Introduction

Hyperkalemic periodic paralysis (HYPP) is a well documented hereditary disease most commonly associated with Quarter horses descendant from a particular stallion (Aleman 2008). Episodes of HYPP during the peri-operative period have been regularly reported since the disease was first identified by Cox in 1985 (Cox 1985; Robertson et al. 1992; Traub-Dargatz et al. 1992; Baetge 2007; Bailey et al. 1996; Cornick et al. 1994; Moody 1995). Of these cases, a limited number have resulted in the successful management of clinical signs (Cornick et al. 1994; Moody 1995). One previous report has documented an episode of HYPP during general anaesthesia, following a previous uneventful anesthetic, though the diagnosis of HYPP was not confirmed (Cornick et al. 1994). We report the onset of signs leading to the presumed diagnosis and successful treatment of HYPP in a horse during general anaesthesia. A previous anesthetic, one week earlier, did not result in an episode of HYPP. The presumptive diagnosis was later confirmed by DNA analysis.

Case Report

A three year old, 400 kg, castrated male Quarter Horse was presented to the Western College of Veterinary Medicine equine service with a history of epistaxis. Following endoscopy, a diagnosis of right guttural pouch mycosis involving the internal carotid artery was made and balloon-tipped catheter occlusion of the artery was planned. Pre-operative haematology was unremarkable (haematocrit, 27%; total protein, 7.0 g dL^{-1}) and the last observed haemorrhage occurred one week previously. The horse was bright, alert and responsive and rectal temperature (38.1°C), heart rate (HR; 48 beats min^{-1}) and respiration rate (fR; 16 breaths min^{-1}) were within normal limits. A cross

match was performed with a sample from a donor mare.

The horse was fasted overnight and water was available ad libitum. On the morning of surgery the right jugular vein was cannulated (BD Angiocath, 14 GA 5.25 in, Becton Dickinson Infusion Therapy Systems Inc. Sandy, Utah, U.S.A.) and antibiotics (Penicillin G Sodium, 22000 IU kg^{-1}, Novopharm, Toronto, Ontario, Canada) and non-steroidal anti-inflammatory drugs (Phenylbutazone, 4.4 mg kg^{-1}, 200 mg mL^{-1}, Vetoquinol, Lavaltrie, Quebec, Canada) administered intravenously (IV) 30 minutes prior to induction. Premedication consisted of xylazine hydrochloride (1 mg kg^{-1}, IV; Rompun, 100mg mL^{-1}, Bayer (Healthcare), Toronto, Ontario, Canada) and butorphanol tartrate (0.05 mg kg^{-1}, IV; Torbugesic, 10mg mL^{-1}, Wyeth, Guelph, Ontario, Canada). Following sedation, general anaesthesia was induced with diazepam (0.1 mg kg^{-1}, IV; Diazepam, 5mg mL^{-1}, Sandoz, Burlington, Ontario, Canada) immediately followed by ketamine hydrochloride (2 mg kg^{-1}, IV; Ketalean, 100mg mL^{-1}, Bimeda-MTC, Animal Health Inc., Cambridge, Ontario, Canada). Induction and orotracheal intubation (26 mm, ID) was achieved without difficulty. After transfer to the operating theatre and positioning in left lateral recumbency, the horse was connected to a large animal anesthetic machine and anaesthesia maintained with isoflurane (Isoflo, Abbott, Saint Laurent, Quebec, Canada) carried in oxygen. Monitoring equipment was connected and consisted of sidestream capnography, electrocardiography (base-apex configuration; ECG), direct systemic arterial blood pressure (BD Insyte, 20 GA 1.16 in, Becton Dickinson Medical(s) Pte Ltd., Singapore; placed in the right metatarsal artery), pulse oximetry and rectal temperature. The capnograph was autocalibrated and the pressure transducer equilibrated with atmospheric pressure prior to use. Physiologic parameters were displayed and recorded

