

**TITLE OF CASE**

Clinical features, anaesthetic management and peri-operative complications seen in three horses with pheochromocytoma

**SUMMARY**

Three horses presenting with colic signs to the Equine Referral Hospital at The Royal Veterinary College underwent general anaesthesia (GA) between September 2013 and November 2017 for emergency exploratory laparotomy. No obvious cause for the colic signs was identified in two horses while a haemoperitoneum was identified in the third. All horses were euthanized within 12 hours of surgery due to deteriorating haemodynamic instability and/or intractable pain. Post-mortem examination (PME) revealed an adrenal mass in each case, confirmed to be a pheochromocytoma on histopathology. In retrospect, each horse had some hallmark characteristics consistent with a functional pheochromocytoma including hyperglycaemia and hyperlactataemia. Extremely high packed cell volumes (>65%) were also identified in two horses with a high-normal PCV found in the haemoperitoneum case. Peri-operative haemodynamic instability was predominantly characterised by episodes of intermittent hypertension and tachycardia.

**BACKGROUND**

Pheochromocytomas are neoplasms that originate from the chromaffin cells of the adrenal medulla, which are part of the sympathetic nervous system.<sup>1</sup> Although still rare, pheochromocytomas are the most frequently occurring medullary adrenal tumour in older horses with a prevalence of 0.95% in horses that presented for necropsy.<sup>2</sup> In general, these neoplasms are mostly unilateral with a low incidence of malignancy.<sup>1</sup>

Both functional and non-functional pheochromocytomas have been described. Functional pheochromocytomas secrete catecholamines such as adrenaline and noradrenaline, which cause clinical signs if secreted at a sufficient rate.<sup>3</sup> The clinical signs of functional pheochromocytomas are generally acute in onset with a fast progression due to extreme adrenergic stimulation. These include severe abdominal pain, tachycardia, tachypnoea, sweating, muscle tremors, hyperthermia, dry and pale mucous membranes, increased capillary refill time and ataxia.<sup>2,4</sup> Haematological and biochemical abnormalities identified in horses with functional pheochromocytomas include profound haemoconcentration, a stress leukogram, hyperglycaemia and hyperlactataemia. Other non-specific biochemical abnormalities seen in these horses include azotaemia, metabolic acidosis, hyponatraemia, hyperkalaemia, hypocalcaemia and hyperphosphataemia.<sup>2, 5</sup>

Overall, the literature on equine pheochromocytomas is quite limited. Yovich et al.<sup>4</sup> published a literature review presenting some clinical and pathological features of pheochromocytomas in 10 horses, all of which had been diagnosed on PME. They concluded that hyperglycaemia is a consistent finding in suspected cases and that a pheochromocytoma in the horse presents a challenging diagnostic problem. More recent case reports and a retrospective study focus on the clinical and pathological features of the disease.<sup>2, 6, 7</sup> Ante-mortem diagnosis of pheochromocytomas in horses is rare with most cases being identified on PME. Reported ante-mortem diagnostics of pheochromocytomas in horses include measurement of blood catecholamines and their metabolites in urine, ultrasonography and blood pressure recordings. However, these methods are only supportive and not definitive when making a diagnosis and also time limits their application in an emergency situation.<sup>2</sup>

This case series describes the presentation, anaesthetic management and peri-operative complications identified in three horses which underwent emergency exploratory laparotomy after displaying severe colic signs with an uncertain preoperative diagnosis. Horses showed haemodynamic instability characterised predominantly by episodes of intermittent hypertension and tachycardia. The peri-operative mortality rate of these horses was 100%. A left adrenal mass confirmed as a pheochromocytoma was diagnosed in each case on PME and was presumed to be responsible for the clinical deterioration leading to the death of each horse. There is only one clinical report describing anaesthetic complications - ventricular fibrillation and cardiac arrest within 15 minutes after induction - of an exploratory laparotomy in a horse, where a pheochromocytoma was diagnosed on PME.<sup>8</sup> The purpose of this case series is to contribute to the limited literature available on the more specific ante-mortem features of equine pheochromocytomas, with the intention of aiding in a presumptive diagnosis of the disease pre-surgery, preventing unnecessary suffering for the horse and wasted finances for the owner. The case series also describes the anaesthetic complications that were identified and their management.

