisms responsible for NMS still remain controversial, they have been linked to intracellular calcium metabolic abnormalities. Blocking dopaminergic receptors results in inhibition of calcium ion uptake in skeletal muscle. Dantrolene impedes the flow of calcium from the sarcoplasmic reticulum into the muscle cytoplasm, thereby counteracting the abnormal muscular contractions [7]. In addition, dantrolene makes it possible to strengthen cell-to-cell junctions tighter and to stabilize sarcoplasmic reticulum membranes [8]. These lines of evidences support a prominent role for dantrolene in treatment of NMS, in the present case.

Secondary complications such as aspiration pneumonia, thromboembolism and renal failure occasionally accompany NMS. Shalve et al. reported that myoglobinuria leading to renal failure is associated with deterioration of NMS and significantly high mortality [2]. Since the peaks of serum creatinine and BUN levels were observed prior to the peak of serum CPK levels in the present case, the finding might agree with Shalve’s report. Therefore, if necessary, hemodialysis should be performed to prevent renal failure. However, it should be noted that hemodialysis alone is ineffective in removing the offending neuroleptics, which are protein-bound and cannot therefore be removed in this way [9]. Although myoglobinemia was observed in the present case, restoration of water and electrolyte balance by fluid replacement was sufficient to prevent renal failure, without the need for hemodialysis.

Several factors other than neuroleptics are considered to play a role in the incidence of NMS. These include other drugs and physical stress such as surgery, water intoxication and dehydration. In this context, the use of CPB which causes changes in the water balance and the plasma protein binding, may help to trigger the incidence of NMS [10]. Although incidences of NMS following surgery have been occasionally reported, there are few reports of NMS following cardiac surgery [3]. It should be, therefore, noted that early recognition and immediate treatments are crucial in dealing with the incidence of NMS following cardiac surgery.

References