

# Malignant Hyperthermia In The Indian Subcontinent: Non-availability Of Dantrolene - A Cause For Concern?

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## Abstract

We report the first case of malignant hyperthermia from the Indian sub-continent and raise the issue of non-availability of dantrolene in a country, where this clinical entity was thought not to exist.

## INTRODUCTION

The overall incidence of malignant hyperthermia in literature has been quoted as 1: 40,000 to 1:50,000 anaesthetics in adults and 1: 15,000 anaesthetics in children<sup>1,2</sup>. it is reasonable to suppose that in a busy, tertiary care hospital in which about 15 –20,000 anaesthetics are conducted annually, one would expect to come across 1-2 cases annually, at the very least. Classic malignant hyperpyrexia, typically heralded by hyperthermia, tachypnoea, tachycardia and muscle rigidity along with rhabdomyolysis and myoglobinuria, has surprisingly never been reported from the Indian sub-continent, neither as published case reports or as presentations in clinical meetings or conferences. We therefore feel it necessary to report the first case of malignant hyperthermia, from the subcontinent of India, and highlight two pertinent issues.

## CASE REPORT

A twenty-one year old sixty-kilogram male from Nepal was diagnosed to have a papillary carcinoma of the thyroid (confirmed by fine needle aspiration cytology) and was scheduled to have a radical thyroidectomy under a general anaesthetic. Pre-operative examination revealed an exceptionally muscular young man, with a 5x6cm thyroid nodule on the right side of the neck. He had no systemic abnormalities, and no evidence of hyperthyroidism. Mallampati grade was I. There was no past anaesthetic history and no family history of anaesthetic related morbidity or mortality.

The patient was premedicated with oral diazepam, 10 mg on the day of surgery and injection morphine 10mg and phenergan 25mg intramuscular one hour before the

anaesthetic. Monitoring established before induction of anesthesia consisted of ECG, non-invasive blood pressure (NIBP) and pulse oximetry (Datex Cardiocap 2). Capnography and gas monitoring (Datex Capnomac Ultima) were introduced at the time of induction. The patient was induced with a sleep dose of thiopentone, and endotracheal intubation facilitated with 8mg of vecuronium. Artificial ventilation was given through a closed circuit, using the Ohmeda 7000 ventilator, with a tidal volume of 600ml, respiratory rate of 10 per minute and a peak airway pressure of 15cm of water. Anesthesia was maintained with 30% oxygen in nitrous oxide and 0.5-1% isoflurane. Analgesia was supplemented with incremental doses of injection morphine. Patient was fully relaxed at intubation and there were no hemodynamic fluctuations at induction. Surgery commenced after he was positioned in the thyroid position. Half an hour after start of surgery, the end-tidal carbon dioxide concentration increased from 35mmHg to 45mmHg, within about fifteen minutes, without any change in minute ventilation. No fault was detected in the anesthetic circuit or the anesthesia machine. Examination of the patient's lungs was apparently normal. Arterial blood gas analysis also showed a respiratory acidosis (PaO<sub>2</sub> 130mmHg, PaCO<sub>2</sub> 45mmHg, pH 7.35, HCO<sub>3</sub> 23.5mmol/L), so the minute ventilation was increased, but the hypercarbia kept increasing steadily. The arterial oxygen saturation as well as pulse rate, blood pressure and ECG were normal at this time. Patient felt hot to touch through the drapes, and a temperature probe inserted in the nasopharynx revealed a temperature of 39°C. Since malignant hyperpyrexia is not reported from India or neighbouring countries, and malaria or dengue is more often seen in these parts, a presumptive diagnosis of malaria/dengue was made. Injection

paracetamol was given intramuscular, and cooling measures initiated. However, the patient started showing a gradual tachycardia and an ETCO<sub>2</sub> that increased from 35mmHg to 65mmHg within 45 minutes. The blood gas analysis with FiO<sub>2</sub> of 0.5 showed PaO<sub>2</sub> of 147.4mmHg, PaCO<sub>2</sub> 63.5mmHg, pH7.17, HCO<sub>3</sub> 19.7mmol/L, serum sodium 145mmol/L and potassium was 6.6mmol/L. The temperature had increased by now to 41°C and a doubt of it being malignant hyperpyrexia was entertained.