**CASE PRESENTATION**

**Case presentation**

Each horse underwent a full colic examination including physical examination, transrectal palpation of the abdomen, passage of a nasogastric tube and abdominal ultrasonography. In addition, blood was collected for a baseline packed cell volume, total plasma solids concentration and a biochemistry analysis. The details of each case are summarised in Table 1 and 2 with the remarkable findings highlighted in red.

In all three horses, intractable pain was the indication for emergency exploratory laparotomy. After induction, each horse was positioned in dorsal recumbency for the surgery and anaesthetic monitoring (Datex; Ohmeda) included electrocardiography, pulse oximetry, side-stream capnography and invasive blood pressure (BP) measurements. An arterial line was placed in the facial artery using a 20G catheter and was connected to the multi-parameter machine via a transducer which was positioned at the level of the heart.

Table 1: Case details and findings of a full colic assessment in three horses later diagnosed with a pheochromocytoma

Case	Signalment	Weight (kg)	Clinical signs	Mucous membranes	T(°C) P(bpm) R(Bpm) on	Nasogastric reflux	Rectal exam	Abdominal ultrasound	Abdominal paracentesis	Borborygmi	Pain assessment
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					arrival at the ERH						(Mild, moderate or severe)
1	<b>17yo</b> MN thoroughbred	501	<b>Acute onset</b> , intermittently rolling in the field, depressed	<b>Congested</b> , dark pink, CRT 3 seconds	T: 37.8 <b>P: 96</b> <b>R: 48</b>	None	Gas filled viscus filling caudal abdomen	Normal	Serosanguinous sample, TP 35g/l, WBC 6.2x10e9/l, PCV 5%	Absent in all 4 abdominal quadrants	Moderate
2	<b>21yo</b> MN Irish Sports horse	570	<b>Acute onset</b> , loose faeces, depressed	<b>Congested</b> , dark pink and tacky, CRT 3 seconds	T: 38.3 <b>P: 88</b> <b>R: 60</b>	4 litres	2 taenial bands coursing through the abdomen	Normal	Unable to perform	Absent in all 4 abdominal quadrants	Moderate
3	<b>18yo</b> F cob	400	<b>Acute onset</b> , violently colicing, continually rolling in the field	<b>Pale pink</b> and tacky, CRT 2.5 seconds	T: 37.1 <b>P: 80</b> <b>R: 40</b>	None	Not performed	3 distended, amotile loops of small intestine. A moderate amount of echoic fluid in the ventral peritoneal cavity	<b>Haemorrhagic sample</b> . Fluid not analysed	Absent in all 4 abdominal quadrants	Severe

MN, male neutered; F, female; kg, kilograms; CRT, capillary refill time; T, temperature; P, pulse; bpm, beats per minute; R, respiratory rate; Bpm, breaths per minute; TP, total protein; WBC, white blood cell count; PCV, packed cell volume.

Table 2: Relevant pre-anaesthetic venous blood results of the three horses presented in this case series

Case	PCV (%) - Normal: 31-43	TS (g/l) - Normal: 58-77	pH - Normal: 7.330-7.410	Lactate (mmol/l) - Normal:0.2-0.7	Glucose (mmol/l) - Normal: 4.9-6.2	Creatinine (umol/l) - Normal: 80-177	Sodium (mmol/l) - Normal: 134.7-142	Potassium (mmol/l) - Normal: 3.53-4.64
1	<b>69</b>	72	7.300	<b>15.8</b>	<b>28.3</b>	201	137.4	3.7
2	<b>78</b>	60	Didn't read	<b>8.3</b>	8.9	<b>249</b>	128	4.1
3	46	60	<b>7.291</b>	<b>16.0</b>	<b>27.0</b>	129	142	3.1

PCV, packed cell volume; TS, total plasma solid concentrations.  
Reference range data from: Corley K and Stephen J.<sup>9</sup>

## Outcome and follow-up

### Case 1

Surgical exploration identified chronic, diffuse thickening of the small intestine and an impaction of the right ventral colon. No other significant findings were detected that could explain the degree of clinical signs.

