

Management of sudden onset of bradycardia and arterial hypotension during pheochromocytoma excision in a dog – a case report

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ABSTRACT

An 11-year-old female spayed Shih Tzu was presented with a history of weight loss, lethargy and a heart murmur. After extensive diagnostics, an adrenal mass was discovered, suspected to be a pheochromocytoma, and surgical excision was planned. During anesthesia, no signs of catecholamine discharge were seen. However, sudden bradycardia and hypotension occurred, necessitating anticholinergic therapy. Such therapy is usually contraindicated in patients with pheochromocytoma due to the risk of significant tachycardia, cardiac arrhythmias, and arterial hypertension. No adverse effects were noted, and the dog recovered uneventfully from the procedure.

Key words: pheochromocytoma; dog, anticholinergics; hypotension; bradycardia

Introduction

Pheochromocytomas are functional neuroendocrine tumors producing catecholamines, predominantly noradrenaline. They arise from chromaffin cells in the adrenal medulla. They can be one of the most challenging conditions for anesthetists to manage as they can produce a sudden discharge of catecholamines, leading to systemic hypertension, tachycardia, and arrhythmias, which can be fatal for the patient (RAMAKRISHNA, 2015). Sudden death can occur if the consequences of catecholamine discharge cannot be controlled. The peri-anaesthetic complications encountered in

this case were unusual and unexpected considering the suspicion of pheochromocytoma. Furthermore, the treatment needed to stabilize the patient is mostly contraindicated in this condition.

Case presentation

An 11-year-old female spayed Shih Tzu weighing 4.6 kg was referred to the Veterinary University Clinic with a history of weight loss and lethargy, a newly discovered heart murmur, and the presence of an adrenal mass found on abdominal ultrasonography. On arrival, the dog was alert, with a heart rate (HR)

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of 100 beats per minute (bpm), respiratory rate (RR) of 24 breaths per minute, pink mucous membranes, capillary refill time (CRT) less than 2 seconds, and a rectal temperature of 38.4°C. A holosystolic murmur (grade 4/6) was found on thoracic auscultation. There was mild thrombocytosis (563 K/ μ L [reference range 148-484 K/ μ L]), mild elevation of urea (0.29 g/L [reference range 0.07-0.27 g/L]), increased albumin level (47 g/L [reference range 23-40 g/L]), as well as elevated liver enzyme activities (alanine transaminase 208 U/L [reference range 10-125 U/L] and alkaline phosphatase 607 U/L [reference range 23-212 U/L]). Electrolyte concentrations were within reference ranges, as was serum vitamin B12. A low-dose dexamethasone suppression test (LDDST) excluded hyperadrenocorticism (HAC).

Abdominal ultrasonography revealed a heterogenous right adrenal mass ($\pm 2 \times 1.1$ cm) and a neoplasia was suspected. Renal cysts and infarcts, splenic myelolipomas, and signs of chronic inflammatory bowel disease were also found. A computed tomography (CT) scan was advised as vessel invasion was suspected. Three-view thoracic radiographic evaluation revealed a slight bronchial pattern, but no evidence of metastatic disease. Thoracic and abdominal CT-angiography showed an enhancing nodule (1.6 x 1 x 1.15 cm) on the cranial pole of the right adrenal gland, with invasion of the phrenicoabdominal vein. A neoplastic etiology (adenocarcinoma or pheochromocytoma [PHEO]) was suspected on the basis of diagnostic imaging. Urinary catecholamines and their ratio to creatinine were measured (QUANTE et al., 2010) to detect PHEO and to prepare the patient adequately for anesthesia and surgery. Results were compatible with either HAC or PHEO (urinary normetanephrine:creatinine 241.8 nmol/L, urinary metanephrine:creatinine 153.8 nmol/L). Since HAC had been excluded with a LDDST, a PHEO was considered highly likely. Cardiological examination was performed as a part of the diagnostic plan, and pre-anesthetic evaluation. Electrocardiography (ECG) showed a sinus rhythm with an HR of 100-120 bpm. Echocardiography revealed mitral endocardiosis staged as ACVIM-B1 and thickening of the aortic leaflets. Systolic arterial

blood pressure (SAP) measured by the Doppler ultrasonic technique (Eickemeyer® Ultrasonic Doppler, Eickemeyer, Germany) on the thoracic limb (neonatal cuff size 3; 6-11 cm) during physical examination was 130 mmHg.

Even though the clinical signs were not highly indicative of a PHEO, diagnostic imaging and laboratory results strongly suggested this diagnosis. Although hypertension was not observed at presentation, antihypertensive therapy was recommended. The drug of choice is phenoxybenzamine (HERRERA et al., 2008), but as it is not available in Belgium, tamsulosin (Tamsulosin, magistral preparation of 0.4 mg per capsule) was prescribed at 0.02mg/kg PO once daily for 2 months, until the scheduled surgery. The last dose was administered the evening before surgery.

