Droperidol-induced neuroleptic malignant syndrome

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CASE REPORT

A 21-year-old female was admitted to the general medical wards via casualty with a suspected overdose of unknown amounts of procyclidine, diazepam and alcohol. She had been a known intravenous drug addict for 3 years.

On examination she was drowsy, agitated and smelling of alcohol. She had venepuncture sites in her antecubital fossae. Her cardiorespiratory observations were normal and her abdomen was soft and non-tender. Glasgow Coma Score was 9 (E4, M4, V1). Her pupils were dilated but equal and reacting to light. Her tone was normal, as was her temperature. Investigations revealed a normal urea and electrolyte screen and a normal full blood picture. Drug screen was positive for benzodiazepines but negative for paracetamol, salicylates, opiates and amphetamines. Electrocardiography showed a sinus rhythm.

She was initially treated with flumazenil 500 μg intravenously and naloxone 1.6 mg intravenously with some improvement in her conscious state. She was given droperidol 10 mg intramuscularly (IM) for agitation and was admitted to a medical ward.

Two days after admission she was increasingly unmanageable, requiring two staff members to control her at all times. She was having auditory and visual hallucinations and was restless. Further droperidol 10 mg IM was given. At this stage, cardiorespiratory observations were still normal, as was temperature. Pupils were dilated, equal and slow to react. Tone was normal. She was reviewed by the psychiatrists who diagnosed drug-induced psychosis, secondary to procyclidine. She was given further droperidol 30 mg IM and transferred to the psychiatric ward for observation. She developed an acute dystonic reaction which was treated with a total of 20 mg of procyclidine IM.

By day 3 she was sweaty, rigid and psychotic. Her temperature was 37.4°C, with a pulse rate of 120 and arterial pressure of 140/90 mm Hg. She was noted to have extensive bruising over her arms and legs. Creatinine phosphokinase was elevated at 1597 mmol/litre (normal < 170 mmol/litre).

During that evening she became tachycardic (pulse 140 beats per minute), hypotensive (blood pressure 50/30 mmHg), tachypnoeic (respiratory rate 50 breaths per minute) and hyperpyrexial, and was found to have a rectal temperature of 42°C. Her pupils were dilated, equal and reacting but she had generalized increased tone and was vasoconstricted. An arrest call was put out and after initial resuscitation she was rapidly transferred to the surgical intensive therapy unit, with a presumed diagnosis of neuroleptic malignant syndrome.

She was intubated and ventilated with 100% oxygen, and received a total of 120 mg dantrolene intravenously. Active cooling measures were initiated. Over several hours her temperature dropped from 42°C to 36.1°C. She was noted to be oliguric (urine output ≈10 ml/hr) with blood-stained urine, positive for myoglobin. She was oozing from venepuncture sites and had a coagulation screen consistent with acute fulminant disseminated intravascular coagulation (prothrombin time 34 secs (normal 12–14 secs), fibrinogen level 1.8 g/litre (normal 2.5–4 g/litre), platelets 100×10^9/litre (normal $150–400 \times 10^9$/litre), D-Dimer >8 mg/litre (normal <0.5 mg/litre), haemoglobin 99 g/litre (normal 110–115 g/litre)). She had a marked metabolic acidosis (H+ 49 mmol/litre (normal 36–43 mmol/litre) (base excess -10)). Her potassium was normal. Her urea and creatinine were 10.6 mmol/litre and 259 μmol/litre respectively (normal 2.5–7.5 mmol/litre and 40–130 μmol/litre). An infective screen was normal. She continued to deteriorate rapidly, despite inotropic support, volume replacement, frusemide infusion and transfusion of fresh frozen plasma, platelets and concentrated red cells.