Severe haemodynamic instability was encountered under GA. Despite aggressive fluid therapy(40 litres crystalloid (Vetivex 11 Hartmann's; Dechra) over 3 hours perioperatively) there was minimal reduction in haematocrit (Table 4) and the horse remained persistently tachycardic with the heart rate (HR) ranging between 84 and 136bpm (Figure 1). One episode of ventricular tachycardia also occurred which subsided with administration of a lidocaine bolus (2mg/kg; Lidocaine Hydrochloride Glucose; Fresenius Kabi) followed by a constant rate infusion (CRI) (30µg/kg/min). Continual undulations in BP (systolic (SAP): 59-105mmHg; mean (MAP): 48-84mmHg; diastolic (DAP): 34-65mmHg trending towards hypotension (Figure 1) were documented with little response to inotropes and vasopressors. A dobutamine (Dobutamine Concentrate; Hameln pharmaceuticals) CRI (0.5 – 2.5µg/kg/min) was administered for the entirety of the GA and noradrenaline (Norepinephrine; Hospira) CRI (0.5 – 1.0µg/kg/min) was added in the last hour of the anaesthetic. By the end of surgery, the BP was relatively stable at SAP: 80mmHg; MAP: 70mmHg; DAP: 58mmHg. Arterial blood gas analysis (Table 4) displayed a respiratory acidosis and a moderate hypoxaemia with only mild improvement achieved with ventilation.

Time to standing in recovery took 100 minutes; the horse made two attempts before successfully getting up and showed intermittent paddling while in lateral recumbency. Within 10 minutes the horse fell and became recumbent again and was unable to get back up. The HR remained extremely increased at 100bpm and frothy pink fluid was pouring from the horses' nostrils. Based on the rapid deterioration the horse was euthanased.

PME revealed an enlarged left adrenal gland containing a mass which was microscopically confirmed to be a pheochromocytoma. There were also gross haemorrhagic changes in the liver and thickened small intestine. Gross evidence of disseminated intravascular coagulopathy with petechiations and haemorrhage was also noted.

## Case 2

Surgery identified a right dorsal displacement associated with mild thickening of the colon wall and a markedly enlarged spleen. No compromised intestine was identified and intestinal motility was normal.

Cardiovascular parameters (HR and BP) were maintained within normal limits using a dobutamine CRI (0.5 – 1.5µg/kg/min) and moderate fluid resuscitation (2 litres hypertonic saline (Hypertonic 72mg/ml; Dechra) immediately prior to anaesthesia; 15 litres crystalloid over 2 hours perioperatively), for the majority of the surgery. The PCV also returned to normal (42%). During the last 40 minutes of anaesthesia a mild hypertension (highest BP - SAP:140mmHg; MAP:110mmHg; DAP: 90mmHg and tachycardia (highest HR - 70bpm) developed (Figure 1) and dobutamine was discontinued. Arterial blood gas analysis (Table 4) indicated respiratory acidosis which deteriorated during the anaesthesia. This horse was spontaneously breathing throughout the surgery to preserve cardiovascular function.

The horse stood after three attempts showing moderate ataxia; time to standing was 40 minutes. Within 1 hour after recovery, the clinical condition of the horse deteriorated. The PCV increased to 54%, the HR increased to 68bpm, the mucous membranes became congested and the horse appeared dull and painful. Ten litres of crystalloid were given rapidly followed by a plasma transfusion. Butorphanol (0.02mg/kg; Alvegesic; Dechra) and flunixin meglumine (1.1mg/kg; Flunixin Injection; Norbrook) were administered IV to manage signs of pain. Supportive treatment failed to improve clinical signs significantly. Eight hours post-surgery, severe colic signs returned and nasogastric intubation yielded 10 litres of reflux. In light of the clinical deterioration and guarded prognosis, the owner opted for euthanasia.

PME identified a pheochromocytoma within the left adrenal gland with associated peri-renal haemorrhage. An incidental small intestinal lipoma was also identified with no associated signs of strangulation.

## Case 3

Exploratory surgery revealed a large volume of blood within the abdominal cavity and a small intestinal entrapment through a mesocolonic rent which was corrected. A large haematoma was found in the left dorsal abdomen (Figure 2) closely associated with the mesocolonic rent. The retroperitoneal space was also distended ventrally with suspected retroperitoneal haemorrhage. Due to uncontrollable bleeding, the horse was euthanized on the surgical table under GA.

