

CASE REPORT

Suspected anaphylactoid reaction following intravenous administration of a gadolinium-based contrast agent in three dogs undergoing magnetic resonance imaging

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Abstract

Observations Anaphylactoid reactions were suspected in three dogs following the intravenous administration of the contrast agent gadobenate dimeglumine 0.05 mmol kg⁻¹ (Multihance®).

Case 1: A 14 kg 6-year-old atopic female dog was anaesthetized for brain magnetic resonance imaging (MRI). All monitored parameters remained stable during the procedure. Fifteen minutes following MR completion; facial, peri-orbital and sublingual oedema were noted. Resolution of the oedema was rapid and uneventful following treatment of clinical signs over 2 hours.

Case 2: A 16 kg 10-month-old male dog was anaesthetized for brain and neck MRI. Ten minutes after MR contrast intravenous (IV) injection; heart rate (HR) increased (85–120 beats minute⁻¹), mean arterial blood pressure (MAP) decreased (from 70 to 43 mmHg) and Pe'CO₂ decreased (from 4.66 to 3.19 kPa). Labial, periorbital and lingual oedema were noted. Clinical signs responded to fluid bolus administration. The dog vomited in recovery but oedema resolved within one hour.

Case 3: A 34 kg 2-year-old atopic male dog was anaesthetized for head MRI. Within 5 minutes of MR contrast IV injection; the dog suffered severe cardiovascular collapse. MRI procedure was aborted and administration of anaesthetics discontinued. Aggressive IV fluid resuscitation and IV epinephrine administration were necessary to re-establish cardiovascular stability. Some periorbital and labial

oedema were noted. The dog vomited once and had soft faeces but made a complete recovery.

Conclusions The administration of contrast medium may result in mild to severe anaphylactoid reactions.

Keywords anaphylactoid, anaphylaxis, contrast agent, dog, gadobenate dimeglumine.

Introduction

Magnetic resonance imaging (MRI) is a diagnostic tool used widely in veterinary species. Often a contrast study is required using an intravenous (IV) gadolinium-based contrast agent such as gadobenate dimeglumine (Multihance®; Bracco S.p.A. Italy). In humans, although the safety of this agent is comparable to that of the other gadolinium-based agents adverse effects have been reported including dyspnoea, nausea, urticaria, hypotension and life threatening hypersensitivity reactions (Shellock et al. 2006; Abujudeh et al. 2010). Changes in heart rate and blood pressure have been reported in dogs following IV ionic iodinated contrast agent and gadolinium injections (Pollard & Pascoe 2008; Pollard et al. 2008) but no severe reactions have been reported in veterinary species with gadobenate dimeglumine. This case series presents three cases of apparent anaphylactoid reaction to the contrast agent gadobenate dimeglumine in dogs undergoing MRI under general anaesthesia. The

cases are presented by order of clinical signs severity.

Case presentations

In all three cases an IV catheter was placed in a cephalic vein and monitoring under anaesthesia consisted of capnography, end tidal gas and agent monitoring, non-invasive blood pressure (oscillometric), and pulse oximetry (*In Vivo* Research Inc. Millenia 3155A remote monitor, FL, USA). All patients received Hartmann's solution (Aquapharm 11; Animalcare Limited, UK) administered IV at 5–10 mL kg⁻¹ hour⁻¹ during anaesthesia. Inhalational anaesthetic agents were delivered via a circle rebreathing system and intermittent positive pressure ventilation (IPPV) was imposed (VentiPac Pneupac limited, England). The same contrast agent, gadobenate dimeglumine 0.05 mmol kg⁻¹ (Multi-hance® Bracco S.p.A., Italy), was administered IV at approximately 2 mL minute⁻¹ in all three cases.

Case 1

A 14 kg, 6-year-old female neutered mixed breed presented with a history of seizures and MRI (GE Signa 1.5 Tesla; GE Medical Systems, WI, USA) of the brain was performed. The patient previously had been diagnosed and treated for atopic dermatitis but was not receiving any treatment prior to anaesthesia. No abnormalities were detected on clinical examination. Butorphanol 0.1 mg kg⁻¹ (Torbugesic; Fort Dodge Animal Health, UK) was administered IV 5 minutes before induction of anaesthesia with propofol 2 mg kg⁻¹ (Propofol; Abbott Laboratories, UK) IV in combination with diazepam 0.2 mg kg⁻¹ (Diazemuls; Dumex Limited, UK) IV. Following endotracheal intubation, anaesthesia was maintained with isoflurane (Isoflo; Abbott Laboratories, UK) delivered using a minimum of 50% oxygen in medical air. Gadobenate dimeglumine was administered 20 minutes after induction of anaesthesia. All monitored parameters remained stable during the procedure. Following completion of the MR scan, and 15 minutes after administration of gadobenate dimeglumine, periorbital and labial oedema was noted. CSF collection was performed and further facial oedema and sublingual fluid-filled vesicles developed during this time. Hartmann's solution was infused IV at 10 mL kg⁻¹ hour⁻¹ for 2 hours. Chlorphenamine 0.4 mg kg⁻¹ (Chlorphenamine injection; Link Pharmaceuticals Limited, UK) was

