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## Anaesthetic management of a unilateral adrenalectomy of an adrenocortical tumour in a dog

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### Abstract

Adrenalectomies in dogs are being more commonly performed, however anaesthetic management of such cases can be challenging due to the multiple aetiologies of adrenal tumours and the physiological role of adrenal glands. This case report describes the anaesthetic management of a dog with clinical signs of hyperadrenocorticism that underwent unilateral adrenalectomy via laparotomy and discusses anaesthetic preparedness, protocol selection and management of complications for dogs undergoing adrenalectomy.

**Keywords:** Adrenal neoplasia, Adrenalectomy, Canine.

### Introduction

Adrenalectomy is the treatment of choice for canine adrenal tumours for a good long-term outcome (Lang *et al.*, 2011). Surgical techniques for adrenalectomies in dogs are increasingly reported (Kyles *et al.*, 2003; Jiménez Peláez *et al.*, 2008; Lang *et al.*, 2011; Massari *et al.*, 2011; Gójska-zygner *et al.*, 2012; Smith *et al.*, 2012; Barrera *et al.*, 2013; Naan *et al.*, 2013). However, anaesthetic management of these cases has rarely been described (Kyles *et al.*, 2003; Jiménez Peláez *et al.*, 2008; Lang *et al.*, 2011; Massari *et al.*, 2011). Complications reported for adrenalectomies are hypotension, hypertension, tachycardia, ventricular arrhythmias and haemorrhage, with a reported incidence of 35 to 100% (Lang *et al.*, 2011). Perioperative mortality rates for adrenalectomies have been reported as 6% for elective procedures increasing to 50% when performed in emergencies (Lang *et al.*, 2011). These mortality rates are higher than that of 1.33% in dogs classified as American Society of Anesthesiologists (ASA) physical status 3-5 in the Confidential Enquiry into Perioperative Small Animal Fatalities (Brodbeck *et al.*, 2008).

The most common primary adrenal tumours are adrenocortical adenomas or adenocarcinomas, and pheochromocytomas (Massari *et al.*, 2011). Less commonly, myelolipomas, aldosteronomas, deoxycorticosterone- or sex hormone- secreting adrenal tumours are found (Massari *et al.*, 2011). Adrenal tumours may be endocrinologically active (Gójska-zygner *et al.*, 2012); thus the presenting clinical signs and the physiological response to anaesthesia and surgery may reflect the type of tumour present.

### Case Details

A 6-year-old female neutered 33 kg Airedale was referred to the Queens Veterinary Hospital, University

of Cambridge, for investigation of an 18-month history of lethargy, weight gain with abdominomegaly, polyuria, polydipsia (PU/PD) and polyphagia. There had been concurrent thinning of the coat with hyperpigmentation of the skin. On examination, the dog was quiet, alert and responsive with a left-sided head tilt and left-sided facial muscle weakness suggestive of facial nerve paralysis. Cardiorespiratory examination was unremarkable. Complete haematology and a comprehensive biochemistry profile showed the following significant abnormalities: PCV 60% (reference range 37–55); total protein 84 g/dL (60–80); urea 9.5 mmol/L (2.5–7.5); ALT 283 iu/L (14–67); ALP 561 iu/L (26–107); cholesterol 14.1 mmol/L (3.3–6.5). Urinalysis of a free catch sample showed isosthenuria (urine specific gravity 1.008). A right adrenal mass was the only abnormality detected by abdominal ultrasonography. A total body computer tomography scan with iodinated contrast confirmed the presence of a well circumscribed hyperplastic right adrenal gland and a hypoplastic left adrenal gland with no evidence of vascular infiltration or metastatic disease. The owners declined further clinical pathology tests. A right-sided adrenocortical tumour causing clinical signs of hyperadrenocorticism was presumptively diagnosed. The patient was scheduled for right adrenalectomy via laparotomy and was assigned an ASA physical status of 3.

The patient was premedicated with medetomidine (1 µg kg<sup>-1</sup>, Sedator; Dechra Veterinary Products, Skipton, UK) and methadone (0.3 mg kg<sup>-1</sup>, Comfortan; Dechra Veterinary Products, Skipton, UK) intramuscularly (IM) followed by the placement of a 20G catheter in the cephalic vein. After preoxygenation, general anaesthesia was induced with propofol (PropoFlo Plus; Zoetis, Tadworth, UK) 2.7 mg kg<sup>-1</sup> and diazepam

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(Diazemuls; Actavis UK Ltd, Barnstable, UK) 0.2 mg kg<sup>-1</sup> intravenously (IV). After oro-tracheal intubation with a 10 mm diameter cuffed tube, anaesthesia was maintained with isoflurane (IsoFlo; Zoetis, Tadowrth, UK) in oxygen. Monitoring included electrocardiography (ECG), pulse oximetry (SpO<sub>2</sub>), invasive blood pressure, oesophageal temperature, end-tidal (ET) gas analysis and capnography. Active warming was provided using a semi-conductive heating device (Hot Dog; Augustine Temperature Management, Eden Prairie, USA) to maintain normothermia.