Peri-operative cardiovascular parameters during the anaesthetic were quite variable and BP in particular was very erratic (Figure 1). The HR rate was initially elevated at 108bpm but then gradually decreased and plateaued towards the end of the GA to 50bpm. Undulations in BP (SAP: 108-180mmHg; MAP: 78-128mmHg; DAP: 70-114mmHg) were also displayed with a mild to moderate hypertension being the predominant trend, despite continuing haemorrhage. Morphine (0.1mg/kg; Morphine Sulphate; Mercury Pharma) and ketamine (0.25mg/kg; Ketamidol; Chanelle) were given IV during the worst period of hypertension to alleviate pain, but a subsequent decrease in BP wasn't seen. Hypotension was not encountered at any point. Towards the end of surgery, the PCV had decreased to 36% as a result of on-going bleeding and fluid resuscitation (2

litres hypertonic saline immediately prior to anaesthesia; 15 litres crystalloid over 100 minutes perioperatively). A mild metabolic and moderate respiratory acidosis and severe hypoxaemia were identified on arterial blood gas analysis (Table 4). A mild improvement was noted between the first and second sample.

PME revealed the presence of a pheochromocytoma within the left adrenal gland (Figure 3) with intravascular metastasis. The tumour was identified as the most likely cause of the retroperitoneal haemorrhage. The ante-mortem mesocolonic rent was confirmed, but the precise cause of the mesocolonic rent was uncertain.

Table 3: Fluid therapy and anaesthetic protocol

Case	Premedication	Induction	Maintenance	Perioperative analgesia	Blood pressure support	Ventilation	Fluid therapy pre-, peri- and post-operatively	GA time (minutes)	Recovery time – time to standing (minutes)	Recovery type and grade (1–5)
1	Romifidine (0.08mg/kg), morphine (0.2mg/kg) IV	Ketamine (2.2mg/kg), midazolam (0.04mg/kg) IV	Isoflurane + O <sub>2</sub>	Lidocaine bolus (2.0mg/kg) x 2 + CRI (30µg/kg/min)	Dobutamine CRI (0.5 – 2.5µg/kg/min), noradrenaline CRI (0.5 – 1.0µg/kg/min)	IPPV (TV:4-9 litres, PIP:28-34 cmH <sub>2</sub> O)	Total volume of CSL received – 40 litres	170	100 - *The horse fell down again shortly after standing	Rope assisted recovery. Grade 3: >2 attempts to stand, moderate ataxia after standing
2	Xylazine (1.0mg/kg) IV, morphine (0.1mg/kg) IM	Ketamine (2.2mg/kg), midazolam (0.05mg/kg), thiopental (0.9mg/kg) IV	Isoflurane + O <sub>2</sub>	Lidocaine bolus (2.0mg/kg) + CRI (30µg/kg/min)	Dobutamine CRI (0.5 – 1.5µg/kg/min)	Spontaneous	Hypertonic saline (2 litres prior to induction), total volume of CSL received – 25 litres, plasma transfusion post-operatively	115	40	Rope assisted recovery. Grade 3: >2 attempts to stand, moderate ataxia after standing

3	Xylazine (1.0mg/kg), morphine (0.1mg/kg) IV	Ketamine (2.2mg/kg), midazolam (0.06mg/kg) IV	Isoflurane + O <sub>2</sub> + air	Lidocaine bolus (2.0mg/kg) +CRI (30µg/kg/min), morphine (0.1mg/kg)	None	IPPV (TV:4-7 lites, PIP:27-30 cmH <sub>2</sub> O)	Hypertonic saline (2 litres prior to induction), total volume of CSL received - 15 litres	105	NA	Euthanized on the table - no recovery
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IV, intravenous; IM, intramuscular; O<sub>2</sub>, oxygen; CRI, constant rate infusion; IPPV, intermittent positive pressure ventilation; TV, tidal volume; PIP, peak inspiratory pressure CSL, compound sodium lactate crystalloid; GA, general anaesthesia; NA, not applicable