administered subcutaneously (SC) followed by methyl-prednisolone 10 mg kg⁻¹ (Solu-Medrone™ V; Pharmacia Animal Health Limited, UK) IV. The patient was monitored (respiratory rate and pattern, heart rate, pulse quality) for 8 hours. Recovery from anaesthesia was rapid and uneventful and the oedema resolved gradually over 2 hours.

Case 2

A 17 kg, 10-month-old male Labrador presented 10 months after the first case with a history of depression, episodes of weakness and neck pain. MRI of the brain and the cervical spine was scheduled. No additional abnormalities were detected on clinical examination and the dog was not receiving any treatment. Following preoxygenation, anaesthesia was induced with propofol 3 mg kg⁻¹ IV in combination with lidocaine 2 mg kg⁻¹ (Lidocaine Hydrochloride Injection 2%; Hameln pharmaceuticals, Germany) IV and midazolam 0.25 mg kg⁻¹ (Hypnovel; Roche Products Limited, UK) IV. After endotracheal intubation, anaesthesia was maintained with sevoflurane (Sevoflo; Abbott Laboratories, UK) delivered using a minimum of 50% oxygen in medical air. Gadobenate dimeglumine was administered approximately 30 minutes after induction of anaesthesia. Ten minutes after contrast agent administration the HR increased from 85 to 120 beats minute⁻¹. MAP decreased from 70 to 43 mmHg and end-tidal carbon dioxide (P_E'CO₂) decreased from 4.66 to 3.19 kPa (35–24 mmHg). Hartmann's solution 10 mL kg⁻¹ was administered over 7 minutes and inhalational agent concentration decreased from a vaporiser setting of 2.2–1.5% (F_E'SEVO 2.1–1.4%). Within 5 minutes the MAP increased to 80 mmHg and P_E'CO₂ to 4.79 kPa (36 mmHg). The heart rate decreased to 85 beats minute⁻¹. Fluid administration was maintained at 15 mL kg⁻¹ hour⁻¹ for the rest of the procedure. At the end of the procedure, labial, periorbital and lingual oedema were noted and the dog vomited in recovery. Chlorphenamine 0.4 mg kg⁻¹ was injected SC. Hartmann's solution 10 mL kg⁻¹ hour⁻¹ IV was maintained for 6 hours and the patient monitored closely. The oedema resolved within 1 hour.

Case 3

A 35 kg, 2-year-old male German shepherd dog presented 2 months after the first case with a

history of recurrent otitis; MRI of the head was performed. The dog had previously been diagnosed and treated for atopic dermatitis but was not receiving any treatment prior to anaesthesia. No abnormalities were detected on clinical examination. Medetomidine $2 \mu\text{g kg}^{-1}$ (Domitor; Pfizer Animal Health, UK) and butorphanol 0.15 mg kg^{-1} were administered by intramuscular (IM) injection 10 minutes before induction of anaesthesia with propofol 2.5 mg kg^{-1} IV. Following endotracheal intubation, anaesthesia was maintained with sevoflurane delivered using a minimum of 50% oxygen and nitrous oxide. Gadobenate dimeglumine was administered 10 minutes after anaesthetic induction. Within 5 minutes HR increased from 60 to 100 beats minute^{-1} although MAP remained stable. Propofol 1 mg kg^{-1} was administered IV to increase the depth of anaesthesia and the percentage of sevoflurane delivered was increased to obtain an end-expired concentration of 3.2%. During the next 10 minutes the heart rate decreased from 100 to 75 beats minute^{-1} , MAP from 110 to 42 mmHg and $\text{PE}'\text{CO}_2$ from 4.79 to 2.93 kPa (36–22 mmHg). No peripheral pulses were palpable and the femoral pulse was barely palpable. The MRI procedure was aborted. Sevoflurane and nitrous oxide administration were discontinued. No changes in heart rate or MAP were seen after administration of Hartmann's solution 10 mL kg^{-1} IV over 10 minutes. Epinephrine $1 \mu\text{g kg}^{-1}$ [Adrenaline (Epinephrine) Injection BP; Hameln Pharmaceuticals, Germany] IV was administered with further Hartmann's solution 10 mL kg^{-1} IV. The femoral pulses became palpable and HR and MAP returned to 100 beats minute^{-1} and 90 mmHg, respectively, over approximately 10 minutes. Some periorbital and labial oedema were noted but no respiratory abnormalities were noticed. Hartmann's solution $10 \text{ mL kg}^{-1} \text{ hour}^{-1}$ was administered IV for 6 hours. The dog vomited once and had soft faeces during recovery but no other adverse events were noted.

