PC So 蘇炳湛

Neuroleptic malignant syndrome induced by droperidol

由droperidol引發的抑制神經惡性綜合症

A case of droperidol-induced neuroleptic malignant syndrome during anaesthesia is presented. An 86-year-old man underwent spinal anaesthesia for open reduction and internal fixation of a trochanteric hip fracture. He received droperidol 5 mg intravenously for sedation towards the end of surgery. He subsequently became very drowsy and experienced marked muscle rigidity and autonomic instability. He became febrile postoperatively. The clinical syndrome resolved after 12 hours. When using droperidol in anaesthesia or intensive care—especially when large doses are given—the development of neuroleptic malignant syndrome should be suspected if the patient becomes febrile and has muscle rigidity and autonomic instability.

本文介紹在麻醉期間由 droperidol 引發抑制神經惡性綜合症的一個病例。一位 86 歲的老翁為了做切開復位術和轉子髖骨折的內固定，進行了脊柱麻醉。患者接受了 5 毫克 droperidol 靜脈注射，以鎮靜到手術結束。隨後他變得非常嗜睡、肌肉殭硬及心律不穩定，手術後發燒。臨床併發症在12小時後消退。當在麻醉和強化護理中—尤其在大劑量給藥—使用droperidol時，如果患者發燒和有肌肉殭硬及心律不穩定，就應懷疑是引發了抑制神經的惡性綜合症。

Introduction

Neuroleptic malignant syndrome is an uncommon but potentially fatal idiosyncratic reaction to neuroleptic agents. It is characterised by muscular rigidity, fever, autonomic dysfunction, and altered consciousness.[1] The syndrome is usually associated with the use of depot and oral neuroleptic drugs such as phenothiazines and butyrophenones. Among the injected neuroleptics, fluphenazine enanthate, fluphenazine decanoate, haloperidol, thioxanthines, and pipotiazine (pipothiazine) palmitate have been implicated. The use of non-neuroleptic agents, however, has also been reported to result in the neuroleptic malignant syndrome.[2] These drugs include tetrabenazine, monoamine-oxidase inhibitors, tricyclic antidepressants, and metoclopramide. The cessation of the use of dopaminergic drugs can also result in the syndrome.

Droperidol is a butyrophenone with a short elimination half-life, which is commonly used in anaesthesiology departments, accident and emergency departments, and intensive care units for sedation. The combination of droperidol and a narcotic analgesic drug achieves a state called 'neurolept anaesthesia', which, alone or in combination with local anaesthesia, provides excellent conditions for minor to intermediate surgery because of the resultant cardiovascular stability and minimal respiratory depression. A fatal case of droperidol-induced neuroleptic

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Department of Anaesthesiology, North District Hospital, 9 Po Kin Road, Sheung Shui, New Territories, Hong Kong
PC So, FFARCS, FHKCA

Correspondence to: Dr PC So

malignant syndrome has been reported following the intramuscular injection of a total dose of 40 mg of droperidol. The syndrome developed some time after the injection and was rapidly progressive.[3] A similar case of neuroleptic malignant syndrome developing in the postanaesthetic care unit after the intra-operative administration of intravenous droperidol 5 mg and metoclopramide 10 mg has also been reported.[4] Using physical means of cooling and muscle relaxation, as well as dantrolene prevented further progress of the syndrome. In this case, coma, hyperthermia, muscle rigidity, and autonomic instability resolved on the second postoperative day.[4] A less severe case of droperidol-induced neuroleptic malignant syndrome in a Chinese patient is described in this report.

Case report

An 86-year-old Chinese man presented to the North District Hospital in August 1999 for a trochanteric fracture of the left hip after a fall, which required internal fixation. He had had uneventful surgery under spinal anaesthesia for a fractured right hip 4 months before this presentation. Apart from having mild chronic obstructive airway disease, the patient had been enjoying good health before the second fall. He was mildly dehydrated; otherwise physical examination and routine investigations gave normal results.

The patient was given ketamine 15 mg before being placed in the right decubitus position. Spinal anaesthesia was established using 2 mL of 0.5% bupivacaine. This treatment caused transient hypotension, which was corrected by administering intravenous Hartmann's solution and a total dose of 12 mg ephedrine.

Towards the end of surgery, the patient became slightly agitated; thus, droperidol 5 mg was given. His blood pressure increased to 160/60 mm Hg and his heart rate increased to 170 beats per minute shortly afterwards. However, he became very drowsy and confused, and he showed marked muscle rigidity. His temperature was normal, but he was very tachypnoeic. Arterial oxygen saturation was maintained by the use of supplementary oxygen.