every five minutes (Cardiocap/5, Datex-Ohmeda, Louisville, CO, U.S.A.). The anaesthetic period was uneventful: mean direct systemic arterial blood pressure (mABP) ranged from 60 – 90 mmHg (8 - 12 kPa), partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) ranged from 36 – 49 mmHg (4.8 - 6.5 kPa), and heart rate ranged from 35-55 beats min^{-1}. Dobutamine (Dobutamine, 12.5 mg mL^{-1}, Sandoz (Canada Inc.), Burlington, Ontario, Canada) was administered intravenously as required to support cardiovascular function and ventilation was controlled with intermittent positive pressure ventilation (IPPV; tidal volume [V_T], 4 L; fR 7 – 10 breaths min^{-1}). End-tidal isoflurane concentration was 1.3 % for the majority of the procedure. Lactated Ringer's Solution (LRS; Lactated Ringer’s, Hospira (Healthcare Corporation), Montreal, Quebec, Canada) was administered IV at a rate of 10 mL kg^{-1} hr^{-1} through a second IV cannula in the right medial saphenous vein. One arterial blood sample was taken using an anaerobic technique thirty minutes after induction of anaesthesia and analysed immediately (Table). Surgery proceeded without complication and estimated blood loss was less than 50 mL. The duration of the anesthetic period was 2.5 hours. Recovery to standing was smooth and rapid (20 minutes). Xylazine (0.25 mg kg^{-1}, IV) was administered prior to transfer to the recovery box.

Seven days following surgery, the animal experienced an episode of acute epistaxis in its stall. Bedding in the stall prevented an accurate estimation of blood loss though the total volume was estimated as less than 2 L. The animal was agitated and difficult to approach. Acepromazine (0.025 mg kg^{-1}, IV), xylazine (0.4 mg kg^{-1}, IV) and butorphanol (0.04 mg kg^{-1}, IV) were administered prior to calling the anaesthesia service. Due to the presence of large blood clots, a thorough evaluation of the right guttural pouch had not

been possible at the time of the initial endoscopic evaluation. The episode of epistaxis after occlusion of the internal carotid artery was attributed to involvement of the external carotid or maxillary artery. Therefore the decision was taken to ligate the right external maxillary artery and occlude the right major palatine artery with a balloon-tipped catheter. The right jugular vein was cannulated (14 GA 5.25 in) and a blood sample sent for haematology (haematocrit, 26%; total protein 5.9 g dL^{-1}). Anaesthesia was induced with diazepam (0.1 mg kg^{-1}, IV) immediately followed by ketamine (2 mg kg^{-1}, IV) and orotracheal intubation performed without difficulty (26 mm ID). The animal was positioned in left lateral recumbency, connected to a large animal anesthetic machine and IPPV initiated (V_T, 4 L; fR, 8 breaths min^{-1}; peak inspiratory pressure [PIP], < 20 cmH_2O). Anaesthesia was maintained with isoflurane from a precision vaporizer in oxygen, and the end-tidal isoflurane was between 1.2 – 1.3% throughout the anesthetic period. Instrumentation and monitoring was as for the first anaesthesia. A whole blood transfusion had been started pre-operatively and was continued following transfer to the operating theatre (approximately 1mL kg^{-1} hr^{-1}). Lactated Ringer's solution was administered through a separate IV cannula (right medial saphenous vein) at 10 mL kg^{-1} min^{-1}. During the anesthetic mABP ranged from 55 – 80 mm Hg (7.3 - 10.7 kPa). The first arterial blood gas analysis (ABG 1; Table) taken approximately 40 minutes after induction showed a respiratory acidosis and V_T was increased to 5L. Respiratory rate was increased to 10 breaths min^{-1} following a second ABG (ABG 2; Table) 40 minutes later. Up to this point mABP varied frequently between 55 – 70 mmHg (7.3 - 9.3 kPa) and heart rate varied between 50 – 85 beats min^{-1}. Dobutamine was infused continuously between 0.2 – 0.4 µg kg^{-1} min^{-1}. Systolic (sABP) and diastolic (dABP) direct

systemic arterial blood pressures ranged between 80 – 100 mmHg (10.7 - 13.3 kPa) and 45 – 60 mmHg (6.0 - 8.0 kPa) respectively. Administration of butorphanol (0.04 mg kg^{-1}, IV) was associated with a decrease in HR (from 85 to 65 beats min^{-1}), and mABP increased from 60 to 75 mm Hg (8.0 - 10.0 kPa) following IV ephedrine (0.05 mg kg^{-1}; administered 15 minutes after butorphanol). A third blood sample (ABG 3; Table) showed a decrease in $PaCO_2$ and a slight increase in potassium (from 3.6 mmol L^{-1} [ABG1] to 4.2 mmol L^{-1}; reference range 3.5 – 5 mmol L^{-1}).

