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Case Report

Sudden discontinuation and reinstitution of olanzapine-associated atypical neuroleptic malignant syndrome in a patient undergoing lung surgery

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Abstracts: Neuroleptic malignant syndrome (NMS) is a potentially life-threatening idiosyncratic reaction generally associated with neuroleptics. NMS is characterized by hyperthermia, extrapyramidal symptoms, elevated creatinine kinase (CK), altered mental state, leukocytosis, and problems with vegetative functions. Due to its lower affinity for dopaminergic receptors and higher affinity for serotonin receptors, olanzapine-associated atypical NMS were less common than typical neuroleptics. Here we report a case of NMS induced by sudden discontinuation and reinstitution of olanzapine in a patient with schizophrenia during perioperative period of lung resection, drawing attention to adverse events occurring with reinstitution of atypical neuroleptics in high-risk patients.

Keywords: Neuroleptic malignant syndrome, perioperative period, atypical neuroleptics

Case report

A 63-year-old man was referred to us for a nodule in the right middle lobe in his chest computed tomography (CT) without any symptoms. He had schizophrenia for more than 30 years, and treated by olanzapine for more than ten years, his psychological illness has subsided with maximal dose of olanzapine (10 mg in the morning and 10 mg at night). No previous history of NMS was recorded. On initial evaluation the patient was afebrile and had a blood pressure of 109/94 mm Hg. Physical examination was unremarkable. Routine laboratory tests demonstrated normal blood counts, metabolic panel, renal function and liver function tests. Tests for syphilis, human immune-deficiency virus, and hepatitis were negative. Electrocardiogram (ECG) and echocardiography of cardiac function were normal. Olanzapine were discontinued on the day of operation.

In the operation room, propofol was used to induce anesthesia and rocuronium bromide was used to facilitate endotracheal intubation. Succinylcholine chloride was used to maintain muscular flaccidity. Anesthesia was maintained with sevoflurane and fentanyl. The operation lasted for 1 h and 10 min. The anesthetic course and the operation, right middle lobectomy, were uneventful. The patient was extubated and transported to the intensive care unit (ICU) as usual, the patient's vital signs were normal and he responded to verbal commands.

The next morning, on Postoperative Day (POD) 1, laboratory result (**Table 1**) showed that the hemoglobin concentration was 154 g/dl and white blood cell count was 9.87 × 10^9/L. Meanwhile, the heart beat was 68 bpm, the temperature was 36.7°C, the respiratory rate was 17 bpm and the blood pressure was 127/80 mm Hg. The patient received his regular oral medication (olanzapine), the drug dose remained unchanged. He also received cefuroxime, ambroxol hydrochloride, lansoprazole, propacetamol, budesonide. On POD 2, at 09:00, his consciousness was orthophrenia and the temperature was 37.5°C. The arterial pressure was 112/66 mm Hg, and the heart beat was 86 bpm. The patient was transferred to the ordinary ward.

Table 1. laboratory result in a patient with fulminant neuroleptic syndrome after admission

		Per-operation	POD1	POD2	POD3	POD4	POD5
Chemistry	Na^+	141	143	144	154	143	140
	K^+	4.1	3.7	3.6	4.7	4.0	3.9
	Creatinine (umol/L)	81	69	93	214	124	106
	ASAT (U/L)	13	25	30	70	85	55
	ALAT (U/L)	22	29	43	63	42	61
	GGT(U/L)	12	12	23	51	42	63
	AKP(U/L)	56	52	53	401	254	70
	CK(U/L)				2250	846	623
	WBC (x 10^9/L)	5.72	9.87	13.45	16.90	14.52	13.09

ASAT, aspartate aminotransferase, *ALAT,* alanine aminotransferase, *GGT,* γ-glutamyltransferase, *AKP,* alkaline phosphatase, *CK,* creatine kinase, *WBC,* white blood cell.

