Ioversol contrast reaction in a dog undergoing computed tomography

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ABSTRACT: Computed tomography (CT) is a widely used imaging modality in veterinary practice, often requiring contrast administration to reach a diagnosis. This case study describes a suspected anaphylactoid reaction in a female, 7-year-old Welsh springer spaniel undergoing CT to assess the skull/bullae.

Keywords: Ioversol; anaphylaxis; dog; anaesthesia; case study

Introduction

Iodinated contrast media administration is common place during computed tomography (CT). The iodine compounds block the X-rays as they pass through the body, allowing the structures that contain the contrast to be delineated from the surrounding structures. Iodinated agents can be divided into ionic iodinated contrast agents (IICAs) and non-ionic iodinated contrast agents (NIICAs). Various studies in both human and veterinary medicine have compared the use of IICAs and NIICAs, concluding that the risk of contrast reactions is lower with NIICAs (Singh & Daftary, 2008; Pollard, Puchalski, & Pascoe, 2008). NIICAs are commonly used in both human and veterinary medicine; previous reports have described mild to severe reactions related to their administration, with moderate to severe reactions resulting in haemodynamic changes including tachycardia, bradycardia, hypertension and hypotension (Scarabelli, Cripps, Rioja, & Alderson, 2016; Vance, Nelson, & Hofmeister, 2012).

Case details

A 7-year-old, female entire Welsh springer spaniel, weighing 17.5 kg, was scheduled for a CT of the bullae to investigate a mass in the left ear canal and plan a total ear canal ablation (TECA). The dog had no previous adverse drug reaction or drug allergy reported by the owner on the admission questionnaire, and had not been administered any iodinated contrast media previously.

Clinical examination, haematology and serum biochemistry were unremarkable. Pre-operative examination was unremarkable; body score was 5 out of 9 (Freeman et al., 2011), the dog was bright and alert, and classified as I according to the American Society Anesthesiologists (ASA) physical status classification system (Posner, 2016). No significant medical problem was reported in the history, except chronic otitis of the left ear. A 20-gauge catheter (Mila, USA) was placed in the right cephalic vein.

Pre-anaesthetic medication was administered intravenously (IV) and consisted of 0.22 mg/kg butorphanol (Alvegesic, Dechra) and 1.14 µg/kg dexmeditomidine (Dexdomitor, Vetoquinol). Anaesthesia (GA) was induced with propofol (PropoFlo, Abbott Animal Health), administered slowly to effect with a total dose of 3.4 mg/kg, and maintained with isoflurane (IsoFlo, Zoetis) delivered in oxygen via a circle rebreathing system, following orotracheal intubation with a 9-mm internal diameter cuffed (high-volume, low-pressure) endotracheal tube. Oxygen (O_2) flow was initially set at 2 litres per minute with a vaporiser setting (Penlon Sigma Delta) of 2%. Hartmann's solution (B Braun) was administered IV at 5 ml/kg/hour. End-tidal

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carbon dioxide ($EtCO_2$), oscillometric non-invasive blood pressure (O-NIBP) and oxygen saturation of haemoglobin (SpO_2) were monitored (Mindray PM 9000 Vet). At this stage, heart rate (HR) ranged from 50 to 70 beats per minute (BPM), respiratory rate (RR) ranged 8–12 breaths per minute (BrPM), and systolic (SAP), diastolic (DAP) and mean (MAP) O-NIBP 100–115, 65–80, 85–95 mmHg, respectively, with SpO_2 98–100%.