Compound sodium lactate crystalloid (Vetivex 11 Hartmann's; Dechra)

Dobutamine (Dobutamine Concentrate; Hameln pharmaceuticals)

Hypertonic saline (Hypertonic 72mg/ml; Dechra)

Isoflurane (IsoFlo; Zoetis)

Ketamine (Ketamidor; Chanelle)

Lidocaine (Lidocaine Hydrochloride Glucose; Fresenius Kabi)

Midazolam (Hypnovel; Roche)

Morphine (Morphine Sulphate; Mercury Pharma)

Noradrenaline (Norepinephrine; Hospira)

Romifidine (Sedivet; Boehringer Ingelheim)

Thiopental (Thiopental sodium; Archimedes Pharma)

Xylazine (Chanazine; Chanelle)

Table 4: Peri-operative arterial blood gas analysis of the three horses presented in this case series

Case	Individual time points	pH - Normal: 7.364 - 7.444	PaCO <sub>2</sub> (mmHg) - Normal: 37.0 - 49.0	PaO <sub>2</sub> (mmHg) - Normal: 89 - 115 *	HCO <sub>3</sub> <sup>-</sup> (mmol/l) - Normal: 23.0 - 30.0	Base Excess ecf (mmol/l) - Normal: 1.1 - 7.1	PCV (%) - Normal: 31.0 - 43.0
1	1 <sup>st</sup>	7.149	77.0	87.5 (FiO <sub>2</sub> =79)	26.5	-2.4	61.4
	2 <sup>nd</sup>	7.157	67.2	130.8 (FiO <sub>2</sub> =91)	25.6	-5.2	59.5
	3 <sup>rd</sup>	7.195	57.0	117.2 (FiO <sub>2</sub> =94)	23.6	-6.3	57.2
2	1 <sup>st</sup>	7.130	77.1	151.0 (FiO <sub>2</sub> =61)	25.9	-3.0	42.0
	2 <sup>nd</sup>	7.080	81.7	117.0 (FiO <sub>2</sub> =78)	24.4	-6.0	42.0

3	1 <sup>st</sup>	7.120	78.0	54.0 (FiO <sub>2</sub> =53)	Not recorded	Not recorded	Not recorded
	2 <sup>nd</sup>	7.130	65.5	105 (FiO <sub>2</sub> =96)	21.3	-8.0	36.0

\*Normal range provided is based on the oxygen content of room air: fraction inspired of oxygen 21% (FiO<sub>2</sub>)

PaCO<sub>2</sub>, partial pressure of carbon dioxide dissolved in arterial blood; PaO<sub>2</sub>, partial pressure of oxygen dissolved in arterial blood; HCO<sub>3</sub><sup>-</sup>, bicarbonate concentration; ecf, extracellular fluid; PCV, packed cell volume

Reference range data from: Corley K, and Stephen J.<sup>9</sup>

## DISCUSSION

The continuous monitoring of anaesthesia described in this case series allowed early detection of unusual and erratic trends of cardiovascular variables, particularly HR and BP that would be deemed abnormal for most common causes of colic. The excess catecholamine release from functional pheochromocytomas may cause severe systemic hypertension and tachycardia, as well as spontaneous sweating and palpitations. Hypertension is generally paroxysmal but can be sustained in some cases.<sup>10</sup> All three horses displayed unpredictable trends in HR and BP. Case 1 was extremely and persistently tachycardic despite aggressive fluid therapy and only mild hypotension. In case 2, the HR was normal throughout (apart from 1 short increase to 70bpm) but BP was consistently, reaching a maximum towards the end of surgery with no apparent reason. In case 3, HR and BP were both variable throughout with a general tachycardia and hypertension seen throughout the GA despite the absence of vasopressors and ongoing haemorrhage. These cases illustrate the usefulness of invasive blood pressure monitoring as a diagnostic tool in horses with a suspected pheochromocytoma.