Approximately 45 minutes after the previous ABG, an increase in $P_{ET}CO_2$ from 52 to 61 mmHg (6.9 - 8.1 kPa) was noted in addition to muscle fasiculations over the animal's flanks and a sinus tachycardia (Fig. 1a) of 78 beats min^{-1} (mABP was 70 mm Hg [9.3 kPa]). Additionally, the ECG showed a narrowed T wave with increased amplitude (Fig. 1a) Ventilatory parameters were unchanged (V_T, 4L; fR, 8; PIP < 20 cm H_2O), the vaporizer had an adequate amount of anesthetic agent and the depth of anaesthesia appeared unchanged from examination of palpebral reflexes and neck muscle tone. The partial pressure of inspired CO_2 was negligible (less than 2 mm Hg [0.3 kPa]). Rectal temperature was unchanged, at 35.5 °C. An ABG (ABG 4, Table) taken at this time revealed a serum potassium concentration of 7.2 mmol L^{-1} and $PaCO_2$ of 78 mm Hg (10.4 kPa).

Hyperkalaemic periodic paralysis was suspected on the basis of clinical signs, ECG changes, ABG results and breed. Over the next 10 minutes respiratory rate was increased to 12 breaths min^{-1} and calcium gluconate (0.1-0.2 mg kg^{-1} min^{-1}; Calcium gluconate, 23%, Calgary, Alberta, Canada) and dextrose 5% in saline (5 mL kg^{-1} hr^{-1}; Dextrose, 50%, Bimeda-MTC, Animal Health Inc., Cambridge, Ontario, Canada) were

administered through two separate IV cannulae. Fluid therapy was changed from LRS to NaCl 0.9% and the whole blood transfusion was stopped. A second dose of ephedrine was given (0.05 mg kg^{-1}, IV) as mABP had decreased to 55 mm Hg (7.3 kPa). The mABP increased to 85 mm Hg (11.3 kPa) shortly afterwards and remained above this level for the remainder of the anesthetic. Approximately 10 minutes after IV calcium gluconate administration had been started, the ECG showed T waves with normal morphology (Fig. 1b; complex six is a premature complex of atrial or junctional origin). Subsequent ABGs (ABG 6 and 7, Table) showed a gradual decrease in $PaCO_2$, HCO_3^{-1}, and potassium, although these parameters remained supranormal. The surgical procedure was successful and terminated one hour after signs associated with HYPP were first observed. The animal was transferred to the recovery box and romifidine (0.01 mg kg^{-1}; Sedivet, 10 mg mL^{-1}, Boehringer Ingelheim, Burlington, Ontario, Canada) administered IV. Anesthetic duration was 4 hours. The total volumes of fluids administered were: LRS, 15L; NaCl 0.9%, 3L; dextrose 5%, 2L; whole blood, 1.5L. Intravenous dextrose and normal saline were continued during recovery. Regular (NPH) insulin (0.05 IU kg^{-1}, subcutaneously; HumulinN NPH, 100 U mL^{-1}, Lilly, Toronto, Ontario, Canada) was administered in recovery box. Unassisted recovery to standing was uneventful and completed in 45 minutes. A jugular venous blood sample (VBG, Table) taken after standing showed a return to normal serum potassium levels. Analysis of the whole blood intended for transfusion revealed a potassium concentration within reference range (Table). Several hours later, a jugular venous blood sample showed a normal potassium concentration (3.8 mmol L^{-1}) and the horse showed no signs of muscle fasiculations or weakness. Questioning of the owner confirmed genetic lineage

to a known carrier of HYPP and a blood sample submitted for DNA analysis confirmed a diagnosis of HYPP (heterozygous).

Discussion

Since the initial reports of HYPP, further investigation identified an autosomal dominant mode of inheritance, resulting in abnormal sodium channels in skeletal muscle (Cox 1985; Naylor et al. 1992; Pickar et al. 1991; Spier et al. 1993; Steiss & Naylor 1986). The defective alpha subunit gene and resultant amino acid substitution (leucine for phenylalanine) form sodium channels that fail to inactivate following depolarisation, causing a reduction (more positive) in the resting membrane potential (RMP) as a result of the increase in sodium permeability (Rudolph et al. 1992a, b). The reduced RMP allows potassium to diffuse out of the cell, potentially leading to hyperkalaemia. As the RMP approaches the threshold potential, potassium efflux increases, eventually leading to clinical signs of HYPP (Aleman 2008; Meyer et al. 1999). The incidence of heterozygous or homozygous carriers within the Quarter Horse population is between 0.4 and 4% (Aleman 2008; Naylor 1994). Factors associated with the development of a clinical episode of HYPP in horses include stress, diets high in potassium, anaesthesia, transportation and concurrent disease (Meyer et al. 1999). In this case, possible reasons why the second anesthetic resulted in clinical symptoms whilst the first did not, include the occurrence of pre-operative stress and agitation associated with sudden haemorrhage, high levels of activity and handling within the stall, and the hypercapnia which developed soon after induction, prior to an elevation in serum potassium. Prior to potassium measurement the whole blood transfusion was considered a source of external potassium as blood products may contain high levels of potassium resulting