After a plain CT scan, approximately 20 minutes after induction of anaesthesia, ioversol (Optiray,Guerbet) was administered IV at a dose of 2 ml/kg at a speed of 3.5 ml/s. The post-contrast CT images were then acquired, with the scan lasting approximately 20 seconds. The dog became apnoeic and hypotensive (SAP 50 mmHg, DAP 30 mmHg, MAP 36 mmHg), HR 50 BPM, peripheral pulses were not palpable. Isoflurane (IsoFlo, Zoetis) administration was immediately discontinued and manual intermittent positive pressure ventilation (IPPV) started with 100% O_2. Ventilation was difficult, with a poorly compliant chest/lung, and $EtCO_2$ was 12 mmHg. The rebreathing system was immediately checked and no fault found. An anaphylactoid reaction was suspected due to the clinical signs and their immediate onset after contrast administration. Chlorphenamine maleate (Chlorphenamine, Wockhardt UK Ltd) was therefore administered IV at a total dose of 0.5 mg/kg, followed by 2.2 µg/kg of adrenaline (Adrenaline, Martindale Pharmaceuticals). A fluid bolus was also started at 999 ml/hour via an Alaris GW volumetric infusion pump (CareFusion), with a total volume of 200 ml to be delivered. Arterial blood pressure (ABP) improved (SAP 125 mmHg, DAP 95 mmHg, MAP 110 mmHg) and HR was 100 BPM. After administration of the initial 200-ml fluid bolus, the fluid rate was decreased to 5 ml/kg/hour. IPPV was continued during this time, and despite the decrease in compliance persisting, $EtCO_2$ increased to 30 mmHg, with an SpO_2 of 99%. Dexamethasone (Dexadreson, MSD Animal Health) was administered IV at 0.1 mg/kg and atipamazole (Antisedan,Vetoquinol) 0.2 mg intramuscularly (IM) in the quadriceps. Fifteen minutes after the initial dose of adrenaline and 20 minutes post-contrast administration, ABP decreased again (SAP 70 mmHg, DAP 25 mmHg, MAP 45 mmHg) with a concurrent decrease in $EtCO_2$ to 24 mmHg (although at this time spontaneous ventilation had returned at a rate 30 BrPM). HR remained stable at 95 BPM. A further three doses of adrenaline were administered incrementally over the next 5 minutes to a total dose of 4 µg/kg. Terbutaline (Bricanyl, AstraZeneca) was also administered slowly IV at a dose of 11 µg/kg, diluted in water for injection with a total volume of 5 ml. Hartmann's solution administration rate was increased again to 30 ml/kg/hour. The dog continued to breathe spontaneously, chest/lung compliance was periodically assessed by manually providing a breath; moderate improvement was noticed. No improvement in ABP was recorded after the last adrenaline dose (SAP 65 mmHg, DAP 30 mmHg, MAP 40 mmHg). At this stage the patient recovered from GA with a return of the gag reflex and was therefore extubated and moved to the intensive care unit (ICU). On extubation there was no noticeable laryngeal swelling or oedema.

On arrival in ICU, flow by 100% O_2 was provided by a tight-fitting face mask at a flow rate of 4 litres/minute. As hypotension persisted, a point of care ultrasound of the heart was performed to subjectively assess volume status and contractility. A parasternal approach was utilised to assess the four chambers of the heart; the examination suggested poor diastolic filling, likely caused by a combination of decreased venous return and vasodilation. The fluid administration rate was subsequently increased again to 999 ml/hour (administering a total volume of 30 ml/kg), resulting in an increase of ABP (SAP 85 mmHg, DAP 48 mmHg, MAP 59 mmHg). This improvement was only transient, lasting 5 minutes before a further reduction in ABP (SAP 60 mmHg, DAP 25 mmHg, MAP 30 mmHg); despite the fluctuating ABP, HR remained stable at 95–100 BPM. An IV adrenaline constant rate infusion (CRI) was therefore started at 70 µg/kg/hour; within 10 minutes of starting the infusion, ABP markedly improved (SAP 115 mmHg, DAP 80 mmHg, MAP 92 mmHg), and HR was 100 BPM. Rectal temperature was checked at this point and recorded as 36 °C; therefore, a Bair-Hugger® blanket (Augustine Medical) was utilised until the patient was normothermic.

Over the next 120 minutes the adrenaline CRI was gradually decreased, halving the dose every 30 minutes if ABP was stable, and Intravenous Fluid Therapy (IVFT) continued at a rate of 5 ml/kg/hour. ABP remained stable (SAP 115–130 mmHg, DAP 70–85 mmHg, MAP 85–110 mmHg), and HR ranged from 70 to 95 BPM. RR remained stable between 20 and 30 BrPM, and SpO_2 98–100%. Flow by oxygen was discontinued 2 hours after contrast administration, and after a further 30 minutes, the adrenaline CRI was also discontinued. At this point the dog was sitting up and alert, with HR 83 BPM, MAP 102 mmHg and peripheral pulses were good.