Therapy

On the day of surgery, the dog's physical exam was the same as on the first presentation, with a slightly higher HR (140 bpm), and an SAP of 125mmHg. The blood type was determined using a commercially available immunochromatography test, indicating Dog Erythrocyte Antigen negative (DEA 1.1 negative). A 22G intravenous cannula (Vasovet® 22G 0.9 x 25mm, BBraun, Germany) was placed into the left cephalic vein and an intravenous infusion of 0.5 μ g/kg/min of remifentanyl (Ultiva 2 mg, Aspen Pharma Trading Limited, Ireland) IV was given over 2 minutes. Anesthesia was induced with 0.2 mg/kg IV midazolam (Dormazolam® 5mg/mL; Le Vet Beheer B.V., Netherlands) and alfaxalone (Alfaxan Multidose 10 mg/mL; Jurox, Ireland) to effect (total dose 1 mg/kg) and a cuffed endotracheal tube (InTube™, Intersurgical, UK) with an internal diameter of 5.5 mm was placed. During patient preparation, general anesthesia was maintained with 1% isoflurane (IsoFlo; Zoetis; Belgium) vaporized in oxygen and delivered via a Bain system (Mapleson D), together with an IV infusion of remifentanyl at 0.4 μ g/kg/min, which was decreased to 0.3 μ g/kg/min after 10 minutes. During this period, another IV cannula (Vasovet®, 20G 1.1 x 33 mm, BBraun, Germany) was placed into the contralateral cephalic vein to ensure two

patent IV cannulas in case a blood transfusion was needed, as well as one in the left dorsal pedal artery (Vasovet® 24 G 0.7 x 19 mm, BBraun, Germany) to allow invasive blood pressure monitoring throughout the procedure. Immediately after intubation, the dog was connected to an anesthesia monitor (VT9000 Multimonitor; Veterinary Technics, Netherlands). Pulse oximetry, ECG, non-invasive blood pressure measurement (NIBP), capnography, esophageal temperature and end-tidal isoflurane concentration (EtIso) were monitored continuously and recorded at 5-minute intervals. Approximately 12 minutes later, the patient was transferred to the operating theatre and connected to a circle coaxial rebreathing system. General anesthesia was maintained with isoflurane 1% vaporized in 2 L/min oxygen and an IV infusion of remifentanyl at 0.3 µg/kg/min. Cefazoline (Cefazoline Sandoz 1g, Sandoz GmbH, Austria) was administered IV at a dose of 20 mg/kg every 90 minutes during the surgery. The dog breathed spontaneously, and all the vital parameters were stable. Blood pressure was measured invasively via the arterial catheter connected to a pressure transducer, zeroed approximately at the level of the dog's right atrium, and connected to the monitor. Approximately 20 minutes into general anesthesia, once the patient had been transferred from preparation room to the operating theatre and the aseptic preparation of the surgical field was started, a sudden decrease in temperature was noted (from 36.5°C to 35.5°C within 5 minutes). This decrease in temperature was soon followed by a decrease in MAP (from 75 mmHg to 55 mmHg) and a 50% decrease in heart rate (from 100-120 bpm to 55-60 bpm) within a 20 second period.

Atropine was administered at a dose of 20 µg/kg IV, after which the HR decreased to 40 bpm. The same dose was injected two minutes later, which helped restore HR to the previous value of 100-120 bpm. The blood pressure was restored more slowly, requiring 15 minutes to achieve normotension. Hypertension was not observed after atropine administration. The procedure was continued as planned, with no further episodes of bradycardia, nor hypotension. Anesthesia was maintained with an IV infusion of remifentanyl at 0.3-0.5 µg/kg/

min and an EtIso of 0.7-0.9 %. The exploratory celiotomy revealed no other abnormality than the right adrenal mass. A right adrenalectomy was performed without peri-operative complications. The invaded right phrenicoabdominal vein was excised *en bloc* with the adrenal gland, and two hemoclips were placed at its insertion into the caudal vena cava. No clinical signs suggestive of catecholamine discharge were recorded during anesthesia. Methadone (Comfortan, Dechra, Belgium) was administered every 4 hours at 0.2 mg/kg IV, for 24 hours post-operatively. The dog was discharged the day after the surgery with tramadol prescribed on demand. Histopathology confirmed the pheochromocytoma and its complete excision.

Discussion

In this case, no signs of catecholamine discharge were observed. However, the dog developed an unexpectedly low HR and BP. This hypotension and bradycardia could have been a direct consequence of remifentanyl infusion. In one study performed in dogs anesthetized with isoflurane and a constant rate infusion (CRI) of remifentanyl, bradycardia was the most frequent drug-related side-effect, with up to 42% of dogs needing glycopyrronium to counteract the decrease in heart rate (ALLWEILER et al., 2007). Other studies have shown that remifentanyl causes not only bradycardia but also hypotension, both more likely when combined with other anesthetic agents (JOSHI et al., 2002.; NOSEIR et al., 2003), as was the case here. However, when doses up to 10x higher than the highest dose we administered were used, a dose-dependent decrease in HR was observed, with a reduction of approximately 35% compared to the baseline HR, while the mean arterial pressure did not vary significantly (MICHELSEN et al., 1996).