As well as the cardiovascular abnormalities, each horse in this case series presented with haematological and biochemical abnormalities that are consistent with a functional pheochromocytoma. In cases 1 and 2, the PCV was excessively high (69% and 78% respectively) with normal TS concentrations (72g/l and 60g/l respectively). In horses a PCV of > 65% is considered a negative prognostic indicator.<sup>11</sup> The likely mechanism behind this excessive haemoconcentration is a result of adrenaline-induced splenic contraction rather than simple dehydration.<sup>8</sup> A normal TS concentration further supports this mechanism as a concurrent increase is generally seen with dehydration. The equine spleen has a large red cell reserve and can more than double the PCV under conditions of intense vasoconstriction.<sup>12</sup> In case 3, a high-normal PCV (46%) was detected despite on-going acute blood loss in the form of a haemoperitoneum. Moreover, the presence of a haemoperitoneum in itself should create suspicion of a pheochromocytoma as these tumours have a tendency to bleed into the abdominal cavity due to their friable nature.<sup>3</sup> In a retrospective study of 37 cases with pheochromocytoma, 10.8% had a haemoperitoneum associated with the ruptured tumour.<sup>2</sup> Excessive hyperglycaemia and hyperlactataemia have also been reported as two of the more specific biochemical abnormalities associated with equine pheochromocytomas. Hyperglycaemia is likely a result of the direct and indirect effects of catecholamines on carbohydrate metabolism mediated via  $\beta$ 2 adrenoceptor activity. Catecholamines stimulate glycogenolysis, gluconeogenesis, and aerobic glycolysis and inhibit glycogen synthesis.<sup>13</sup> Hyperlactataemia may be due to catecholamine-mediated vasoconstriction and haemorrhagic shock in cases of haemoperitoneum.<sup>3</sup> In all 3 of the cases both these parameters were high with case 1 and 3 having exceptionally high values.



Once diagnosed, the main treatment option described for a pheochromocytoma in companion animals and humans is an adrenalectomy.<sup>14</sup> In dogs, it is recognised that these surgeries carry a moderate morbidity and mortality rate with numerous surgical and anaesthetic complications described. These include tachyarrhythmias, bradyarrhythmias, hypertension, hypotension and haemorrhage.<sup>10</sup> Pre- and peri-operative medical management is very important in patients with a suspected pheochromocytoma and certain drugs are recommended to reduce the incidence of anaesthetic complications if surgery is performed. Pre-operative medical therapy aims to reduce catecholamine-induced hypertension with the use of a long-acting  $\alpha$ -1 blocker (phenoxybenzamine) treatment initiated 1 – 2 weeks before surgery.<sup>15</sup> During anaesthesia, short acting vasodilators are recommended for the management of hypertension. These include sodium nitroprusside, phentolamine and magnesium sulphate. Peri-operative tachyarrhythmias can be managed with lidocaine or  $\beta$ 1 antagonists such as esmolol.<sup>16</sup> It is important to also fully assess the hydration status and correct any deficits prior to surgery as the chronic sympathetic stimulation and vasoconstriction displayed with pheochromocytomas can cause intravascular volume depletion.<sup>17</sup> Finally, blood loss should be monitored very closely as haemorrhage from the tumour site is common.<sup>10</sup> The surgical management of an adrenalectomy to remove this tumour type has yet to be reported in horses but theoretically would be very challenging to perform as visualisation and access to the adrenals is difficult.<sup>3</sup> Moreover, there is no information available in horses on the drugs used in companion animals and humans for pre- and peri-operative pharmacologic management.

