

COMPANION OR PET ANIMALS

Suspect anaphylaxis following intravenous buprenorphine administration in a dog

Matteo Rossanese,^{1,2} Clara Rigotti¹

¹School of Veterinary Science,
University of Liverpool,
Neston, UK
²Parkside Veterinary Surgery,
Neston, UK

Correspondence to
Matteo Rossanese,
matteo.rossanese@gmail.com

Received 21 February 2015
Revised 26 March 2015
Accepted 30 March 2015

SUMMARY

A seven-month-old French Mastiff was scheduled to undergo exploratory laparotomy for the removal of gastric foreign bodies. Buprenorphine 20 µg/kg was administered intravenously as preanaesthetic medication. Five minutes after the injection, tachypnoea, dyspnoea, cyanosis and tachycardia developed; periorbital, labial and lingual oedema were also noted. Anaesthesia was induced with 4 mg/kg of propofol, and laryngeal visualisation revealed severe laryngeal oedema. The trachea was intubated with a 6 mm endotracheal tube and anaesthesia was maintained with isoflurane in oxygen. Fluid therapy was started and glucocorticoids were administered. The exploratory laparotomy was completed and gastric foreign bodies were removed. A temporary tracheostomy was performed as no improvement of the laryngeal oedema was detected. The patient recovered uneventfully and after 48 hours the tracheostomy tube was removed successfully. The reaction may be attributed to histamine release following injection of buprenorphine.

BACKGROUND

Anaphylactic IgE-mediated and non-IgE-mediated reactions are medical emergencies that involve an unpredictable systemic reaction, potentially fatal, due to the activation of mast cells and basophils (Lorenz and others 1978, Tomar and others 2012, Boggs and others 2013, Shmuel and Cortes 2013). Symptoms commonly affect the skin, respiratory tract and cardiovascular system, but the gastrointestinal system and the CNS may also be involved. In human and veterinary medicine, numerous agents have been identified as causes of anaphylactic reactions in the perioperative period. The most common are neuromuscular blocking agents, latex, antibiotics, iodinated contrast agents, colloids, hypnotics and opioids (Lorenz and others 1978, Yamaha and others 2004, Cohn and others 2007, Armitage-Chan 2010, Girard and Leece 2010, Carter and others 2011; Tomar and others 2012, Boggs and others 2013).

Opioids are commonly administered in human and small animal patients and they may cause histamine release; however, they rarely cause an anaphylactic reaction (Armitage-Chan 2010, Baldo and Pham 2012, Tomar and others 2012).

To the authors' knowledge, this is the first report of a suspected anaphylactic reaction that is non-IgE mediated due to an intravenous injection of buprenorphine in a dog.

CASE PRESENTATION

A seven-month-old, 25 kg, body condition score 4 out of 9, female entire French Mastiff was presented with a 24-hour history of vomiting, anorexia and lethargy. No other concurrent conditions were reported. At presentation, the patient was depressed and hypersalivating and abdominal palpation showed a painful and distended cranial abdomen. Heart rate (HR) was 96 bpm and respiratory rate (fr) was 24 breaths per minute, mucous membranes (MM) were pink, capillary refill time (CRT) was 1.5 seconds and peripheral pulses (PP) were strong. On thoracic auscultation no abnormalities were detected.

Serum biochemistry was unremarkable and mild neutrophilia was detected on haematology. Survey abdominal radiographs showed a dilated stomach filled with mixed gas and fluid and several soft-tissue opacities located in the pyloric antrum. An American Society of Anaesthesiology grade of 2 was assigned to the dog.

An exploratory laparotomy to remove the gastric foreign bodies was planned. A catheter was placed on the right cephalic vein, and as preanaesthetic medication, buprenorphine (Vetergesic, Alstoe Animal Health, single vial) 20 µg/kg was administered intravenously as a bolus.

After five minutes, the dog became tachypnoeic (fr 56 bpm) and successively dyspnoeic with increased inspiratory effort; periorbital and labial oedema developed, MM were pale with a prolonged CRT (>2 seconds), PP were poor and HR increased to 150 bpm.