One must also consider that at the time when these cardiovascular events happened, the dog's core temperature fell below 36°C, in a rapid manner, probably as a consequence of the surgical field preparation. Hypothermia is known to affect drug metabolism because many of the enzymes involved in biotransformation are highly thermosensitive (REYNOLDS et al., 2008). Therefore, a relative overdose with remifentanyl was possible, given the

fact it is metabolized by plasma cholinesterases. This hypothesis is reinforced by the lack of external nociceptive stimulation while waiting for the surgery to start, which could have led to administration of a higher than needed dose of remifentanyl.

Another possible cause of hypotension is the pre-operative administration of tamsulosin. It is an uroselective α_1 -adrenergic receptor antagonist showing higher affinity for α_{1A} and α_{1D} receptors, than for the α_{1B} subtype. The principal subtype in vasculature smooth muscle in dogs is the α_{1B} subtype, while the other two are primarily found in the urethra and prostate. This renders tamsulosin less than ideal for pre-operative blood pressure management in PHEO patients, but it should provide more cardiovascular stability in patients during anesthesia. However, its potential for effects on peripheral vasculature should be considered, especially when combined with anesthetics. According to one study, the hypotensive effect of tamsulosin in dogs was potentiated by increasing age and increasing dosage (KOBAYASHI et al., 2009). The age-related effect has also been recorded in humans, probably due to the increased α_{1B} adrenoreceptor expression that occurs with aging, as a consequence of chronic catecholamine exposure (RUDNER et al., 1999). To the authors' knowledge, only two cases of severe hypotension with concurrent use of tamsulosin and isoflurane have been reported in humans (KUMAR and KHAN, 2010; CHAUHAN et al., 2013). It is therefore possible that the hypotensive episode was in fact a consequence of tamsulosin administration, followed by isoflurane inhalation, even though no similar data have been published in dogs.

The rapid onset of bradycardia and hypotension warranted a prompt response. Although not usually recommended in PHEO, atropine was used for its anticholinergic action, and was chosen in preference to glycopyrronium due to its faster onset. Atropine is used to block the parasympathetic stimulation of the heart, thus increasing the sinoatrial discharge rate, improving atrioventricular conduction, and increasing the heart rate. However, in lower doses atropine can produce a paradoxical effect at the

sinoatrial and atrioventricular nodes, thus slowing the HR even more (DAS, 1989). Even though non-specific for various muscarinic receptors (M), there is a dose-dependent effect of atropine that will lead to binding to the M_1 receptors (found in salivary and sweat glands) first. Heart-based M_2 receptors are less susceptible, and therefore a higher dose of an anticholinergic is needed to prevent the muscarinic effect. Therefore, the paradoxical effect is usually explained due to the blockade of the inhibitory presynaptic M_1 receptors on parasympathetic postganglionic nerve terminals, before the postsynaptic M_2 receptors are blocked. This will lead to the removal of the inhibitory M_1 effect, therefore releasing acetylcholine (ACh) in the synapse and causing bradycardia. As atropine is a competitive antagonist, its effect will be seen once a sufficient concentration has been achieved in the synapse, therefore preventing the binding of ACh (BROADLEY and KELLY, 2001). Even though the standard dose of atropine for treatment of bradycardia in dogs was administered, a paradoxical reaction was recorded after its application. The same dose was repeated, and the expected parasympatholytic effect of atropine was finally achieved. Knowing that the combination of the anticholinergic administered and a sudden catecholamine discharge from the PHEO could create potentially fatal tachyarrhythmias and hypertension, nitroprusside had been prepared and was ready to be infused if hypertension developed, along with esmolol for treatment of potential tachyarrhythmia. However, no side-effects from atropine administration were seen, nor was there any catecholamine discharge during the PHEO excision.

Conclusion

The use of anticholinergics is possible in PHEO anesthesia, if indicated by the patient's status. An analysis of risk and benefit should be made for each individual patient before administering these drugs. Furthermore, side-effects must be anticipated and drugs to correct them must be ready and available to administer rapidly, should side-effects occur. Anesthetists should be prudent and have a clear

understanding of the pathophysiology of these tumors and the pharmacological mechanism of problems.

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SAŽETAK

Sterilizirana ženka pasmine ši-cu, starosti 11 godina, zaprimljena je zbog gubitka težine, letargije i srčanog šuma. Nakon opsežne dijagnostike, otkrivena je tvorba na nadbubregu te je postavljena sumnja na feokromocitom i planirana je njegoza kirurška ekscizija. Tijekom anestezije nisu uočeni znakovi otpuštanja katekolamina. Naprotiv, nastupile su iznenadna bradikardija i hipotenzija, koje su zahtijevale terapiju antikolinergicima. Takva je terapija obično kontraindicirana u bolesnika s feokromocitomom zbog rizika razvoja tahikardije, srčanih aritmija i arterijske hipertenzije. Nisu primijećeni nikakvi štetni učinci terapije antikolinergicima, niti postoperativne komplikacije.

Ključne riječi: feokromocitom; pas; antikolinergici; hipotenzija; bradikardija