Each of the horses described in this case series received a very similar anaesthetic protocol, which is usually adopted in horses undergoing colic surgery. This consisted of an  $\alpha$ -2 agonist and morphine premedication, induction with ketamine and midazolam and maintenance with isoflurane in oxygen and air. Dobutamine was used as first line for blood pressure support and a lidocaine infusion was administered peri-operatively for its analgesic, anti-arrhythmic and inhalational agent sparing properties. In people and companion animals there are some specific recommendations when deciding on an anaesthetic protocol for a pheochromocytoma removal. In terms of anaesthetic monitoring, multi-parameter monitoring as well as invasive BP monitoring via an arterial line is considered essential to promptly address any cardiovascular instability.<sup>10</sup> This monitoring is considered routine in our hospital and was performed in each of the cases described above. Multiple routes of vascular access are advisable as several drugs may be required along with intensive fluid therapy and potentially a blood transfusion.<sup>18</sup> Each horse only had one route of IV access via a jugular catheter but access to the neck peri-operatively was available allowing the placement of a second jugular catheter if deemed necessary. It is advised to avoid any drug that is sympathomimetic or vagolytic such as ketamine and atropine in order to reduce the occurrence of adverse haemodynamic responses. Moreover, drugs that may precipitate arrhythmias in the presence of increased catecholamine's should not be used, such as thiobarbiturates and halothane. Drugs that may cause histamine release such as morphine should also be avoided if possible.<sup>18, 19</sup> The use of acepromazine is also not advisable to avoid worsening hypotension following tumour removal.<sup>10</sup> Both morphine and ketamine were used in every horse in this case series. Potentially if a pheochromocytoma had been suspected prior to GA, a different opioid could have been used with less pro-histaminic properties. Administering prophylactic anti-histamines and injecting morphine IM may also reduce the incidence of histamine release. Avoiding the use of ketamine is difficult as it is the fundamental drug in a lot of equine induction protocols and is considered the best available option.<sup>20</sup> The alternative choice of thiopental is also advised against and the use of propofol is too expensive, unlicensed and is only available in concentrations that are too low to induce a horse rapidly. In retrospect, apart from pre-operative medical management and more aggressive fluid resuscitation intra-operatively, little change in anaesthetic protocol could have been made in these cases, if a pheochromocytoma had been identified or suspected prior to anaesthesia. However, earlier recognition of the underlying cause of these horse's anaesthetic instability would have allowed the anaesthetist to trouble shoot more effectively and manage the anaesthetic to the best of their ability.

Overall, horses presenting with clinical signs associated with a functional pheochromocytoma are considered to have a poor prognosis. Currently, the literature doesn't present an option to improve the outcome if raised clinical suspicion is achieved. Euthanasia is currently considered the most sensible and ethical option for both the horse and owner. This case series highlights the importance of early recognition of the expected clinical

presentation in future cases, which will provide the owner with a more realistic prognosis before surgery and should reduce unnecessary pain and distress for the horse. In conclusion, each of the horses in this case series displayed several features consistent with the presence of a phaeochromocytoma. This case series highlights these features and their use in identifying the presence of a phaeochromocytoma. It also documents the significant impact of this type of neoplasia on anaesthetic management and supports the high mortality rate previously reported for phaeochromocytomas in horses.

#### **LEARNING POINTS/TAKE HOME MESSAGES**

- A full colic assessment including biochemical and haematological analysis is invaluable prior to proceeding with colic surgery, in order to assist with a presumptive diagnosis.
- Hyperlactataemia, hyperglycaemia and extremely high packed cell volumes with tachycardia are consistent anomalies in horses with pheochromocytoma. In cases of haemoperitoneum, a pheochromocytoma should be high up on the differential list.
- Invasive blood pressure monitoring is a useful diagnostic tool in horses with a suspected pheochromocytoma.
- Early recognition of the common clinical signs associated with a functional pheochromocytoma is required in order to provide the owner with a realistic prognosis before proceeding with exploratory surgery and to reduce unnecessary pain and distress for the horse.

#### **REFERENCES**

- 1. Toribo RE. Disorders of the endocrine system. In: Reed SM, Bayly WM, Sellon DC, eds. *Equine Internal Medicine*. 3<sup>rd</sup> edn. St. Louis, USA: Saunders Elsevier, 2010:1250.
- 2. Luethy D, Habecker P, Murphy B, et al. Clinical and pathological features of pheochromocytoma in the horse: A multi-centre retrospective study of 37 cases (2007-2014). *J Vet Intern Med* 2016;**30**:309-313.
- 3. Toribo RE. Disorders of the endocrine system. In: Reed SM, Bayly WM, Sellon DC, eds. *Equine Internal Medicine*. 4<sup>th</sup> edn. St. Louis, USA: Saunders Elsevier, 2018:1078-1079.

