INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare but life threatening idiosyncratic reaction related to the use of antipsychotic drugs characterised by hyperthermia, muscle rigidity, elevated creatinine kinase level and autonomic instability. NMS usually develops after an increase in dosage of neuroleptic medication. Treatment is primarily supportive, prompt withdrawal of the offending agent, and administration of drugs such as bromocriptine and dantrolene. Electroconvulsive therapy (ECT) has been found to be effective not only in patients with schizophrenia refractory to pharmacotherapy but also in severe or treatment resistant neuroleptic malignant syndrome patients. The similarity of clinical and physiological features between malignant hyperthermia (MH) and NMS poses a challenge to anaesthesiologists in relation to the use of MH triggering agents such as succinylcholine. Combination of rocuronium and sugammadex has been used successfully as an alternative to succinylcholine in this patient.

CASE REPORT

A 46 year old gentleman, with underlying benign thyroid nodules and paranoid schizophrenia with prominent mood symptoms under regular psychiatric follow-up presented to our hospital with a one week history of fever, inability to speak, sialorrhoea, limb stiffness, profuse sweating, tremors and rigidity of bilateral upper and lower limbs. Medical records revealed that he had been on oral olanzapine for the last five years with a recent increase in dosing from 10 mg to 20 mg.He had also been concomitantly started on oral fluoxetine 20 mg to replace oral fluvoxamine in view of worsening mood symptoms five days prior to hospital presentation.

Upon arrival in the Emergency Department, he was able to spontaneously open his eyes but was aphasic and diaphoretic. Standard vital sign monitoring devices were applied and revealed fever, with a temperature of 38.2, systolic BP of 158 - 189 mmHg, diastolic blood pressure of 95 - 100 mmHg, and tachycardia at 125 beats per minute. Neurological examination showed prominent lip and jaw muscle twitching, tremor of both hands and cogwheel rigidity of bilateral shoulders, elbows and wrist, and areflexia consistent with Parkinsonism.

Laboratory investigations revealed mild leukocytosis (11.2 x 10^9/L), a raised creatinine kinase (CK) levels of 906 U/L and mildly elevated levels of aspartate aminotransferase of 61 U/L. Other electrolytes were within normal range. Chest X-ray was normal and electrocardiographic examination showed sinus tachycardia with no ischemic changes. Urinalysis was positive for myoglobin.

Conventional work up and laboratory parameters pointed towards a diagnosis of neuroleptic malignant syndrome (NMS), in accordance with the Levenson criteria where the patient exhibited all three major signs (rigidity, raised CK and hyperthermia) and five minor signs (abnormal arterial pressure, tachycardia, diaphoresis, cognitive impairment and leukocytosis). Thus, both olanzapine and fluoxetine were immediately discontinued and he was transferred to ICU for critical care support. We utilised lorazepam and prescribed bromocriptine and his NMS symptoms improved. However, in view of residual catatonic symptoms, decision was made to commence ECT. A combination of rocuronium sugammadex was used successfully in all his ECT procedures and found to be an excellent alternative to succinylcholine in this patient.
He was initially admitted to the general ward and given oxygen supplementation, hydrated with 3 litres of normal saline per day and had his vital signs monitored closely. Despite the initial supportive management, patient continued to have spiking temperature and worsening limb rigidity. He was then referred for critical care support and transferred to the Intensive Care Unit (ICU) for stabilisation. In the ICU, he was put on oxygen therapy and prescribed oral lorazepam 1 mg. Oral bromocriptine 2.5 mg 6 hourly was promptly initiated for the treatment of NMS. Dantrolene was initially considered as an alternative to bromocriptine but was not administered as patient showed signs of improvement over a period of a few days.

Complete resolution of rigidity and normothermia were seen four days after commencement of bromocriptine. In view of his catatonic state of schizophrenia with unresolving prominent mood symptoms, the psychiatry team decided to initiate electroconvulsive therapy (ECT) as an attempt to improve the patient's psychotic symptoms.

In consideration of the patient's underlying illness and current diagnosis, the anaesthesia team decided to support his ECT procedures in the major operating theatre and not in the remote ECT procedure room located in the psychiatry ward where it is usually performed. After pre-oxygenation with high flow 100% oxygen, anaesthesia was induced with intravenous propofol (2 mg/kg) and rocuronium (0.6 mg/kg) and patient was ventilated via laryngeal mask airway Proseal® connected to the anaesthetic machine. ECT stimulus was then applied, and produced an ensuing seizure. Sugammadex 200 mg (2 mg/kg) was administered after ECT approximately 10 minutes after the administration of rocuronium. Vital signs were measured prior to the induction of anaesthesia, pre-seizure, post-seizure, and every minute for 10 min thereafter, and remained stable throughout the procedure. Propofol-rocuronium-sugammadex combinations at similar doses were used in all subsequent ECTs except on one occasion, where a Sevoflurane-rocuronium-neostigmine combination was used successfully. However, despite six ECT sessions, patient's symptoms persisted and he was then rechallenged carefully with oral olanzapine to manage his symptoms.