Discussion

Anaphylactic and anaphylactoid reactions are rare events. Due to the timing of events, the reactions described here were highly likely to be related to the administration of the contrast medium. These three cases with suspected anaphylactoid reactions were identified during a period of 18 months during which time a total of 1500 dogs received gadolinium dimeglumine.

Anaphylactic reactions to gadolinium-based contrast agent have been described in humans (Shellock et al. 2006; Kalogeromitros et al. 2007; Abujudeh et al. 2010) but the mechanism remains unknown. Anaphylactoid reactions have a similar presentation as anaphylaxis but the pathophysiology differs. Immunoglobulin E (IgE) directed against a hapten mediates the degranulation of mast cells and basophils in anaphylaxis whereas direct release of mast cell and basophil mediators and/or complement activation occurs in an anaphylactoid reaction (where the immune system has not been previously sensitised to a hapten). A rapid decrease in blood pressure and a sudden increase in heart rate were not representative of just the cardiovascular effect of a deep depth of anaesthesia. The vaporizer settings had not changed and the inhaled partial pressures of anaesthetic vapour were within normal limits. No drugs had been recently administered to the dogs apart from the contrast agent so were unlikely to have triggered the reaction. In case 3, the administration of propofol and concomitant increase in sevoflurane concentration during the early stages of the suspected reaction to gadolinium make it impossible to state that the cardiovascular manifestations observed were caused by an anaphylactoid reaction alone. This is because both propofol and sevoflurane will depress cardiovascular function and may have produced the same cardiovascular effects. However, the dog also exhibited periorbital and labial oedema which suggest histamine release, which propofol and sevoflurane are unlikely to have triggered. In all three cases described above, the clinical signs were consistent with an anaphylactoid reaction. None of the three cases had previously received a gadolinium-based contrast agent so were unlikely to have produced IgE although anaphylactic shock after first exposure to gadoterate meglumine has been reported (Hasdenteufel et al. 2008). Two dogs had atopic dermatitis, which increases the risk for human patients to developing anaphylaxis (Laxenaire et al. 1992; Mertes et al. 2003). The production of high levels of IgE in these patients makes cross-reaction more likely. Both dogs with a history of atopic dermatitis received butorphanol during pre-anaesthetic medication. Some opioids may cause histamine release (Schurig et al. 1978) but butorphanol did not increase histamine plasma concentrations after administration in human patients (Schurig et al. 1978).

The high osmolarity and/or the chemical structure of gadobenate dimeglumine may produce a

direct effect on mast cell membranes which triggers histamine release (Brockow et al. 2005). Combined with intravenous administration, this may increase the chance of reaction at first exposure. No further investigations, such as skin testing or serum tryptase concentration, were performed to rule out other causes of adverse reactions. Serum mast cell beta-tryptase concentration analysis has been used to demonstrate activation of mast cells. An increased concentration provides evidence of either an IgE-mediated anaphylaxis or direct anaphylactoid degranulation of mast cells, the latter providing similar concentrations of serum tryptases (Payne & Kam 2004).

Recognition of signs of hypersensitivity reactions under anaesthesia is often delayed, particularly where patient access is restricted, such as during MRI. The most common clinical manifestations described in humans are flushing, urticaria, increased peak inspiratory pressure, increased $\text{Pe}'\text{CO}_2$, wheezing, bronchospasm, tachycardia, hypotension, cardiac arrest and disseminated intravascular coagulation (Hepner & Castells 2003). The most frequent manifestation of adverse reactions to MR contrast media in human patients was found to be nausea and vomiting (40%) followed by urticaria and rash (33%) (Li et al. 2006). The majority of those manifestations were mild and transient (96%) and only one patient among 9528 suffered an anaphylactoid reaction (0.01%). In dogs, the early cutaneous signs are difficult to detect. When tachycardia and hypotension occur, moderate to severe reactions are already in progress. For this reason an appropriate management plan should be prepared and applied according to the rapidity and severity of clinical signs.