182 from hemolysis (Hohenhaus 2006). From published reports of peri-operative HYPP,
183 common clinical signs include elevated $P_{ET}CO_2$ and hypercapnia, muscle fasiculations
184 and hyperkalaemia associated with altered T wave morphology (narrowing and
185 increased amplitude) (Baetge 2007; Bailey et al. 1996; Cornick et al. 1994; Moody
186 1995; Robertson et al. 1992; Traub-Dargatz et al. 1992). Many of these signs overlap
187 with those of the hypermetabolic syndrome malignant hyperthermia (MH; hyperthermia,
188 muscle contractions and rigidity, hyperkalaemia, hypercapnia, tachypnea, tachycardia,
189 systemic hypertension, arrhythmias, sudation), which has been confirmed and
190 suspected in the horse (Aleman et al. 2005, 2009; Klein et al. 1989). Compared with the
191 other reports of confirmed/ suspected HYPP during the perioperative period, Cornick et
192 al. (1994) reported a suspected case which exhibited repeated hyperthermia during
193 several anesthetics, peaking at a body temperature of 40.2°C.
194 In the case reported here the differentiation between MH and HYPP was based on the
195 stability of rectal temperature, and absence of sudation and muscle rigidity. Similar to
196 our case, previous reports have reported tachycardia during an episode of HYPP
197 (Bailey et al. 1996; Cornick et al. 1994). In conscious horses, hyperkalaemia results in
198 bradycardia and a progressive deterioration of the cardiac rhythm as the RMP
199 approaches and eventually exceeds the threshold potential. The ECG changes mirror
200 serum potassium concentration, progressing from a widening and flattening of P waves,
201 to an increase in P-R interval, S-T segment elevation, increased T wave amplitude,
202 widening of the QRS complex and eventual ventricular fibrillation (Meyer et al. 1999;
203 Spier et al. 1990). This apparent paradox of tachycardia in the face of hyperkalaemia
204 may reflect the opposing effects of hyperkalaemia and hypercapnia on heart rate as

these reports also reported the concurrent presence of hypercapnia. The site of muscle fasciculation varies between reports and the following sites have been described: thoracic limb alone, all limbs, head, generalized (Baetge 2007; Bailey et al. 1996; Cornick et al. 1994). As reported by Bailey et al. (1996) and Baetge (2007), we also found that the hypercapnia was difficult to control despite IPPV. Recorded levels of serum potassium associated with HYPP in the perioperative period range from 3.5 – 8.2 mmol L^{-1} (Baetge 2007; Bailey et al. 1996; Cornick et al. 1994; Moody 1995; Robertson et al. 1992).

Recommended treatment for clinical cases of HYPP aim to address the hyperkalaemia, associated arrhythmia and respiratory acidosis. This includes administration of potassium-free fluids, a source of intravenous calcium and glucose, increased minute ventilation to reduce $PaCO_2$, and insulin (Bailey et al. 1996; Meyer et al. 1999). The administration of sodium bicarbonate is occasionally advocated as alkalinization of the blood results in an exchange of potassium for hydrogen ions, lowering serum potassium. However, the potential benefits of sodium bicarbonate are tempered by numerous risks, including hypotension associated with rapid administration, a decrease in myocardial contractility resulting from a decrease in ionised calcium concentration, and iatrogenic metabolic alkalosis. The administered fluid was changed from LRS to 0.9% NaCl in an effort to limit any further contribution to serum potassium though this approach has been recently questioned in hyperkalemic cats with urinary obstruction (Drobatz 2008). Intravenous calcium gluconate is useful for limiting the arrhythmic effects of hyperkalaemia by raising the threshold potential for the generation of action potentials. As it does not address the hyperkalaemia directly, specific treatments for