**DISCUSSION**

NMS is a rare but life threatening idiosyncratic reaction related to the use of antipsychotic drugs. It was first described by Delay and colleagues in 1967 as ‘akinetic hypertonic syndrome’. Adnet et al. (2000) showed that the risk of developing NMS is between 0.07-2.2%. The mortality rate of NMS is reported between 10% to 30% despite increased awareness associated with the use of typical antipsychotics drugs.

NMS is diagnosed based on Levenson’s clinical criteria. The presence of all three major or two major and four minor manifestations indicates a high probability of NMS, if supported by clinical history. Based on the above manifestations, our patient had fulfilled the clinical criteria with history suggestive of NMS.

There are two postulated theories to explain NMS, which are central dopamine receptor blockade and a skeletal muscle defect. Central dopamine receptor blockade contributes to the thermoregulatory failure seen in NMS. Serotonin stimulation in the hypothalamus leads to heat production and dopamine inhibits this process resulting in hyperthermia. The muscle rigidity and hypermetabolic state seen in NMS is a result of blockade of dopamine receptors in the nigrostriatal system.

Based on the second theory, NMS is thought to share a common pathophysiology with malignant hyperthermia (MH). This theory is based primarily on three features shared between the two conditions. These are: (i) presence of hyperthermia, rigidity and increased CK levels; (ii) treatment options for both conditions include dantrolene and (iii) presence of abnormal results in ‘in vitro’ contractility tests in both NMS and MH. Both in-vitro investigations of patients with NMS and MH revealed multiple skeletal muscle defects associated with increased release of calcium from sarcoplasmic reticulum.

NMS can be fatal if untreated. The most important step in management of NMS would be to remove the causative agent. Supportive management, including maintenance of adequate hydration, achieving normothermia, cardiorespiratory stability, control of agitation, and prevention of deep vein thrombosis, is vital in the management of NMS. In terms of pharmacotherapy, bromocriptine and dantrolene sodium are the most frequently used medications. Bromocriptine helps to restore the balance of dopaminergic activity in the central nervous system. Meanwhile, dantrolene is a muscle relaxant that acts by inhibiting calcium release from sarcoplasmic reticulum. A case control analysis by Rosenberg et al (1989) demonstrated the use of bromocriptine together with supportive measures shortened the mean time to clinical response from 6.8 to 1.03 days. In our case, the use of bromocriptine was effective in improving his symptoms.

ECT was commenced in our patient as he had persistent catatonia despite the resolution of the acute metabolic symptoms of NMS. ECT may be effective if psychotic symptoms are refractory to pharmacotherapy or psychiatric disease-associated catatonia cannot be excluded. It can also be used
as a treatment for NMS, because it supposedly increases circulating dopamine level in the central nervous system. A neuromuscular blocking agent (NMBA) is administered during ECT for the prevention of complications such as myalgia and bone fracture. Succinylcholine is the most commonly used NMBA as it has a short duration of action and rapid recovery. In view of the common pathophysiology shared by NMS and MH, there is a likelihood of a patient with history of NMS to be more prone to develop MH. Despite this belief, there have been several case reports and reviews that demonstrate the safe use of succinylcholine for ECT in those with history of NMS.

An alternative method of muscle relaxation in a patient with history of NMS is non-depolarising muscle relaxants. In our case, we have used rocuronium and reversed with sugammadex. The option of 0.6 mg/kg rocuronium-16 mg/kg sugammadex as an alternative to succinylcholine was first described by Hoshi et al (2011). Kadoi et al (2011) compared the recovery times from 0.6 mg/kg rocuronium-induced muscle relaxation after reversal with three different doses of sugammadex, with recovery from succinylcholine, and showed that 8 mg/kg of sugammadex produces equally rapid recovery from rocuronium-induced muscular relaxation compared with spontaneous recovery from 1 mg/kg succinylcholine in terms of induction time of neuromuscular effects and recovery from the effects. In our patient, we have successfully conducted ECT using a combination of 0.6mg/kg rocuronium and 2mg/kg Sugammadex.

CONCLUSION

In view of a common pathophysiology that has been suggested between NMS and MH, the possibility of patients with a history of NMS being vulnerable to developing MH is an important factor when considering anaesthesia for ECT. Hence, we conclude that rocuronium-sugammadex is a safe and effective alternative in patients with a history of NMS.

REFERENCES: