Suspected anaphylaxis from intravenous cefazolin during general anaesthesia in a dog

Ms Melanie Prebble¹ RVT VTS (Anesthesia/Analgesia) and Dr Daniel SJ Pang² BVSc PhD DACVAA Dipl. ECVAA

¹Western Veterinary Specialist and Emergency Centre, 1802 10th Avenue SW, Calgary, AB, Canada, T3C 0J8
²University of Calgary Faculty of Veterinary Medicine, Veterinary Clinical and Diagnostic Sciences, 3280 Hospital Drive NW, Calgary, AB, Canada, T2N 4Z6

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Corresponding author:

Dr Daniel Pang
dsjpang@ucalgary.ca
Summary

A 6-year-old female Shetland Sheepdog with a history of cardiorespiratory compromise during general anaesthesia was referred for ovariohysterectomy surgery. Clinical examination was unremarkable at presentation and physiologic parameters under general anaesthesia were within expected ranges during preparation for surgery. Shortly after completion of an intravenous injection of cefazolin, the audible signal from the Doppler ultrasound unit stopped. A rapid survey of the patient revealed tachycardia with weak femoral pulses, tachypnoea, hyperpnoea and substantially increased resistance to manual positive pressure ventilation. Stopping inhalant anaesthesia, administering salbutamol, corticosteroids and diphenhydramine were associated with resolution of clinical signs. However, marked hypotension and resistance to ventilation recurred approximately 25 minutes later. Low dose intravenous epinephrine (5 mcg/kg) was effective at increasing arterial blood pressure and reversing respiratory dysfunction. Surgery was completed and the patient recovered uneventfully. Initial reliance on second line therapy and delay in administering epinephrine, the recommended treatment for anaphylaxis, may have slowed resolution of clinical signs.

Background

Anaphylaxis, defined by the World Allergy Organization as “a severe, life-threatening generalised or systemic hypersensitivity reaction” (Johansson et al. 2004) occurs uncommonly perioperatively, with an incidence in humans of 1 in 10,000 to 20,000 anaesthetics (Dewachter et al. 2009, Harper et al. 2009). However, it is associated with a high mortality rate of approximately 4-10% (Axon and Hunter 2004, Gibbs et al. 2013, Reitter et al. 2014). The most common triggers of anaphylaxis in human anaesthesia are neuromuscular blocking agents (NMBAs), latex and antibiotics (Dewachter et al. 2009, Harper et al. 2009, Mertes et al. 2003). Limited reports in the veterinary literature preclude identifying common triggers. Suspected triggers include antibiotics, opioids, radiocontrast media, non-steroidal anti-inflammatory drugs (NSAIDs) and intravenous anaesthetics (Clutton 1987, Davis 1984, Girard...
The clinical presentation of anaphylaxis does not vary according to the trigger or mechanism (allergic or non-allergic). Treatment is based on addressing cardiovascular collapse, impaired ventilation and oxygenation, relative hypovolaemia, and removing potential causative agents (Dewachter et al. 2009, Harper et al. 2009, Simons et al. 2011, Simons et al. 2013). However, despite well-established evidence-based guidelines for treating anaphylaxis with epinephrine as a first line therapy, compliance is poor (Choo et al. 2012, Grabenhenrich et al. 2012). Largely unproven, second line therapies (corticosteroids, salbutamol, antihistamines) continue to be used for initial treatment in recent human and veterinary reports (Carter et al. 2011, Grabenhenrich et al. 2012, Harðardottir et al. 2015, Pollard and Pascoe 2008, Rossanese and Rigotti 2015).

The aim of presenting this case is to raise awareness of anaphylaxis as an uncommon but life-threatening perioperative complication and to highlight the risk of initiating treatment with second line therapy.

Case presentation

A 9.2 kg, 6-year-old female Shetland sheepdog was referred for an elective ovariohysterectomy surgery following a history of an adverse event during recovery from general anaesthesia for caesarian section nine months earlier. History provided at referral was as follows: premedication with butorphanol (dose not indicated) and induction of general anaesthesia with propofol (6.2 mg/kg IV). Following orotracheal intubation, anaesthesia was maintained with isoflurane carried in oxygen via a circle rebreathing system. Cardiorespiratory parameters were stable during anaesthesia with the following recorded at completion of surgery: heart rate 132 beats per minute (bpm), respiratory rate 20 breaths/minute, systemic arterial blood pressure (SABP, systolic/diastolic) 107/47 mmHg, capillary refill time < 2s, pink mucous membranes. Approximately 50 minutes after induction of anaesthesia, shortly after the vaporizer was turned off, bradycardia was noted. This was accompanied by cyanosis, tachypnoea and hyperpnoea, pale mucous membranes and a slow capillary refill time. Pulmonary oedema was suspected. The following drugs were
administered over several minutes: dexamethasone (0.9 mg/kg IV), followed by oxytocin (0.2 IU IM), furosemide (9.4 mg/kg IV) and epinephrine (0.1 mg/kg IV). The patient recovered uneventfully, remained stable during observation at the clinic and was sent home later the same day. The following day, the dog was admitted as an emergency to a different clinic, presenting with dehydration and haemorrhagic diarrhoea. Fluid resuscitation and supportive therapy were effective and the dog returned home after 3 days.

At presentation to our hospital the patient was bright and alert, and no abnormalities were detected during physical exam (heart rate 128 bpm, panting, pink mucous membranes, capillary refill time < 2 seconds, rectal temperature of 38.0°C and unremarkable thoracic auscultation). An American Society of Anesthesiologists physical classification status of I was assigned. On the morning of anaesthesia and surgery packed cell volume, total solids, and blood glucose were 51%, 7.1 g/dL and 5.9 mmol/L, respectively.

A 20-gauge, 1 inch, cannula was placed in the right cephalic vein and the patient was premedicated with hydromorphone (0.05 mg/kg IV, Sandoz Canada), and acepromazine (0.01 mg/kg IV, Boehringer Ingelheim (Canada) Ltd.). Fifteen minutes later the patient’s level of sedation was assessed as “moderate” (scale consists of “none”, “slight”, “moderate”, “extreme”). General anaesthesia was induced with 2 mg/kg alfaxalone (Alfaxan, Jurox Pty Ltd.) administered IV to effect (6 mg administered). Orotracheal intubation was performed (8.5-mm internal diameter endotracheal tube), the patient connected to a Bain non-rebreathing system and isoflurane (1.5%, Fresenius Kabi) carried in oxygen (3 L/min) delivered to maintain general anaesthesia. An isotonic crystalloid fluid solution (Plasma-Lyte A, Baxter Corporation) was administered at 10 ml/kg/hr IV.

Following connection to the breathing system, the patient was positioned in lateral recumbency, a multiparametric physiologic monitor (LifeWindow, Digicare Biomedical Technology Inc., Boynton Beach, FL, USA) connected and the following parameters monitored and recorded every five minutes: haemoglobin saturation with oxygen (SpO₂, probe placed on tongue), partial pressure of end-tidal carbon dioxide (P’ETCO₂, sidestream), and oscillometric non-invasive blood
pressure. A Doppler ultrasound probe (Parks Medical, Parks Medical Electronics Inc., Aloha, OR, USA) was placed over the left palmar metacarpal artery, to provide audible monitoring of the pulse. Initial recorded values were: heart rate; 75 bpm, SABP; 125/105 (mean 115) mmHg, SpO₂; 96%, P’ETCO₂; 22 mmHg.

The patient was positioned in dorsal recumbency for clipping and aseptic preparation of the surgical site. SABP was 82/51 (mean 63) mmHg and heart rate 95 bpm before giving the antibiotic cefazolin (22 mg/kg, IV, timed over 5 minutes, Fresenius Kabi). At injection completion, a sudden audible increase in heart rate was detected from the Doppler ultrasound probe (from 95 to 160 bpm). Initially, on the assumption of an inadequate plane of anaesthesia, the vaporizer setting was increased from 1.5 to 2%. This was followed within a few seconds by complete loss of the Doppler signal. Rapid assessment of the patient revealed audible heart sounds with thoracic auscultation (160 bpm), weak femoral pulses, pale mucous membranes, absent palpebral reflexes, tachypnoea and hyperpnoea. During this time, the oscillometric device failed to measure an arterial blood pressure. When squeezing the reservoir bag to provide positive pressure ventilation a marked increase resistance to ventilation was appreciated. The peak airway pressure (pressure gauge between the common gas outlet and breathing system) required to achieve visible thoracic excursions was 25 cm H₂O.

Treatment

Isoflurane was immediately discontinued and 3 metered doses (100 mcg/dose) of salbutamol (Glaxo Smith Kline Inc.) given through an aerosol chamber (AeroKat Feline Aerosol Chamber, Trudell Medical International) connected between the endotracheal tube connector and breathing system. Manual intermittent positive pressure ventilation was continued at approximately 10-12 breaths/minute and diphenhydramine (2 mg/kg IM, Fresenius Kabi) and dexamethasone (0.2 mg/kg IV, Vétoquinol N-A Ltd.) were given. Approximately 5 minutes later, a lateral thoracic radiograph was taken, which did not reveal any abnormalities and isoflurane was recommenced at 1.25%. At this time there was an audible signal from the Doppler unit (heart rate 110 bpm), SABP was measurable (97/83 [mean 92] mmHg), spontaneous ventilation had returned (16 breaths/
minute) and resistance to ventilation had reduced (peak airway pressure < 15 cm H₂O to achieve thoracic excursion).

Following a discussion with the owner it was decided to continue with the planned procedure.

Over the next 10 minutes, during clipping and preparation of the surgical site, physiologic parameters were within normal limits. After a preliminary scrub of the clipped area with chlorhexidene, an incisional line block was performed with 17.5 mg of bupivacaine (Marcaine, Hospira Healthcare Corp.). Aspiration was performed prior to each injection of bupivacaine.

Within a few minutes of completing the incisional line block, as the patient was about to be moved to the operating theatre, there was a precipitous drop in SABP, from 105/85 (mean 95) mmHg to 45/20 (mean 28) mmHg and an increase in resistance to manual positive pressure ventilation. Hypotension was confirmed with a sphygmomanometer and cuff placed on the antebrachium (systolic SABP, 40 mmHg). Epinephrine (0.005 mg/kg IV, Epiclor, Rafter Products) was given resulting in a rapid increase in heart rate from 105 to 220 bpm, over approximately 30 seconds, before decreasing to approximately 130 bpm over the next 60-90 seconds. The systolic SABP (measured with Doppler, sphygmomanometer and cuff) increased to 80 mmHg.

Cardiorespiratory parameters stabilised over the next 15 minutes (heart rate 125-135 bpm, SABP 75/35 [mean 50] mmHg and respiratory rate 16 breaths/min) and the patient developed mucoid diarrhoea. Following further discussion with the owner, it was agreed to proceed with surgery.

During surgery, mean arterial blood pressure was maintained above 60 mmHg with a combination of isotonic crystalloid fluid therapy (10 mL/kg/hr) and intermittent infusion of dobutamine (1-3 mcg/kg/min IV, Hospira Healthcare Corp.). At the end of the procedure isoflurane and dobutamine were discontinued and the patient allowed to recover from general anaesthesia.

Immediately before extubation SABP was 120/85 (mean 100) mmHg with a heart rate of 140 bpm. Extubation was performed within 10 minutes of isoflurane being discontinued.