Early next morning (day 4) she was diagnosed as having multisystem organ failure and developed fixed dilated pupils, the latter presumed due to cerebral haemorrhage. Active treatment was withdrawn and she died shortly afterwards. A post-mortem showed pulmonary oedema but no apparent cerebral haemorrhage.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction to neuroleptic agents. This report describes NMS in a 21-year-old female who was admitted with a drug overdose and who was given droperidol for psychosis during admission.

It highlights the malignant nature of NMS and the difficulty, but importance, of making an early diagnosis and instituting early treatment. It is important for all medical practitioners to be aware of this rare condition as neuroleptics are such commonly used drugs.

DISCUSSION

NMS is a rare, potentially fatal, idiosyncratic reaction to neuroleptic drugs such as haloperidol, droperidol and metoclopramide. The clinical features include hyperthermia (in 80%), an altered level of consciousness (in 30%) and autonomic instability (in 100%) (Ebaldi et al, 1990). An increased creatinine phosphokinase (CPK) level, disseminated intravascular coagulation, rigidity, rhabdomyolysis and myoglobulinuria may also be seen (Kellam, 1987).

The reported frequency of NMS in patients treated with neuroleptic drugs is of the order of 0.07–2.24 % (Pope et al, 1986). NMS may be precipitated by dehydration, agitation, acute hyponatraemia and stress, and may occur at any age (Keck et al, 1987).

Complications of NMS include congestive cardiac failure and acute myocardial infarction, adult respiratory distress disorder, acute renal failure and disseminated intravascular coagulation.

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The differential diagnoses include malignant hyperpyrexia, a similar hyperthermic syndrome caused by various anaesthetic agents such as suxamethonium and halothane. Ingestion of MDMA (Ecstasy), a recreational drug, also produces a fulminant hyperthermic syndrome on rare occasions. Heat stroke and intoxication with strychnine or carbon monoxide can also produce a similar clinical picture (Caroff et al, 1991).

NMS may occur within a few hours of neuroleptic drug administration or over several days. Signs of autonomic instability, such as tachycardia, labile blood pressure and sweating may precede the onset of hyperthermia, acting as early warning signs.

The exact pathophysiology of NMS is not known. Several neuromediators, including dopamine, serotonin, norepinephrine, gamma aminobutyric acid, excitatory amino acid (EAA) and N-methyl-δ-aspartate (NMDA) are thought to play a role in the pathogenesis of the syndrome. Current concepts are based on a functional dopamine deficient state, triggered by neuroleptic drug-mediated post-synaptic dopamine receptor blockade and ensuing hyperactivity of EAA neurotransmission in the basal ganglia and hypothalamus (Mann et al, 1991).

Treatment of NMS includes immediate withdrawal of the suspected agent, measures to decrease temperature, adequate volume replacement and supportive treatment for the respiratory, cardiovascular, haematological and renal abnormalities. Specifically, intravenous dantrolene (up to 10 mg/kg) is used to prevent muscle spasm by inhibiting release of calcium ions from the sarcoplasmic reticulum and also lowers temperature and reduces CPK. Oral bromocriptine has also been used. Both these agents have significantly reduced the recovery period from NMS. Anticholinergics, benzodiazepines and electroconvulsive therapy are often considered to be controversial therapeutic alternatives.

There are several noteworthy points particular to this case. First, NMS can be, as the name suggests, a highly malignant and rapidly fatal disease, despite aggressive treatment. Studies have shown it to be fatal in 15% of all patients (Moore and O'Donohoe, 1986).

Second, with neuroleptic agents being in such common use, as major tranquillisers in psychiatric and general wards and also in anaesthesia, a high index of suspicion and early diagnosis are essential.

Droperidol was first administered on the day of admission, however, the clinical picture of NMS did not present until the third day. The diagnosis was made on the evening of day 3 but unfortunately the patient died the following morning.

CONCLUSION

NMS is a rare, potentially fatal idiosyncratic reaction to the commonly used neuroleptic drugs. It requires a high index of suspicion and early diagnosis and treatment if a successful outcome is to be obtained. HM

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