In anticipation of intraoperative haemorrhage, an 18G catheter was placed in the contralateral cephalic vein to enable rapid fluid administration. Blood products, hetastarch and crystalloids were placed in theatre. Intravenous fluid therapy (IVFT) consisted of Hartmann's solution (Compound Sodium Lactate for Infusion BP; Baxter, Staines-upon-Thames, UK) administered at 5 ml kg<sup>-1</sup> hr<sup>-1</sup> during surgical preparation, doubled during the surgical procedure. Intraoperative blood loss was monitored using a combination of haemoglobin concentration measurement in the suction system and the swab gravimetric method.

Atracurium (Tracrium; GlaxoSmithKline, Uxbridge, UK) 0.2 mg kg<sup>-1</sup> was administered IV to facilitate the surgical approach. The neuromuscular blockade was monitored with accelerometry (TOF watch™; Wardray Premise, Thames Ditton, UK) placed across the ulnar nerve. Additional atracurium 0.1 mg kg<sup>-1</sup> IV was administered as needed during the procedure to maintain a train of four (TOF) reading of one. The dog was mechanically ventilated to maintain normocapnia. Analgesia was provided using lidocaine (Lidocaine 2% BP; Hameln Pharmaceuticals Ltd, Gloucester, UK) and fentanyl (Sublimaze; Janssen-Cilag Ltd, High Wycombe, UK) IV infusions, respectively at 40 µg kg<sup>-1</sup> min<sup>-1</sup> and 2-15 µg kg<sup>-1</sup> hr<sup>-1</sup>, both preceded by loading boluses of 1 mg kg<sup>-1</sup> and 2 µg kg<sup>-1</sup> IV respectively. Paracetamol (Perfalgan; Bristol-Myers Squibb Pharmaceutical Ltd, Uxbridge, UK) 10 mg kg<sup>-1</sup> was administered IV towards conclusion of surgery and bupivacaine (Marcaïn 0.5% Polyamp Steripack; AstraZeneca, Luton, UK) 10 ml was splashed on the rectus abdominus muscles once sutured. Cefuroxime (Zinacef; GlaxoSmithKline, Uxbridge, UK) 20 mg kg<sup>-1</sup> IV was administered every 90 minutes throughout surgery.

Approximately 30 minutes after commencement of surgery, when the mass was being manipulated via blunt dissection around the adrenal capsule, the dog became acutely hypertensive (systolic 200 mmHg and diastolic 110 mmHg) with an increased HR of 110 bpm and premature supraventricular complexes. Thus a fentanyl bolus of 2 µg kg<sup>-1</sup> IV was administered followed by an increased infusion rate of 15 µg kg<sup>-1</sup> hr<sup>-1</sup>. Methadone 0.3 mg kg<sup>-1</sup> IV was also administered. These

interventions resolved the arrhythmia and reduced the systolic blood pressure to 100 mmHg. During further manipulation of the mass, a sudden increase in systolic pressure (200 mmHg) occurred with concurrent severe bradycardia (30 bpm) with third-degree atrioventricular blocks. Promotion of vasodilation by increasing the isoflurane percentage and administering acepromazine (ACP Injection; Novartis Animal Health, Basingstoke, UK) 5 µg kg<sup>-1</sup> IV increased the heart rate to 60 bpm and reduced the systolic blood pressure to between 80 and 90 mmHg. The patient remained stable for the remainder of anaesthesia as the right adrenal gland and associated tumour were excised en mass via further blunt dissection and vessel ligation.

Prior to recovery, a lumbosacral epidural injection of morphine (Morphine BP; Martindale Pharmaceuticals UK, Wockhart, UK) 0.15 mg kg<sup>-1</sup> diluted with sterile saline to a volume of 0.12 ml kg<sup>-1</sup> was administered and an 8 Fr Foley urinary catheter (Infusion Concept, Sowerby Bridge, UK) was placed. The neuromuscular blockade was not antagonized as two equal twitches in response to double burst stimulation were seen. Anaesthesia and surgery times were 290 minutes and 225 minutes, respectively.

The dog recovered from anaesthesia in the intensive care unit (ICU). Post-operative monitoring consisted of hourly assessments of pulse rate and quality, ECG, respiratory rate and pattern, Doppler blood pressure monitoring, mucous membrane colour and capillary refill time. Urinary output was monitored hourly and electrolytes levels were monitored every six hours for the first 24 hours. Pain was assessed every two hours using a modified Glasgow pain scale. If the pain score exceeded six, methadone 0.2 mg kg<sup>-1</sup> IM was prescribed as rescue analgesia. Paracetamol 10 mg kg<sup>-1</sup> was continued per os twice daily and lidocaine 40 µg kg<sup>-1</sup> h<sup>-1</sup> IV was infused for 24 hours. Prednisolone (Prednicare; Animalcare, Nether Poppleton, UK) 0.2 mg kg<sup>-1</sup> was administered once orally in the early postoperative period. Omeprazole, cefuroxime and vitamin A were prescribed by the attending clinicians. Two hours into the recovery period, the systolic blood pressure increased to 200 mmHg without concurrent arrhythmias. Therefore, acepromazine (ACP tablets; Elanco Animal Health, Basingstoke, UK) 1 mg kg<sup>-1</sup> was administered orally, which reduced the systolic pressure to 140 mmHg within 30 minutes. The patient had no further complications and was discharged from intensive care the following day. Histopathological analysis defined the resected mass as an adrenocortical carcinoma.

### Discussion

Although adrenalectomy is the preferred treatment for adrenal tumours in dogs (Lang *et al.*, 2011), complications during anaesthesia and surgery are common and sometimes fatal. This case provides an

opportunity to reflect on anaesthetic preparedness, protocol selection and management of possible complications that may occur in dogs undergoing anaesthesia for adrenalectomy.

A functional adrenocortical tumour may cause clinical signs of hyperadrenocorticism, such as PU/PD, abdominal enlargement, hypertension, prolonged healing, skin changes, lethargy, polyphagia and facial paralysis (Johnson and Norman, 2007). Uncommonly, adrenocortical tumours may also produce excess mineralocorticoids, causing clinical signs of Addison's disease. Pheochromocytomas produce excess catecholamines which may cause hypertensive episodes. Pheochromocytomas often invade adjacent blood vessels or organs, which may cause haemorrhage into the retroperitoneal space. Therefore, clinical signs of pheochromocytoma are often nonspecific and include weakness, tachypnoea, collapse, tachyarrhythmias and seizures (Herrera *et al.*, 2008). In our patient, the presence of many clinical signs of hyperadrenocorticism without evidence of hypertensive episodes or local tumour invasion lead to a preoperative presumptive diagnosis of an adrenocortical tumour producing excess cortisol. Further preoperative diagnostic testing such as adrenocorticotropic hormone stimulation testing and urine protein-to-creatinine ratio may have provided additional supporting evidence. As commonly occurs with adrenal tumours, a definitive diagnosis of adrenocortical adenocarcinoma was not made until postoperative histopathology was performed on the resected mass.

In patients suspected to have a pheochromocytoma due to documented hypertensive episodes, preoperative stabilisation with phenoxybenzamine has been advocated to decrease perioperative mortality (Kyles *et al.*, 2003; Herrera *et al.*, 2008; Massari *et al.*, 2011). Phenoxybenzamine, an  $\alpha$ -adrenergic antagonist, irreversibly binds to  $\alpha_1$  and  $\alpha_2$  adrenergic receptors to block the response to circulating catecholamines (Herrera *et al.*, 2008). Preoperative treatment of human patients is for at least two weeks (Kyles *et al.*, 2003), while the literature for dogs reports time frames between 7 and 120 days (Herrera *et al.*, 2008). As our patient had no preoperative clinical signs of hypertension, phenoxybenzamine was not prescribed.

The most common intraoperative complication reported is haemorrhage, more likely when a cavotomy is required. Preoperative blood typing would have been required if our patient had received previous blood transfusions (Tocci and Ewing, 2009). Preoperative coagulation parameters may allow for preoperative management of any abnormalities detected. Hypercoagulability has classically been described as a consequence of hyperadrenocorticism. However, this has recently been disputed in dogs (Klose *et al.*, 2011). This patient had no preoperative clinical signs of

hyper- or hypo-coagulopathies, therefore coagulation parameters were not measured. Having pre-emptively placed large bore peripheral IV catheters in the patient and also the placement of resuscitative fluids in theatre meant that rapid treatment of major haemorrhage could occur. The swab gravimetric method has been reported to accurately quantify intraoperative haemorrhage in dogs (Lee *et al.*, 2006). Therefore, the additional measurement of haemoglobin concentration of the suction fluid to approximate the volume of haemorrhage was likely unnecessary, as this technique is reportedly of similar accuracy to the gravimetric technique (Clark *et al.*, 2010).

The ideal anaesthetic protocol for adrenalectomies should maintain homeostasis despite potential sudden physiological changes. Surgical manipulation of the adrenal gland can lead to a catecholamine surge and subsequent cardiovascular manifestations, regardless of the adrenal tumour type present (Lang *et al.*, 2011). The anaesthetic protocol should also provide analgesia and muscle relaxation.

Premedication with a pure mu agonist such as methadone (Kyles *et al.*, 2003; Massari *et al.*, 2011) provides pre-emptive analgesia, sedation and a reduction in the required inhalant minimum alveolar concentration (MAC) with minimal cardiovascular effects. Previous studies report the use of an opioid-benzodiazepine combination in dogs undergoing adrenalectomy (Jiménez Peláez *et al.*, 2008; Lang *et al.*, 2011). Benzodiazepines cause minimal cardiovascular depression; however, in adult dogs the sedation can be unreliable and dysphoria may occur (Sanchez *et al.*, 2013). Sedation with acepromazine may provide benefit to hypertensive patients due to the  $\alpha$ -1 adrenergic blockade it produces (Monteiro *et al.*, 2007). However, the prolonged and irreversible duration of action of acepromazine may impede the treatment of hypotension during anaesthesia. In this case, medetomidine was selected to provide sedation and MAC reduction of isoflurane beyond that of an opioid alone (Lerche and Muir III, 2006). An additional benefit of medetomidine is the profound sympatholytic effect attributable to central  $\alpha_2$ -adrenoreceptor activation, which may partially counteract the effect of a catecholamine surge (Väisänen *et al.*, 2002). The marked cardiovascular effects caused by  $\alpha$ -2 agonists such as decreased cardiac output and transient hypertension are dose-dependent and short acting, and an antagonist drug is available (Pypendop and Versteegen, 1998).

Previous studies describe the use of propofol (Jiménez Peláez *et al.*, 2008), etomidate or propofol co-administered with midazolam (Lang *et al.*, 2011) as induction agents prior to adrenalectomy. In a paper describing anaesthesia protocols for humans undergoing adrenalectomies, etomidate was avoided due to its ability to suppress the adrenocortical axis and

thus production of mineralo- and gluco-corticosteroids (Domi and Sula, 2011). In contrast, Dabbagh *et al.* (2009) reported infusing etomidate to control the clinical signs of hyperadrenocorticism preoperatively. Our choice of co-induction with propofol and diazepam has been described in the veterinary literature (Robinson and Borer-Weir, 2013; Sanchez *et al.*, 2013), although the only benzodiazepine achieving a significant reduction in propofol dose has been midazolam. However, most patients in the study from Robinson and Borer-Weir (2013) were healthy dogs of ASA status 1 or 2, with an insufficient number of ASA 3 dogs in the treatment group to speculate association with ASA category. In our clinical experience, benzodiazepenes as co-induction agents at lower doses than those published often reduce the induction agent dose required in debilitated patients. All published reports utilise inhalant techniques for the maintenance of anaesthesia (Jiménez Peláez *et al.*, 2008; Lang *et al.*, 2011). Isoflurane was used in this case as the maintenance agent because sevoflurane was unavailable. The acute episode of severe vasoconstriction, hypertension and reflex bradycardia that occurred during adrenal gland manipulation was likely due to a catecholamine surge. The vasodilatory effect of isoflurane was utilised to manage this event. Ideally, anti-hypertensive drugs should be short-acting and titratable to effect. The use of sevoflurane may have allowed for more rapid changes in ET agent concentrations due to its lower blood-gas coefficient (Lopez *et al.*, 2009). Other reportedly used vasoactive drugs such as phentolamine (Kyles *et al.*, 2003), a short acting competitive  $\alpha$ -1 adrenergic blocking drug, or sodium nitroprusside (SNP) (Kyles *et al.*, 2003; Lang *et al.*, 2011) were unavailable. One study reported that the vasodilation induced by isoflurane was advocated to maintain better overall tissue perfusion than SNP (Humm *et al.*, 2007). On this occasion, the short action of phentolamine would have been more suitable than acepromazine to provide additional vasodilation. Acepromazine likely contributed to the subsequent mild hypotension. Furthermore, the long and irreversibly action of acepromazine may have impeded management of blood pressure were it to worsen (Monteiro *et al.*, 2007). If the reflex bradycardia had not responded to the induction of vasodilation, treatment with an anticholinergic such as atropine would have been indicated.

Tachyarrhythmias commonly occur due to adrenal gland manipulation, nociceptive input or in response to hypotension. Supraventricular tachycardias (SVT) and ventricular arrhythmias (Kyles *et al.*, 2003; Lang *et al.*, 2011) have been reported during adrenalectomy. In this instance, opioids successfully treated the supraventricular tachycardia by reducing both sympathetic tone and nociception as reported in older studies. A more recent paper (Garofalo

*et al.*, 2008) failed to demonstrate a protective effect of remifentanyl against ventricular arrhythmias induced by adrenaline in halothane-anaesthetised dogs. Myocardial sensitization to catecholamine-induced arrhythmias by halothane as used in Garofalo's study may have made tachyarrhythmias more difficult to treat compared to isoflurane. The second-line treatment for SVT would have been ultra short-acting beta-blockers such as esmolol (Kyles *et al.*, 2003; Lang *et al.*, 2011). If ventricular arrhythmias had occurred, treatment with higher doses of lidocaine or with procainamide would have been indicated (Lang *et al.*, 2011).

Multimodal analgesia was provided with the co-administration of fentanyl and lidocaine; the latter also for its MAC sparing (Valverde *et al.*, 2004) and antiarrhythmic properties (Bruchim *et al.*, 2012). Opioids have been used in all published studies, with hydromorphone, methadone, morphine and fentanyl infusions reported (Jiménez Peláez *et al.*, 2008; Lang *et al.*, 2011). Nonsteroidal anti-inflammatory drugs (NSAIDs) were avoided as they may precipitate gastrointestinal ulceration in patients with excess glucocorticoids (Kukanich *et al.*, 2012). To avoid this, paracetamol was preferred as an adjunctive analgesic in this case (Benitez *et al.*, 2015).

Neuromuscular blockade may facilitate surgical approaches to deep structures during laparotomies (Clarke *et al.*, 2014) but has only been described in one veterinary paper describing adrenalectomies (Lang *et al.*, 2011). In a case report of two human adrenalectomies (Domi and Sula, 2011), cis-atracurium was selected for its short duration of action and plasma degradation; for similar reasons, atracurium was administered to our patient.

Post-operative complications occur with high incidence following adrenalectomies (30% according to Lang *et al.* (2011)), necessitating close monitoring in ICU settings. Reported complications include hypo- or hyper-tension, arrhythmias, vomiting, oesophagitis, seizures, pancreatitis, acute renal failure, haemoperitoneum, hyperthermia, hypokalaemia, tachypnoea and cardiopulmonary arrest (Kyles *et al.*, 2003; Lang *et al.*, 2011; Gójska-zygner *et al.*, 2012). Many complications relate to inadequate function of the remaining adrenal gland, leading to acute adrenal insufficiency and crisis. Corticoid administration using various protocols in the perioperative period features in all published studies. Most commonly reported is glucocorticoid supplementation with dexamethasone once the adrenal tumour is removed, followed by administration of prednisolone in the recovery period (Kyles *et al.*, 2003; Lang *et al.*, 2011). In this case, as commonly occurs, it was unknown whether the remaining hypoplastic adrenal gland was capable of producing sufficient corticoids postoperatively. Therefore, a single postoperative dose of prednisolone

was administered to provide additional glucocorticoid support for recovery from the physiological stress of anaesthesia and surgery. Close monitoring of vital signs was undertaken to detect signs of an adrenal crisis, such as cardiovascular shock or vomiting. Serum electrolytes were measured every six hours in the early postoperative period to identify any acute mineralocorticoid deficiency and prompt treatment if required. The only identified postoperative complication in our case was mild hypertension, which responded to the administration of acepromazine. In conclusion, the anaesthetic management for adrenalectomies is challenging because of the high incidence of severe complications. A good understanding of the physiological derangements that may be induced by both the tumour itself and the surgical procedure is required. Adequate preparations for anticipated problems, including availability of resuscitative fluids and short-acting drugs, will minimize patient morbidity and mortality.

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