Postoperative rectal temperature was 35.9°C and SpO₂ on room air was 94%. The patient was warmed with a forced air warmer and blanket during recovery and the following parameters
monitored overnight: mentation, pain score (Glasgow Composite Measures Pain Scale-short form), temperature, heart rate, pulse, respiratory rate, mucous membrane colour, capillary refill time, and indirect blood pressure. The patient was stable overnight and returned to the owner the following day. A note was added to the patient’s records warning of anaphylaxis associated with cefazolin.

**Outcome and follow-up**

Further communication with the referring veterinarian confirmed exposure to cefazolin (22 mg/kg IV) during the previous anaesthetic with the drug administered before the onset of clinical signs. Twelve months later the dog was anaesthetised for elective dental treatment. One of the authors (DP) was present to supervise the anaesthesia and the following anaesthetic protocol was used: premedication with acepromazine (0.02 mg/kg IV) and hydromorphone (0.1 mg/kg IV), followed by induction of general anaesthesia with alfaxalone (1.5 mg/kg IV) and maintenance with isoflurane carried in oxygen. Locoregional anaesthesia for tooth extractions was provided by bupivacaine (1.5 mg, right infraorbital canal). The anaesthetic procedure (180 minutes) and recovery were uneventful with all cardiorespiratory parameters (heart and respiratory rates, systemic arterial blood pressure, \( \text{SpO}_2 \), \( \text{P'ETCO}_2 \)) within expected ranges.

**Differential diagnosis**

Differential diagnoses include causes of hypotension and difficult ventilation, such as anaesthetic overdose, hypovolaemia and equipment malfunction. However, in this case, a presumptive diagnosis of anaphylaxis was made based on the confluence of cardiovascular and respiratory signs coinciding with completion of the cefazolin and bupivcaine injections and a history, albeit vague, of perioperative cardiorespiratory compromise.

**Discussion**

Anaphylaxis, an extreme hypersensitivity reaction, may result from allergic (antibody-mediated, typically IgE, or cell-mediated, typically lymphocytes) or non-allergic (direct mast cell activation e.g. certain opioids, historically classed as “anaphylactoid”) origins (Johansson et al. 2004, Kemp et al. 2008, Simons et al. 2011). It is not possible to distinguish allergic from non-allergic causes.

Classification of hypersensitivity reactions by clinical signs was originally described by Ring and Messmer (1977) and recently updated for cases presenting during general anaesthesia (Dewachter et al. 2009, Ring and Messmer 1977). This classification describes four grades of increasing severity: I; cutaneous-mucous signs (e.g. urticaria), II; moderate multivisceral signs (involvement of additional systems such as the cardiovascular, respiratory and gastrointestinal), III; life-threatening mono- or multivisceral signs (such as cardiovascular collapse and bronchospasm), IV; cardiac arrest. The presented case falls under grades III and IV, meeting the criteria for anaphylaxis, as defined by the World Allergy Organization (Johansson et al. 2004).

It is critically important to appreciate that the development of anaphylaxis does not necessarily progress in the order of the classification scale: grade III and IV reactions often present very acutely (within seconds to minutes of administration of the causative agent) and signs associated with a grade I reaction may not be seen before or even during anaphylaxis (Carter et al. 2011, Dewachter et al. 2009, Girard and Lecce 2010, Harper et al. 2009, Kroigaard et al. 2007, Kushner and Trim 1994, Mason 1976, Okushima et al. 2013, Simons et al. 2013). Cardiovascular collapse or cardiac arrest were the sole features present in approximately 10% of peri-anaesthetic cases of anaphylaxis in humans (n = 518) (Mertes et al. 2003).

Anaphylaxis during general anaesthesia commonly includes cardiovascular dysfunction (arterial hypotension, cardiovascular collapse, cardiac arrest) and difficult ventilation (Mertes et al. 2003). Tachycardia and hypotension are usually observed, though bradycardia (resulting from the Bezold-Jarisch reflex) may occur in up to 10% of cases during general anaesthesia (Dewachter et al. 2009, Harper et al. 2009, Kroigaard et al. 2007).

