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Unusual hyperthermia related to general anaesthesia in an Anatolian shepherd dog

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ABSTRACT: This case report describes the diagnosis, the treatment options available in the absence of dantrolene and outcome of anaesthesia-related hyperthermia seen for the first time in an Anatolian shepherd dog. The case consisted of a nine-month-old male Anatolian shepherd dog with bilateral antebrachium fractures. For surgical treatment, the patient was pre-medicated with xylazine; anaesthesia was induced using ketamine and maintained with isoflurane. Approximately 40 minutes after isoflurane administration, tachypnoea, tachycardia, increase in body temperature and rigidity in the forelegs and masseter muscles was noticed. Inhalation anaesthesia was discontinued and hyperventilation was performed with 100% O_2. Due to its vasodilatory properties, diazepam was administered both to achieve muscle relaxation and to decrease body temperature. Alfentanil was used in an attempt to lower respiratory and heart rates. Intravenous administration of cold crystalloid solutions and external ice packs was used to lower body temperature. All these interventions kept the patient alive.

Keywords: hyperthermia; respiratory rate; heart rate; muscle rigidity; diazepam; alfentanil

Malignant hyperthermia (MH) is a disorder of the skeletal muscles manifesting in a hypermetabolic response to inhalation anaesthetics and depolarising muscle relaxant drugs (Brunson and Hogan 2004).

Findings include an increase in body temperature, tachypnoea, tachycardia, rigidity in skeletal muscles as well as in serum glucose, potassium (K^+) and creatine kinase levels (Kirmayer et al. 1984; Chohan and Greene 2011).

Dantrolene sodium is most commonly used to treat MH. However, in the absence of dantrolene, alternative drugs, effective in lowering body temperature and eliciting muscle relaxation, may be used (Lemke 2007; Adami et al. 2012).

Malignant hyperthermia has been reported in dog breeds such as Greyhounds and Saint Bernards (Chohan and Greene 2011). In this paper, we present the first description of hyperthermia in an Anatolian shepherd dog and evaluate the treatment options.

Case description

A nine-month-old male Anatolian shepherd dog weighing 20 kg was examined for bilateral antebrachium fractures. Surgical treatment was planned. The pre-anaesthesia red blood cell, haemoglobin, haematocrit, white blood cell, alanine aminotransferase, aspartate aminotransferase, creatine kinase, glucose, total protein, urea and creatinine results of the patient were within limits.

The dog was sedated with 1 mg/kg xylazine (Rompun, Bayer, Turkey) *i.v.* General anaesthesia was induced with 5 mg/kg ketamine (Alfamine, Alfasan International B.V., Holland) *i.v.* and maintained with 2% isoflurane in oxygen.

Heart rate (HR), heart rhythm, respiratory rate (RR) and oxygen saturation (SpO_2) were monitored using an ECG monitor (Advisor V9212 AR, Surgivet, USA). Rectal temperature was measured using a digital thermometer. An isotonic crystalloid solution (0.9% sodium chloride, Eczacibasi-

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Baxter, Turkey, 10 ml/kg/h) *i.v.* was administered. Measurements were recorded every five minutes.

Approximately 40 minutes after isoflurane administration, an increase in the patient's RR and HR was observed. The RR of 12 breaths/min recorded throughout anaesthesia increased to 40 breaths/min. The HR, which had remained stable at a mean level of 76 beats/min, increased to 150 beats/min. The body temperature was measured as 41.8 °C. Mild rigidity was observed in the forelegs and the masseter muscles. A diagnosis of hyperthermia related to anaesthesia was made and isoflurane was discontinued. The patient was hyperventilated with 100% O_2 at an RR of 20 breaths/min manually. Blood gases (ITC Edison, NJ 08820, USA) were examined in samples taken from the jugular vein.

Since dantrolene was unavailable, 0.5 mg/kg diazepam (Diazem, Deva, Turkey) *i.v.* was used to produce vasodilatation, which in turn would decrease body temperature and provide muscle relaxation. Alfentanil (10 µg/kg, Rapifen, Janssen-Cilag, Belgium) *i.v.* was added to the treatment to try and decrease RR and HR. Attempts to lower body temperature were made with cold 0.9% sodium chloride (90 ml/kg/h, *i.v.*), external ice packs on the body surface and alcohol application on the soles of the feet.