- 4. Yovich JV, Horney FD, Hardee GE. Pheochromocytoma in the horse and measurement of norepinephrine levels in horses. *Can Vet J* 1984;**25**:21-25.
- 5. Yovich JV, Ducharme NG. Ruptured pheochromocytoma in a mare with colic. *J Am Vet Med Assoc* 1983;**183**:462-464.
- 6. Fouché N, Gerber V, Gorgas D, et al. Catecholamine metabolism in a Shetland pony with suspected pheochromocytoma and pituitary pars intermedia dysfunction. *J Vet Intern Med* 2016;**30**:1872-1878.
- 7. De Cock HEV, MacLachlan NJ. Simultaneous occurrence of multiple neoplasms and hyperplasia's in the adrenal and thyroid gland of the horse resembling multiple endocrine neoplasia syndrome: case report and retrospective identification of additional cases. *Vet Pathol* 1999;**36**:633-636.
- 8. Johnson PJ, Goetz TE, Foreman JH, et al. Pheochromocytoma in two horses. *J Am Vet Med Assoc* 1995;**206**:837-841.
- 9. Corley K, Stephen J. Appendix. In: Corley K, Stephen J, eds. *The equine hospital manual*. Oxford, UK: Blackwell Publishing Ltd, 2008:678.
- 10. Adams JG, Figueiredo JP, Graves TK. Physiology, pathophysiology, and anesthetic management of patients with gastrointestinal and endocrine disease. In: Grimm KA, Lamont LA, Tranquilli WJ, et al, eds. *Veterinary Anesthesia and Analgesia. Lumb and Jones*. 5<sup>th</sup> edn. Iowa, USA: Wiley Blackwell, 2015:650-651.
- 11. Cook VL, Hassel DM. Evaluation of the colic in horses: decision for referral. *Vet Clin North Am Equine Prac* 2014;**30**:383.
- 12. Fielding CL, Magdesian KG. Review of packed cell volume and total protein for use in equine practice. *AAEP proceedings* 2011;**57**:318-321.
- 13. Barth E, Albuszies G, Baumgart K, et al. Glucose metabolism and catecholamines. *Crit Care Med* 2007;**35**:508-518.
- 14. Galac S, Korpershoek E. Pheochromocytomas and paragangliomas in humans and dogs. *Vet and Comp Onc* 2017;**15**:1158-1170.
- 15. Herrera MA, Mehl ML, Kass PH, et al. Predictive factors and the effect of phenoxybenzamine on outcome in dogs undergoing adrenalectomy for pheochromocytoma. *J Vet Intern Med* 2008;**22**:1333-1339.
- 16. Wall III RT. Endocrine disease. In: Hines RL, Marschall KE, eds. *Stoelting's Anesthesia and Co-Existing Disease*. 6<sup>th</sup> edn. Philadelphia, USA: Saunders Elsevier, 2012:376-406.
- 17. Brainard BM. Pheochromocytoma. In: Silverstein D, Hopper K, eds. *Small Animal Critical Care Medicine*. St Louis, USA: Saunders Elsevier, 2009:314-317.

- 18. Ramakrishna H. Pheochromocytoma resection: Current concepts in anesthetic management. *J Anaes Clin Pharma* 2015;**3**:317-323.
- 19. Domi R, Sula H, Kaci M *et al*. Anesthetic considerations on adrenal gland surgery. *J Clin Med Res* 2015;**1**:1-7.
- 20. Taylor PM, Clarke KW. Intravenous anaesthesia. In: Taylor PM, Clarke KW, eds. *Handbook of equine anaesthesia*. 2<sup>nd</sup> edn. Philadelphia, USA. Saunders Elsevier, 2007:33-35.

- **FIGURE/VIDEO CAPTIONS**

Figure 1: Perioperative cardio-respiratory anaesthetic trends in the three cases including heart rate, blood pressure and respiratory rate

**Key:** •, heart rate (beats per minute); √, systolic arterial blood pressure (mmHg); X, mean arterial blood pressure(mmHg); ∧, diastolic arterial blood pressure (mmHg); Δ, respiratory rate (breaths per minute); □, each horizontal box represents a 5-minute time period

Figure 2: Post mortem image from case 3 – Left dorsal abdomen showing haemorrhage around the left kidney (+) and adrenal gland (\*).

Figure 3: Post mortem image from case 3 - Left adrenal gland (post fixation) showing massive expansion, necrosis and haemorrhage of the medulla (pheochromocytoma). The black bar in the bottom right corner represents 5cm.