On POD 3, the patient had confusion (paraphasia, mania and disorientation as to time and place) and plenty of phlegm. The patient also suffered from dysarthria, tremble and muscle rigidity in the left leg. The blood pressure was 168/88 mm Hg and the heart beat was 106 bpm, but the body temperature was 37.2°C. A lumber puncture revealed normal cerebral spinal fluid (CSF) values and a brain computer tomography (CT) scan was normal. Laboratory results (**Table 1**) showed the creatinine kinase (CK) was 2250 U/L, serum creatinine was 214 μmol/L and the white blood cell count was 16.9 × 10^9. A psychiatrist was consulted, and neuroleptic malignant syndrome (NMS) was suspected as a result of olanzapine reinstatement. Olanzapine therapy was withheld. Dantrolene at a dosage of 70 mg was started intravenously and bromocriptine at a dosage of 2.5 mg 3 times daily was administered. Adequate hydration was maintained and vitals were monitored. And he was readmitted to the ICU.

On POD 4, his muscle tone decreased, the vital signs stabilized, renal function returned to normal and the CK level fell to 846 U/L (**Table 1**). On POD 5, he was responding to voice and body temperature was 37.4°C. He was weaned off dantrolene and bromocriptine as he continued to improve. Pathological results showed adenocarcinoma of lung. The patient was discharged on POD 12 without obvious sequelae, with CK, serum creatinine returning to normal. He was followed up by a psychologist.

Six months later, the patient was treated with clozapine, at a dosage of 400 mg daily. The schizophrenic symptoms were fairly controlled, without any recurrence of his emotional liability or other symptoms.

Discussion

NMS, a potentially fatal consequence due to typical neuroleptics have been described so far, whereas cases of NMS related to atypical neuroleptics, such as olanzapine, are less common in spite of increasing cases reported in the literatures [1-3]. NMS is thought to be caused by the blockade of dopaminergic receptors in basal ganglia and hypothalamus, and the disturbance of calcium uptake in skeletal muscle [4]. We described a case of atypical NMS induced by sudden discontinuation and reinstitution of olanzapine presented in postoperative period.

Several diagnostic criterions are used for NMS worldwide, including the Levenson criteria [5], and the DSM IV-TR criteria [6], sharing quite similar main content. Typical symptoms are hyperthermia, autonomic dysfunction, altered consciousness, muscular rigidity, and an elevation of creatine kinase (CK). However, the patients developing NMS induced by olanzapine are usually afebrile [1-3], identical to our case. In the present case, the patient demonstrated tachycardia (106 bpm), dysarthria, leukocytosis (white blood cell count of 16.9 × 10^9), tremble, mania, mental confusion and muscle rigidity after reinstitute of olanzapine, and he was sensitive to antagonist therapy with bromocriptine and dantrolene, all of which supported the diagnosis of NMS.

Definite diagnosis of NMS is based on clinical manifestation, thereafter differential diagnose are of prime importance [7]. Viral infection of the central nervous system, brain lesions, toxic, drug-induced acute idiosyncratic reaction, hyperthyroidism or anesthesia-related and other

causes should be excluded. In the present case, brain CT and CSF values, blood and urine cultures, thyroid function tests and bed-side chest film were all normal. Anesthesia-induced NMS have been reported [8, 9], but usually develop very immediately after surgery. No medications used were related to the symptoms presented in this patient, except olanzapine, as we know.

Increasing evidence shows that psychomotor agitation, dehydration, pervious episodes of NMS, parenteral medication and surgical stress increase the risk of NMS. The rapid occurrence of psychotic symptoms on POD2 was associated to antipsychotics discontinuation. Abrupt removal of neuroleptic drugs lead to a great risk of early relapse of psychological disorder, therefore gradual dose reduction is recommended [10]. However, NMS occur rarely after the sudden interruption of the neuroleptics [11]. In our opinion, the development of NMS in this case was more related to the drug reinstitution than the interruption. A rapid loading of antipsychotics was supposed to be the causal factors in the development of NMS by causing a massive and sudden down-regulation of dopaminergic transmission [12], leading to overly sensitive postsynaptic dopamine receptors. We recommend gradual dose escalation for reinstitution of neuroleptics and close observation of patients with risk factors.

In summary, there is still possibility for reinstitution of atypical neuroleptic drugs to induce NMS in high-risk patients who have been administered the drugs for many years. Gradual dose escalation for reinstitution of neuroleptics and close observation of patients with risk factors is essential.

Disclosure of conflict of interest

None.

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