Post-operative analgesia to eliminate pain due to surgical intervention was achieved with meloxicam tablets (Melox, Nobel, Turkey) given for five days at a dose of 0.1 mg/kg. The dog was observed by a veterinary surgeon regularly.

The patient exhibited a pattern of seizures manifesting in muscle contractions, in the forelegs and the masseter muscles, twice daily after recovering from anaesthesia and during the following three days. Muscle spasms were particularly prominent in the masseter muscles and extensor muscles of the forelegs. Diazepam (0.5 mg/kg, *i.v.*) injection was administered to control these contractions occurring during the seizures.

On day four, a brain tomography was performed to investigate any potential structural or inflammatory lesions in the brain as the patient was unable to stand up and suffered from occasional seizures. For this, the patient was re-anaesthetised. Anaesthesia was induced with 2 mg/kg propofol (Propofol, Fresenius, Sweden, *i.v.*). Approximately 15 minutes later, the body temperature increased (39.6 °C) and rigidity was observed particularly in the masseter muscles. Anaesthesia was discontinued and the patient was hyperventilated with 100% O_2. The same cooling methods were used to decrease the body temperature. Intravenous diazepam was given to provide muscle relaxation.

On day five, blood analyses were carried out. Due to the high creatine kinase values, 0.5 g/kg mannitol in a 20% solution (Mannitol, Eczacibasi-Baxter, Turkey) was administered *i.v.* The treatment was supplemented with 2 mg/kg frusemide (Lasix, Aventis Farma, Turkey) *i.v.* Due to a high level of leucocytes, 20 mg/kg ceftriaxone (Novosef, Zentiva Ilac, Turkey) intramuscularly were administered for five days. Crystalloid solutions (0.9% sodium chloride) were administered at 20 ml/kg/h, *i.v.* for 10 days. Blood analyses were repeated on the following days.

Following the diagnosis of hyperthermia, the surgical intervention was completed and the other leg was bandaged. Muscle relaxation was established with diazepam. RR and HR returned to limits with alfentanil. Body temperature decreased to 38 °C with cooling applications. The dog recovered from anaesthesia; however, it was seen to be in a state of tetraparesis.

Blood gas analysis results were pH 7.32 (7.31–7.42), $PvCO_2$ 49 (32–49) mm Hg, HCO_3^- 23.1 (20–29) mmol/l, PvO_2 82 (24–48) mm Hg, SpO_2 95% (93–100%), K 8.8 (3.5–5.8) mmol/l.

No lesions were identified in tomography.

On day five, blood analysis results were white blood cell 36.60 (6.00–17.00) × 10^9/l, glucose 12.49 (3.3–6.94) mmol/l, urea nitrogen 51.77 (2.50–9.64) mmol/l, creatinine 132.6 (35.4–159.1) µmol/l, aspartate aminotransferase 142 (5–55) IU/l, alanine aminotransferase 51 (5–60) IU/l, creatine kinase 2213 (10–200) IU/l, Ca 3.05 (1.93–2.83) mmol/l, P 3.0 (0.68–2.03) mmol/l, $PvCO_2$ 44 mm Hg, PvO_2 53 mm Hg, SpO_2 85%, Na 172 (144–160) mmol/l and K 3.1 mmol/l.

On day seven, white blood cell levels had returned to within limits. However, urea nitrogen was 17.49 mmol/l and creatinine was 159.1 µmol/l.

On day 13, urea nitrogen was 29.63 mmol/l, creatinine 106 µmol/l, aspartate aminotransferase 116 IU/l and alanine aminotransferase 95 IU/l.

During the whole process the dog was given assistance with oral food and water intake. The patient was kept alive for 16 days. However, since there was no improvement in the clinical condition, the patient was euthanised upon the owner's request.

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DISCUSSION AND CONCLUSIONS

Malignant hyperthermia (MH) is a disorder of the skeletal muscles occurring as a result of mutation in the *RYR1* gene (Brunson and Hogan 2004). Inhalation anaesthetics, trauma and stress may trigger MH (Gronert and Milde 1981; Nelson 1991). In this case, pre-anaesthesia examination, ECG and blood values gave normal results. Hyperthermia occurred as a result of isoflurane anaesthesia.