Three hours post-contrast the patient started to pass haemorrhagic diarrhoea, and colloids (Gelofusine, B. Braun) were started at 2 ml/kg/hour as well as antibiotic therapy with cefuroxime (Zinacef, GSK) 20 mg/kg TID, metronidazole (Metronidazole, B. Braun) 10 mg/kg BID. Gastroprotection with omeprazole (Omeprazole, SofarimexIndustria) 1 mg/kg BID and ranitidine (Ranitidine, Alliance Pharmaceuticals) 2 mg/kg BID was started. Methadone (Comfortan, Dechra) 0.2 mg/kg IM was also administered every 4 hours. The dog remained stable overnight, but continued to pass both haemorrhagic diarrhoea and frank blood. Biochemistry and haematocrit (HCT) were checked the following morning: total protein was decreased at 45 g/l (54–77), albumin decreased at 19 g/l (25–40), urea decreased at 2.3 mmol/l (2.5–7.4) and HCT decreased at 0.340 l/l (0.37–0.55). Treatment continued as above for 48 hours, by which point the diarrhoea had stopped and the dog was discharged with a 5-day course of cefalexin (Cephacare, Animalcare) and prokolin (Protexin Veterinary). Eleven days later the dog returned for repeat blood analysis, which showed no abnormality; therefore, surgery was performed.

Discussion

Anaphylaxis is a systemic hypersensitivity reaction; traditionally the term anaphylactic refers to reactions mediated by immunoglobulin E (IgE) and implies previous exposure to the antigen, while the term anaphylactoid is used to describe IgE-independent events, which can occur in the absence of previous exposure. Despite this difference, they are clinically indistinguishable and are therefore treated identically. Histamine is the main mediator in anaphylaxis; nevertheless, multiple other mediators have been implicated such as heparin, tryptase, chymase, carboxypeptidase A3 and proteoglycans. Downstream activation of inflammatory mediators derived from arachidonic acid includes prostaglandin D2, leukotriene B4, cystenylleukotrienes and PAF (Stone, Cotterell, Isbister, Holdgate, & Brown, 2009). Shock develops due to these potent inflammatory and vasoactive mediators resulting in increased vascular permeability, hypovolaemia and vasodilation. They may also directly impair cardiac function. Severe analphylactoid reactions are associated with mixed distributive-hypovolaemic shock, one of the main contributing factors being fluid extravasation and

vasodilation (Brown, 2005). There are also well-recognised species differences in the organs affected by acute anaphylaxis: this is due to variations in immune response, location of smooth muscle, rate of antigen degradation and response to inflammatory mediators (Khan & Kemp, 2011). The primary organs affected in the dog are the liver and gastrointestinal tract (GIT) due to the location of the largest population of mast cells (Quantz, Miles, Reed, & White, 2009). Histamine is released from the GIT into the portal vein causing hepatic arterial vasodilation, hepatic venous outflow obstruction, severely reducing venous return and therefore cardiac output (Qt) (Quantz et al., 2009).

Anaphylactic and anaphylactoid reactions are relatively uncommon in dogs receiving NIICAs. Scarabelli et al. (2016) reported a rate of 37% of dogs suffering a reaction (132 out of 356); however, only 0.8% (three dogs) suffered a severe reaction. Nevertheless, anaphylaxis should be suspected after any acute cardiovascular change occurring after the administration of any drug. Because potentially any excipient (edetate calcium disodium, tromethamine hydrochloride, tromethamine, hydroxide, sodium hydroxide, hydrochloric acid) in Optiray may cause anaphylacotid reactions, we cannot categorically conclude that ioversol was the sole agent responsible in triggering histamine release in this case, but it is very likely the cause.