Surgery was discontinued. The anesthetic circuit was changed to a Bains circuit, patient ventilated with 100% oxygen and respiratory rate increased to minute ventilation of more than 10L per minute. Cooling consisted of lowering the ambient temperature of the room, iced lavage through the Ryles tube (which was inserted for this purpose), cold intravenous fluids and iced sponging of the whole body. A central venous line was inserted (internal jugular pressure was 8 mm of mercury) and a urinary catheter inserted. Despite these measures, the patient's temperature went up to 44°C, and end-tidal carbon dioxide concentration till 114 mmHg. His pulse rate was 150/min but regular and NIBP was 90/60. Dantrolene is not available in India, presumably because it has never been required, and only supportive measures could be undertaken. Blood samples were sent to the laboratory for estimating creatinine phosphokinase (CPK), CPK (MB) and lactic dehydrogenase (LDH). Based on the blood gas report, 200 mmoles of injection sodabarbonate was given, insulin dextrose drip was started, and forced diuresis established, using furosemide. In the meantime, the oxygen saturation had fallen to 94% and blood pressure to 80/50, so patient was put on 100% O<sub>2</sub>, a dopamine infusion was started to maintain a blood pressure of at least 90mm Hg systolic and the patient shifted to the intensive care unit and ventilated with the Drager Evita2 ventilator, using the SIMV mode with a rate of 30 per minute, in an attempt to bring down the carbon dioxide levels of the blood. While shifting, the patient was noted to be extremely rigid and difficult to move.

Two and half hour after the start of the episode and about half an hour after shifting to the intensive care unit, the patient developed diffuse bleeding from all sites. A diagnosis of diffuse intravascular coagulation (DIC) was made, a coagulation profile was asked for, and he was infused with fresh blood, fresh frozen plasma and platelet concentrates over the next 2 hours. By this time his temperature as well as the end-tidal carbon dioxide

concentration had begun to decrease and his hemodynamic and blood gas parameters gradually deteriorated, despite maximum inotropic support (ETCO<sub>2</sub> 65mmHg, temperature 40°C, PaO<sub>2</sub> of 51mmHg on FiO<sub>2</sub> of 1.0, PaCO<sub>2</sub> 68.5 mmHg, pH 7.09, HCO<sub>3</sub> 15.8 mmol/L, base excess -13.4, serum sodium 139mmol/L and potassium was 5.9mmol/L). He continued to bleed from all sites, developed hematuria and subsequently anuria. Twelve hours after the initial episode, patient suffered a cardiac arrest, and despite all resuscitative measures, could not be revived. The laboratory investigations received, in the mean time showed the following values:

CPK 29,900 U/L (N= 0-180 U/L); CPK (MB) 40 U/L (N= 0-20 U/L); LDH 1245 IU/ml (N= 140-300 IU/ml); prothrombin time (PT) 4min (Control 11 seconds); aprotinin partial thromboplastin time (APTT) 7min (Control = 45sec.); fibrinogen degradation products (FDP) 320ugm/ml (N=0-10ugm/ml). These values along with the clinical course of the disorder clinched the diagnosis of malignant hyperthermia with DIC

The patient lived in India with his elder brother, while the rest of the family (another brother, one sister, mother and father) resided in Nepal. The nature of the episode was explained to the brother, and he was advised to get his resting CPK level estimated, which was found to be raised (384units/L). The same test has been advised for the rest of his family, who are staying in a small village of Nepal. Since this test is not being done there, they along with the elder brother have been given laminated cards, mentioning their disposition to have malignant hyperpyrexia, and advised to mention this to a doctor, when necessary. The caffeine halothane contracture test is not available in this region and so could not be done on any of the family members.

## **DISCUSSION**

This appears to be a very typical case of malignant hyperthermia probably triggered by isoflurane in a susceptible patient. A differential diagnosis, in this patient could have been a thyroid storm or hyperthermia due to associated infections. However, the rapidity of onset of the clinical condition, and non-responsiveness of the patient to routine anti-pyretic and body cooling measures precluded any other diagnosis<sub>4</sub>.

There are several reasons for reporting this case. MH, which is a clinically heterogeneous autosomal dominant, pharmacogenetic disorder, with a reduced penetrance and

variable expression, has been reported from many countries. Epidemiological studies have been reported to be difficult in MH and no mention is made in literature, if a particular race is more or less likely to develop this syndrome<sup>1, 2,3</sup>. Of-course there is no reason to believe that a particular geographical region or people from a particular background may have a lower susceptibility to the development of MH<sup>5,6</sup>, but it is a fact, that no patients have been reported from the Indian subcontinent, either in Indian or international literature. Clinical teaching in Indian medical colleges has usually focussed on MH as not being seen on the Indian subcontinent. In light of the above, the diagnosis of MH was delayed in this patient, although the presentation was typical. On the other hand, the clinically related syndrome of malignant neuroleptic syndrome<sup>2, 3</sup> has been described from this region and is well documented<sup>7, 8</sup>.

The second reason for reporting this case is the non-availability of the drug dantrolene in India. The

anaesthesiologists in India have not demanded that this drug be made available, presumably because its need was not felt. The report of a single case from this sub-continent raises pertinent questions about guidelines of use and availability of dantrolene, which need to be addressed.

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