While body temperature normally decreases during general anaesthesia, it increases in MH. This increase may occur 10–70 minutes after halothane or isoflurane administration in patients pre-medicated prior to general anaesthesia (Nelson 1991; Chohan and Greene 2011; Adami et al. 2012). Due to their protective effects against MH, the findings of MH may be delayed (Gronert and Milde 1981; O'Brien et al. 1983). In this case, anaesthesia was continued since no abnormal temperature increase was determined in the first 40 minutes of isoflurane. Premedication of the patient using xylazine and induction with ketamine generated a protective effect and delayed the increase in body temperature.

The patient had been breathing spontaneously during anaesthesia until, 40 minutes after isoflurane administration, tachypnoea occurred. Tachypnoea that develops due to increasing levels of CO_2 in patients with spontaneous respiration is an expected outcome for MH (Nelson 1991). In the authors' opinion, the delay in the tachypnoea was due to the effects of the premedication.

Heart rate increased above the limits, accompanied by mild rigidity (Roberts et al. 2001) in the foreleg and the masseter muscles (Krause et al. 2004). A definitive diagnosis based on detection of the gene mutation (Chohan and Greene 2011) could not be performed due to the lack of appropriate tools and reagents. A diagnosis of hyperthermia was made according to the clinical findings observed in the patient.

Since dantrolene (Adami et al. 2012) was unavailable in the hospital, alternative treatment options were utilised to keep the patient alive. Diazepam is an effective muscle relaxant and anticonvulsant (Lemke 2007). The vasodilatation caused by the drug (Adami et al. 2012) also leads to a lowering of body temperature. The drug provided sufficient muscle relaxation following administration.

Alfentanil, which contributes to lowering body temperature by producing vasodilatation and curbing raised HR and RR (Lamont and Mathews 2007), was added to the treatment. This procedure reduced the HR and RR to within normal ranges. Lidocaine was not chosen for the treatment of tachycardia due to the assumption that the drug would increase myoplasmic calcium and worsen the hyperthermic condition (Chohan and Greene 2011).

The increase in PvO_2 was attributed to the hyperventilation performed on the patient. The increase in K^+ resulted from the damage occurring in muscle fibres due to the progressive spasms in the muscle (Nelson 1991; Kahraman et al. 2009). Considering the fact that treatment would have to be given in the event of permanent hyperkalaemia (Kirmayer et al. 1984), and since K^+ values had returned to within limits, no treatment was deemed necessary.

It has been reported that propofol does not trigger MH and is thus a safe anaesthetic for MH patients (Fruen et al. 1995; Barhoumi et al. 2007; Migita et al. 2007). In this case, hyperthermia developed again following propofol administration. This result shows that, in predisposed patients, propofol may trigger hyperthermia to the same extent as inhalation anaesthetics (Murao 2010).

Increases in creatine kinase, glucose and P are expected findings in MH on the day after tomography (Kirmayer et al. 1984). The extreme increase of creatine kinase in this patient was due to rhabdomyolysis (O'Brien et al. 1983; Antognini 1995) developing as a result of the surgical treatment of the fractures caused by trauma and hyperthermia. The increase in urea values was due to the impairment of kidney perfusion caused by the high density of myoglobin and proteins as a result of rhabdomyolysis (Kahraman et al. 2009). The patient was given mannitol and frusemide to protect against kidney damage.

Neither the diazepam nor alfentanil used for treatment have any effect on the mechanism of MH. However, in situations where dantrolene is unavailable, both drugs can be considered as treatment options for their ability to both lower HR and RR as well to decrease body temperature by producing vasodilatation and sufficiently relaxing the muscles. Also, alfentanil administration decreases the pain caused by surgery and alleviates stress (Brunson and Hogan 2004) and, therefore, may prevent the triggering of hyperthermia.

After unexpectedly developing hyperthermia during anaesthesia, the dog was treated as de-

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scribed above and kept alive for 16 days. However, no change was observed in the clinical condition. The factors adversely affecting the treatment outcome in this case included the unavailability of dantrolene, the administration of propofol to the patient for the tomography, subsequent recurrence of hyperthermia and the trauma caused by surgical correction of the fracture. After gaining the owner's consent, the dog was euthanised.

In conclusion, in this report we have for the first time described complications related to anaesthesia in an Anatolian shepherd dog. Further, we outline the treatment options available in the absence of dantrolene and show that propofol may also trigger hyperthermia in dogs suspected of having this condition.

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