Supportive treatment was instigated immediately in this case, addressing the clinical signs, and treating the likely anaphylactoid reaction. An anaphylactoid reaction was suspected due to the marked cardiovascular changes and bronchoconstriction that occurred immediately post-contrast administration. Although cardiac arrest did not occur, the cardiovascular and respiratory signs were of such severity that administration of GA agents were immediately discontinued. Atipamazole was administered to antagonise the dexmeditomidine administered as part of pre-anaesthetic medication, as during cardiovascular collapse it is advisable to antagonise any drugs that may be contributing to cardiovascular depression.

Adrenaline, an alpha (α) and beta (β) adrenoreceptor agonist, was administered; α_1 effects include vasoconstriction leading to increased coronary artery perfusion, as well as increased ABP due to increased systemic vascular resistance. B_1 effects include positive inotropic and chronotropic activity, whereas β_2 effects result in bronchodilation as well as suppression of the release of inflammatory mediators (Shmuel & Cortes, 2013). Adrenaline is the treatment of choice and the first drug to be administered for anaphylaxis confirmed by the consensus anaphylaxis guidelines (Simons et al., 2011).Treatment with initial bolus administration of adrenaline transiently improved the patient's cardiovascular parameters. Further cardiovascular support was required, including IVFT and an adrenaline CRI. There is evidence to support the use of an adrenaline CRI in the treatment of anaphylaxis, with this being the preferred route of choice over IM or IV bolus injections (Mink, Simons, Simons, Becker, & Duke, 2004). Shock-rate fluid resuscitation was undertaken to treat the severe hypotension. Hartmann's solution was used, but any isotonic crystalloid would be suitable (Shmuel & Cortes, 2013).

Chlorphenamine and dexamethasone were also administered. Chlorphenamine is an H_1-antihistamine which acts as an inverse agonist, stabilising the histamine receptors shifting them to an inactive state. The use of H_1-antihistamines in severe anaphylaxis is under review as they have no effect on the multiple other inflammatory mediators released, nor do they prevent further release of histamine. A Cochrane systematic review found no significant evidence for or against their use in the treatment of anaphylaxis (Sheikh, Ten Broek, Brown, & Simons, 2007). Treatment with a combination of both H_1- and H_2-antihistamines (e.g. ranitidine, cimetidine) has been reported to be effective treating cutaneous symptoms of anaphylaxis; however, there is limited evidence to support their use as yet (Shmuel & Cortes, 2013).

Dexamethasone is a short-acting glucocorticoid with strong anti-inflammatory activity; it may aid in the downregulation of pro-inflammatory mediators and blocks the arachidonic acid cascade, the hypothesis being it may relieve protracted signs preventing biphasic anaphylaxis. Nevertheless, the Cochrane systemic review found no evidence for the use of glucocorticoids for acute anaphylaxis (Choo, Simons, & Sheikh, 2010).

Marked bronchoconstriction persisted despite adrenaline's potent β_2 effects, which should result in bronchodilation. Terbutaline, a β_1 and $\beta_2$adrenergic receptor agonist, was therefore administered. Bronchodilation is mediated by terbutaline's β_2 effects, with severe tachycardia due to the β_1 effects occasionally seen. In order to limit this potential side effect the dose was diluted into 5 ml of water for injection, allowing the drug to be administered slowly. The compliance of the lungs on crude assessment by the anaesthetist providing a positive pressure breath via the rebreathing bag seemed to improve, with a larger tidal volume being able to be provided. Adrenaline remains the first choice of drug to treat bronchoconstriction caused by anaphylaxis, but bronchodilators may be beneficial as adjunctive therapy (Simons et al., 2011), as in this case. It is also worth noting that a pure β_2 agonist will have no effect on laryngeal oedema or airway obstruction, which can also be encountered during anaphylaxis.