Perioperative anaphylaxis in humans is uncommon, with an estimated incidence of 1 in 10,000 to 20,000 anaesthetics, but carries a mortality rate of around 4-10% (Axon and Hunter 2004, Dewachter et al. 2009, Gibbs et al. 2013, Harper et al. 2009, Reitter et al. 2014). From the limited number of published veterinary reports it is impossible to ascertain a mortality rate. Several
reasons account for this low publication rate, including under-reporting of anaphylaxis due to failure of recognition, difficulty in confirming a suspected causative agent and publication bias (preference for novelty and a positive outcome, and a reduction in the publication of single case reports). Reports in the veterinary literature have implicated antibiotics, vaccines, opioids, NSAIDs, intravenous anaesthetic induction agents, radiocontrast media and non-medicinal causes (BAER et al. 1962, Carter et al. 2011, Clutton 1987, Davis 1984, Girard and Lecce 2010, Harðardóttir et al. 2015, Kushner and Trim 1994, Mason 1976, Okushima et al. 2013, Pollard and Pascoe 2008, Rossanese and Rigotti 2015).

In humans, the most common triggers of perioperative anaphylaxis are NMBAs, latex, and antibiotics (Dewachter et al. 2009, Harper et al. 2009, Mertes et al. 2003). The majority (approximately 70%) of anaphylaxis caused by antibiotics in human medicine result from penicillins and cephalosporins (e.g. cefazolin, used in this case), which share the beta-lactam ring and are typically mediated by IgE (Harper et al. 2009, Pichichero and Casey 2007).

The association between completion of the incisional block and the second period of cardiorespiratory compromise raises the possibility that bupivacaine was involved in the anaphylactic reaction. However, anaphylaxis from local anaesthetics is very uncommon and primarily associated with ester rather than amide compounds (Harper et al. 2009). Furthermore, when an amide local anaesthetic (bupivacaine or mepivacaine) was administered during an earlier general anaesthetic in 2010 for a tooth extraction, there were no complications reported, the onset of clinical signs in this case preceded administration of bupivacaine and the use of bupivacaine for dental locoregional anaesthesia during a subsequent general anaesthetic did not result in a reaction.

Early recognition of anaphylaxis and aggressive intervention are central to a successful outcome. However, diagnosis and treatment of anaphylaxis is easily delayed if clinical signs are restricted to a single body system. For example, hypotension is a common side effect of anaesthetic drugs and tachycardia often reflects a nociceptive response (Harper et al. 2009). Treatment of anaphylaxis is based on the ABC (“airway”, “breathing”, “circulation”) principles of...
cardiopulmonary resuscitation. Additional considerations specific to anaphylaxis include: 1. removal of potential causative agents, 2. continuation of anaesthesia, if necessary, with inhalational agents (these have never been associated with anaphylaxis), 3. early administration of epinephrine (for cardiovascular support and bronchodilation), 4. provision of supplemental oxygen, 5. fluid resuscitation (to offset vasodilation associated with histamine release), 6. exclusion of other causes of clinical signs e.g. anaesthetic overdose, obstruction of the endotracheal tube. Secondary management includes administration of antihistamine, corticosteroids, a bronchodilator and close post-procedure monitoring (Harper et al. 2009, Kemp et al. 2008, Simons et al. 2013, Vadas and Perelman 2012).

Unfortunately, the clinical management of anaphylaxis deviates significantly from recommended guidelines (Choo et al. 2012). A multinational study of 2114 human patients with anaphylaxis reported the administration of epinephrine in only 12% of cases, with 50% of cases receiving antihistamines or glucocorticoids, or both (Grabenhenrich et al. 2012). A similar pattern appears in the veterinary literature, including the case reported here, with the minority of suspected cases of anaphylaxis receiving epinephrine (Girard and Leece 2010). The dose of epinephrine used in this case (5 mcg/kg) was higher than the 1 mcg/kg dose recommended in people. There is currently no dose recommendation in the treatment of anaphylaxis in companion animals.