In the postanaesthetic care unit, the patient's blood pressure was very labile and varied between 190/150 and 80/40 mm Hg. The central venous pressure was 13 cm H_2O. The electrocardiogram showed supraventricular tachyarrhythmia, which did not respond to adenosine 10 mg. After digoxin 0.5 mg was given, his heart rate stabilised at approximately 130 beats per minute. He remained very drowsy and continued to have muscle tremor and rigidity. A postoperative complete blood count showed a haemoglobin level of 97 g/L (normal range, 140-180 g/L), white blood cell count of 8.6 x 10^9/L (normal range, 3.2-9.8 x 10^9/L), and a platelet count of 82 x 10^9/L (normal range, 150-450 x 10^9/L). One unit of blood was transfused. Apart from an elevation in the serum levels of total bilirubin (22 mmol/L [normal range, 2-18 mmol/L]) and alkaline phosphatase (174 U/L [normal range, 30-120 U/L]), the serum biochemistry was normal. Four hours afterwards, however, the patient's temperature rose to 38.6°C. He remained in the same critical state for another 12 hours before his vital signs became stable. By the second postoperative day, the concentrations of creatine kinase and lactate dehydrogenase were 285 U/L (normal range, 62-297 U/L) and 392 U/L (normal range, 213-395 U/L), respectively. He made a subsequent smooth recovery.

Discussion

Neuroleptic malignant syndrome has been estimated to occur in 0.5% to 1.0% of all patients exposed to neuroleptics.[5] This syndrome predominantly affects young psychiatric patients who are taking long-acting neuroleptic drugs. The ability of neuroleptic drugs to precipitate neuroleptic malignant syndrome appears to be related to their antidopaminergic potency. Clinical features of the syndrome include hyperthermia, tremor, rigidity of skeletal muscles, and autonomic imbalance, as well as fluctuating levels of consciousness, which can range from random non-purposeful movements, mutism, and confusion to coma. Abnormal results of laboratory investigations, while not specific for the detection of neuroleptic malignant syndrome, include leukocytosis and elevated concentrations of liver enzymes and creatine kinase.

In this patient, the diagnosis was made because of the clinical triad of hyperthermia, muscle rigidity, and autonomic imbalance associated with altered consciousness. An altered state of consciousness alone does not characterise neuroleptic malignant syndrome, because an altered state of consciousness can be produced by any central depressant, such as ketamine and droperidol in this case. In addition, it is well known that droperidol may increase the incidence of emergence delirium from ketamine administration. The small dose of ketamine given, however, is unlikely to give rise to prolonged coma. Droperidol, as a component of neurolept anaesthesia, usually produces remarkable cardiovascular stability, although there can be transient hypotension from its α-adrenergic

receptor–blocking effect. Muscle rigidity may also occur when droperidol is used. If there is a high degree of autonomic instability, as well as fever, coma, and muscle rigidity when droperidol is used during anaesthesia, the diagnosis of the neuroleptic malignant syndrome must be considered. Neuroleptic malignant syndrome is assumed to be precipitated by central dopaminergic blockade. Levodopa, carbidopa, amantidine, and bromocriptine have been used successfully in its treatment.[6] Fever resulting from neuroleptic malignant syndrome appears to have a central and presynaptic origin. Similarly, autonomic dysfunction is attributed to sympatho-adrenomedullary hyperactivity. Once triggered, neuroleptic malignant syndrome can run a rapidly progressive course and have a mortality rate of 20% to 30%.[7]

Treatment, apart from withdrawal of the neuroleptic agent, is mainly supportive. The use of physical means of cooling, as in other types of the pyrexial syndrome, should be instituted early. When there is supraventricular tachycardia or other tachyarrhythmia, adenosine triphosphate, digoxin, and propranolol should be given.

The most serious complication of neuroleptic malignant syndrome is rhabdomyolysis. Rhabdomyolysis produces extremely high levels of serum creatine kinase, hyperkalaemia, myoglobulinuria, and acute renal failure. Caroff et al[8] provided evidence of a similarity between neuroleptic malignant syndrome and malignant hyperthermia. Muscle biopsy tissue from a patient who had recovered from neuroleptic malignant syndrome was shown to have a hypercontractile response to fluphenazine but also a similar abnormal response to halothane. Such a response to halothane is found in patients who are known to be susceptible to malignant hyperthermia, although they do not demonstrate the same sensitivity to fluphenazine.[9] Dantrolene, which is used for the treatment of malignant hyperthermia, has also been used with some success in the treatment of the neuroleptic malignant syndrome. Dantrolene reduces the amount of available intracellular calcium by blocking calcium efflux in muscle cells, thereby interfering with the excitation-contraction coupling and acting as a direct-acting muscle relaxant. In doses as small as 100 mg/d, dantrolene reduces the amount of muscle rigidity, hyperpyrexia, and the excessive oxygen consumption of this condition.[10]

Conclusion

In this case of neuroleptic malignant syndrome precipitated by droperidol, the course of events was self-limiting, probably because of the short half-life of the drug and the small dose given. Although there was no progression to rhabdomyolysis, the clinical syndrome of coma, rigidity, and autonomic instability was sufficiently critical. When using droperidol in anaesthesia or critical care—especially when large doses are given—the development of neuroleptic malignant syndrome should be suspected if the patient develops fever, muscle rigidity, and autonomic instability. Because of the high mortality rate of patients with this syndrome, the early recognition and prompt institution of supportive care are essential factors of the treatment. Physical cooling and dantrolene and/or bromocriptine should be used when there are signs of early progression of the syndrome.

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