Due to the GIT being a target organ in canine anaphylaxis, haemorrhagic enteritis is one of the most common symptoms. Antibiotics were administered to prevent bacterial translocation from the damaged GIT, and gastroprotectants administered to try and prevent any further damage; ranitidine (H_2 receptor agonist) and omeprazole (proton-pump inhibitor) decrease stomach acid production and secretion, respectively, with the former protecting gastric mucosa from the direct effect of histamine. In this case these drugs were not administered until the dog was moved to the ICU, to avoid the possible adverse effect on haemodynamics resulting from their intravenous administration. Administration of both cefuroxime and metronidazole in response to the diarrhoea could be questionable, as a recent publication (Ortiz et al 2018) suggests that there is no benefit of adding metronidazole to amoxicillin–clavulanate in this situation. Analgesia was also provided to treat any potential discomfort; in this case an opioid (Methadone) was utilised every 4 hours, although an agonist–antagonist like butorphanol may have been more effective in treating visceral pain, and ideally administration based on pain assessment may have been more appropriate. Colloids were administered pre-emptively after the onset of diarrhoea to try and treat the expected hypoproteinaemia caused by gastric losses, again due to the injured GIT.

Conclusion

Examining previous reports by both Vance et al. (2012) and Scarabelli et al. (2016), anaphylactoid reactions may cause changes of HR and ABP in either direction with tachycardia and bradycardia reported along with hypertension and hypotension. Pollard and Pascoe (2008) reported bronchospasm and diarrhoea in one dog; however, this was associated with profound hypertension and bradycardia, which was not seen in the above case. It is also important to note that the reported reaction

Table 1. Table of drugs utilised.

Drug	Dosage	Recommended treatment	Reference
Adrenaline Patients already in shock should be administered an intravenous infusion (IV) of adrenaline	• 0.01 mg/kg (of 1:1000/1 mg/ml solution) intramuscularly • Maximum dose 0.3 mg in patients <40 kg, 0.5 mg in patients >40 kg • Doses can be repeated every 5–15 minutes as needed • IV infusion 0.05 µg/kg/minute, titrating dose to clinical effect	Adrenaline is the treatment of choice and the first drug to be administered for anaphylaxis	Mink et al. (2004)
Fluid therapy/crystalloids	• Dog: 90 ml/kg • Cat: 60 ml/kg	Aggressive fluid therapy resuscitation is recommended for hypotensive patients	Cohen (1995)
Chlorphenamine/H_1 antihistamines	• Dog: 2.5–10 mg/dog IM, slow IV • Cat: 2–5 mg/cat IM, slow IV	No high quality evidence for or against their use.	Sheikh et al. (2007)
Ranitidine/H_2 antihistamines	• 0.5–2.5 mg/kg IV, SC, PO if given IV it should be infused slowly ideally diluted over 5–10 minutes	May relieve cutaneous signs (urticaria/pruritis) as well as decrease gastric acid secretion	Shmuel and Cortes (2013)
Terbutaline	• Bronchodilation: 0.01 mg/kg IM, SC, IV Q4 hours	May be beneficial in anaphylaxis as adjunctive therapy for treatment of respiratory signs	Simons et al. (2011)
Dexamethasone/Glucocorticoids	• 1–4 mg/kg IV	Downregulation of the late-phase eosinophilic inflammatory response. They may prevent biphasic anaphylaxis. No evidence to support their use in acute anaphylaxis	Choo et al. (2010)
Omeprazole	• Dog: 1–1.5 mg/kg q 12–24 hours (IV, PO) • Cat: 0.75–1 mg/kg q24 (PO)	To decrease further damage to the GIT, by reducing the acidity of the gastric secretions	Tolbert et al. (2011)
Amoxicillin-clavulanate	• 8.75 mg/kg (combined) IV Q8 hours, IM, SC Q24 hours • PO: 12.5–25 mg/kg (combined) Q8–12 hours	Antibiotics were administered to prevent bacterial translocation from the damaged GIT	Ortiz et al. (2018)

by Pollard and Pascoe (2008) was also associated with the older IICAs contrast agent. Although there have been multiple reports of NIICAs contrast reactions in dogs, to the authors' knowledge bronchoconstriction has not been reported. Due to the immediate reaction post-contrast administration, it seems most likely for this to be the cause. Immediate discontinuation of the GA and swift treatment to support the cardiovascular system allowed a positive outcome (Table 1). Although the incidences of NIICA contrast reaction is very low, it is something to consider whenever it is administered, and resources to treat anaphylaxis should be readily available in all locations where contrast media are administered.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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