Volume resuscitation is recommended during initial management of anaphylaxis (Perel et al. 2013, Simons et al. 2011, Simons et al. 2013). Fluids were provided in this case as part of the anaesthetic management plan, but additional boluses could have been given as supportive therapy during the periods of hypotension.

Antihistamine and corticosteroid administration should not replace epinephrine as neither relieve the life-threatening symptoms of anaphylaxis (Simons et al. 2013). The administration of antihistamines is not supported by high-quality evidence: they have a relatively slow onset of action (compared with epinephrine), do not relieve hypotension or bronchoconstriction and may cause sedation (Simons et al. 2013). Similarly, there is a significant absence of evidence...
supporting the use of glucocorticoids in the primary management of anaphylaxis, except for a
potential role in preventing biphasic anaphylaxis (Choo et al. 2012, Tole and Lieberman 2007).
Though applied successfully in this case and another in the veterinary literature, the use of
inhaled bronchodilators should not replace epinephrine, which has positive chronotropic,
inotropic and vasoconstrictive effects in addition to bronchodilator properties (Harðardottir et al.
2015).
In this case, the resolution of symptoms after initial treatment followed by recurrence of a second
episode consistent with anaphylaxis suggests that either the first episode had not fully resolved or
that biphasic anaphylaxis occurred (Alqurashi et al. 2015, Ellis and Day 2007, Tole and
Lieberman 2007) Biphasic anaphylaxis occurs in 1-20% of anaphylactic reactions, with the
second episode of anaphylaxis occurring at an unpredictable interval (1-38 hours, most occurring
within 8 hours) after the first (reviewed in Tole and Lieberman 2007). Though there has been
some suggestion that corticosteroids administered during initial anaphylaxis may reduce the
likelihood of a second episode, the evidence is weak (Choo et al. 2012, Simons et al. 2013).
Predictive factors for biphasic anaphylaxis are undetermined but a severe initial reaction and
undertreatment with epinephrine (delayed or low dose) may be related to risk (Alqurashi et al.
2015, Ellis and Day 2007, Tole and Lieberman 2007). The underlying mechanisms of biphasic
anaphylaxis are unknown. Based on clinical presentation and management of this case it is
unclear if it represents a true biphasic response or protracted anaphylaxis with temporary
resolution of symptoms. Early initiation of epinephrine therapy may have shortened the duration
of symptoms and prevented the second episode.
Confirming anaphylaxis and identifying potential allergens requires serological and skin tests.
Serial blood samples, taken to measure tryptase, an enzyme released by mast cells and basophils
during anaphylaxis can be used to confirm anaphylaxis. Samples should be taken approximately
one hour after the onset of clinical signs, with subsequent samples several hours in to the
recovery period (to establish a patient-specific baseline) (Harper et al. 2009, Sheldon and Philips
2015). Skin testing is the gold standard for identifying IgE mediated allergy but will not identify a
causative agent in non-allergic anaphylaxis. Maximal concentrations for testing different putative
agents are available for humans to avoid false positives and minimise the risk of triggering
anaphylaxis (Dewachter et al. 2009). After consulting a dermatologist, skin testing to confirm the
suspected allergy to cefazolin was offered to the owner; however, after discussing the potential
risks along and the inability to guarantee a definitive diagnosis, it was determined that it was not
in the patient’s best interest to proceed.

As predicting anaphylaxis is difficult without a clear history of hypersensitivity and the mortality
rate high even with appropriate treatment, prevention and vigilance are important. In this case, the
patient’s records were clearly marked in several locations with a warning to indicate suspected
hypersensitivity to cefazolin (Elliott and Liu 2010).


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