lowering plasma potassium are necessary, including glucose and insulin. The effect of glucose is to stimulate insulin release, which drives cellular uptake of glucose and potassium, resulting in a lowering of serum potassium concentration. Insulin has an additional effect of activating the Na^+-K^+ ATPase pump, increasing cellular uptake of potassium ions. Efforts to reduce $PaCO_2$ by an increase in minute ventilation were partially successful. Hypercapnia results in an increase in serum potassium levels, further contributing to hyperkalaemia. At the end of the surgery, potassium levels remained elevated (ABG 7, Table 1) and a low dose of insulin was administered upon transfer to recovery. The horse was left to recover unassisted in an effort to minimize any further stress provoking a second episode of HYPP. An attempt to limit the risk of administering insulin, during a period when blood glucose monitoring was not possible, was made by administering intravenous dextrose (in normal saline) until the horse started to move.

Our case differs from that of Bailey et al. (1996) in the therapy pursued. In addition to calcium gluconate, dextrose and insulin were administered. The combined effects were a reduction in serum potassium concentration to within the normal range shortly after the end of the anesthetic. This may have contributed to the smooth recovery observed and absence of muscle fasiculations. Additionally, the whole blood transfusion was stopped as a potential source of potassium (Hohenhaus 2006). With the exception of insulin administration, all treatment had been initiated in the operating theatre. The slow response to therapy, in terms of serum potassium levels (ABG 6 and 7), likely reflect the short duration over which the treatments were administered. Only 3L of 0.9% NaCl were administered during this time and treatment was directed to ensuring the adequate

administration of calcium and dextrose, which were considered more important in terms of correcting the arrhythmia.

This case was similar to that reported by Cornick et al. (1994) in that an initial anaesthetic period did not result in clinical signs of HYPP or an elevation in serum potassium concentrations. Of the cases reported in the literature, diagnosis was confirmed by DNA analysis in two cases (Bailey et al. 1996; Moody 1995). Our case differs from others in the unique combination of the following factors: signs of HYPP became evident intra-operatively following a previous uneventful general anesthetic using an identical anesthetic protocol. Diagnosis was rapidly achieved and aggressive treatment instituted promptly, resulting in the resolution of clinical signs and an unassisted, uneventful recovery. The diagnosis was later confirmed by DNA analysis. Following a previous (1998) recommendation for testing of foals with known HYPP ancestry (related to the stallion Impressive), the American Quarter Horse Association has made testing a requirement for all foals born after 1st January, 2007 with known HYPP ancestry.

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Table. Blood-gas and electrolyte results from the first and second surgeries.

ABG = arterial blood-gas and electrolytes. VBG = venous blood-gas and electrolytes. *start of treatment for suspected HYPP. †sample taken when horse recovered to standing following anaesthesia.

Fig. 1a: Base-apex ECG recorded prior to therapy for suspected HYPP. Sinus tachycardia of 78 beats min^{-1} and tall, narrow T waves exhibited. Paper speed, 25 mm sec^{-1}. Height 0.5 mV per division.

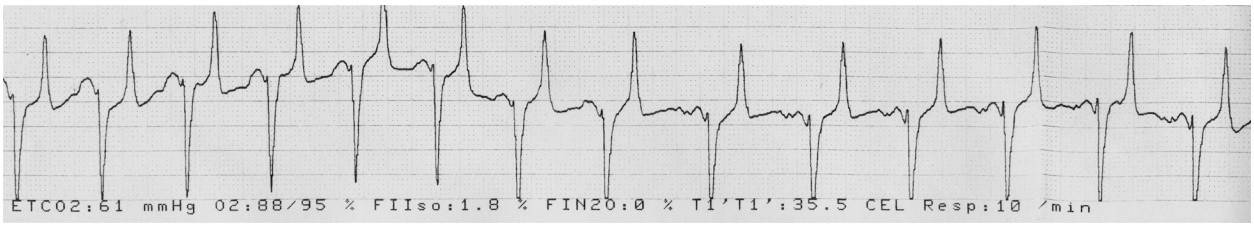

Fig. 1b: Base-apex ECG recorded following initiation of therapy for suspected HYPP. Return of normal T wave morphology. Heart rate of 59 beats min^{-1}. Complex six is a premature complex of atrial or junctional origin. Paper speed, 25 mm sec^{-1}. Height 0.5 mV per division.