The management of anaphylaxis/anaphylactoid reaction (as a group) in human medicine comprises three phases. The first phase is to withdraw the patient from the exposure of the drug incriminated, when possible. The second phase is to counteract the clinical effects of anaphylaxis/anaphylactoid reaction. If the patient is severely affected, discontinuation of the anaesthetic, administration of IV fluids for cardiovascular support, airway management and administration of 100% oxygen should be provided. Epinephrine is also used for its cardiovascular and bronchodilator effects. The efficacy of epinephrine treatment in canine anaphylactic shock has been investigated (Mink et al. 1998, 2004; Bautista et al. 2002). An infusion of epinephrine at $0.05 \mu\text{g kg}^{-1}$ per minute produced haemodynamic improvement during recovery from anaphylactic

shock compared to a single IV bolus (10 or $25 \mu\text{g kg}^{-1}$), which produced a short-lived increase in MAP and cardiac output (Mink et al. 2004). The third phase of management is prevention of further release of mediators. Histamine receptor (type 1 and 2) antagonists and corticosteroids (especially hydrocortisone because of its fast onset) are the drugs of choice for this phase. Corticosteroids may prevent/decrease airway oedema with their anti-inflammatory/immunomodulatory properties.

Each case in the series reported here presented differently, and was managed by a different anaesthetist, accounting for the various treatments. In the first case diagnosis was delayed, and as no cardiovascular or respiratory impairment were noted, treatment consisted of prevention of release of further mediators. Chlorphenamine is a type 1 histamine receptor antagonist; administration of this type of antagonist during the acute phase of the reaction can worsen cardiovascular signs and is controversial in humans (Brown et al. 2006). The presence of subcutaneous oedema could have reduced absorption of chlorphenamine and perhaps the IM or IV route would have been more appropriate. Methyl-prednisolone was administered to minimise the progression of the oedema and decrease the risk of laryngeal oedema. More severe cardiovascular reactions were seen in the second and third cases. In the third case, the initial rise in HR was mistaken for an insufficient depth of anaesthesia. The heart rate then decreased, which may have been due to propofol administration or the medetomidine that had been used for preanaesthetic medication. Severe hypotension then developed which did not improve with intravenous fluid therapy. In anaphylactoid reactions a compensatory tachycardia usually develops in association with hypotension and the propofol could have worsened the consequences of the presumed anaphylactoid reaction. In this case the $\text{Pe}'\text{CO}_2$ decreased during the suspected reaction. In human patients, some of the clinical manifestations of anaphylactoid reaction is an increase in $\text{Pe}'\text{CO}_2$ and bronchoconstriction. Case 3 was maintained under anaesthesia with sevoflurane, which produces bronchodilation in dogs (Hashimoto et al. 1996) and may have, hypothetically, counterbalanced the bronchoconstrictive effect of the histamine release and the reduction of $\text{Pe}'\text{CO}_2$. Histamine release is also responsible for peripheral vasodilation which may have reduced venous return, hence cardiac output. More plausibly the decrease in $\text{Pe}'\text{CO}_2$ in this case

may be due to a cardiovascular cause and not due to decreased ventilation exchanges from bronchoconstriction. The anaesthetist decided not to administer antihistamines to this case in the light of their controversial use in man (Brown et al. 2006).

Administration of histamine receptor antagonists (type 1 or 2) or corticosteroids as a preanaesthetic medication in known allergic human patients has been suggested (Tramer et al. 2006) but may not prevent life-threatening reactions (Setlock et al. 1993). In humans receiving iodinated contrast agent, premedication was considered unnecessary due to the large number of patients needed to be treated to avoid one severe reaction (Tramer et al. 2006). In dogs, preanaesthetic medication with H₁ and/or H₂ receptor antagonists or corticosteroids seems unnecessary also, due to the rare occurrence of reactions. However, high-risk patients, including dogs with atopy, may benefit from preanaesthetic medication as a precedent report seems to also support that atopic dogs might be at increased risk of developing contrast agent reaction (Pollard et al. 2008). Such medication of every patient may delay the early cutaneous response making early recognition difficult (Hepner & Castells 2003). The training of the MRI staff to diagnose and treat early signs of acute reaction to the contrast agent and information on the allergic status of the animal before undertaking the procedure are potential important points to reduce morbidity and mortality risks.

In conclusion, administration of gadolinium may result in anaphylactic or anaphylactoid reactions, in consequence close haemodynamic monitoring of canine patients following administration of gadobenate dimeglumine is recommended.

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