As clinical signs progressively worsened and cyanosis became evident, propofol (Propoflo Plus, Abbott) at 4 mg/kg was administered intravenously to induce anaesthesia and to ensure patency of the airways. On oral and laryngeal examination, a marked lingual and supraglottic oedema was present: the laryngeal inlet was not visible despite the use of a laryngoscope and two tongue depressors. With difficulty, the dog's trachea was intubated without direct visualisation using a cuffed 6.0 mm endotracheal tube (ETT). The ETT was connected to a circle breathing system and tracheal intubation was confirmed by the synchronised movement of the rebreathing bag with the chest excursion and by audible airflow through the ETT. Oxygen was administered at 3 l/minute, MM colour turned pink and pulse oximetry reading was above 97 per cent. Anaesthesia was maintained with isoflurane (Isoflo, Abbott) with vapouriser settings between 1 and 2 per cent. Dexamethasone (Dexadreson, Intervet) was administered intravenously



To cite: Rossanese M, Rigotti C. *Vet Rec Case Rep* Published online: [please include Day Month Year] doi:10.1136/vetreccr-2015-000190

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at 0.4 mg/kg and chlorphenamine (Chlorphenaminem Archimedes Pharma) subcutaneously at 0.4 mg/kg. After three boluses of 10 mg/kg of crystalloids (Hartmann's solution, Aquapharm n°11, Animalcare limited) over 30 minutes, the HR decreased to 100 bpm and PP quality improved. A maintenance rate of crystalloids was set at 5 ml/kg/hour for the rest of the anaesthesia. As the dog was considered cardiovascularly stable it was decided to proceed with an exploratory laparotomy to remove the gastric foreign bodies.

OUTCOME AND FOLLOW-UP

Once the surgery was completed the oral cavity was reassessed; the larynx was severely oedematous and no improvement was detected. As extubation was at high risk for the patient due to upper airways obstruction, a temporary tracheostomy was performed. The patient was then allowed to recover from anaesthesia and recovery was uneventful with the exception of an episode of vomiting and loose faeces three hours after recovery.

Postoperative analgesia was provided with methadone (Comfortan, Dechra) 0.3 mg/kg intramuscularly every four to six hours and no adverse reactions were noted. Vital parameters (MM, CRT, HR, PP quality, fr and respiratory pattern) and tube dislodgement or obstruction were monitored closely postoperatively. Stoma cleaning and tube suctioning were performed every four hours. Dexamethasone at 0.2 mg/kg (Dexadreson, Intervet) was administered intravenously 24 hours after the first dose. The periorbital and labial oedema resolved four hours after recovery.

Twelve hours after anaesthesia the dog ate a small amount of food and was ambulatory and comfortable. Gastroprotectant therapy with sucralfate (Antepsin, Chugai) 500 mg orally every eight hours, ranitidine (Zantac, GlaxoSmithKline) 2 mg/kg intravenously every eight hours and omeprazole (Losec, Astrazeneca) 1 mg/kg intravenously every 24 hours was started.

Forty-eight hours after anaesthesia the tracheostomy tube was removed uneventfully and the patient was able to breathe effortlessly. The patient was discharged with a course of sucralfate (Antepsin, Chugai) 500 mg orally every eight hours for 10 days, ranitidine (Zantac, GlaxoSmithKline) 2 mg/kg orally every 12 hours for seven days and omeprazole (Losec, Astrazeneca) 1 mg/kg every 24 hours orally for 10 days. Four days postoperatively the patient was reassessed and all vital parameters were within normal limits, and the tracheostomy incision was healing by second intention.

DISCUSSION

This case report describes a suspected anaphylactic non-IgE mediated reaction after an intravenous injection of buprenorphine.

The term anaphylaxis describes a severe life-threatening systemic reaction that results from the sudden release of mediators such as histamine, tryptase, prostaglandins and leucotrienes from mast cells and basophils (Lorenz and others 1978, Boggs and others 2013, Shmuel and Cortes 2013, Sheldon and Philips 2015).

In human medicine, the incidence of intraoperative anaphylaxis has a range from 1 in 3500 to 1 in 20000 anaesthetics and the initial presentation can vary from case to case (Tomar and others 2012, Sheldon and Philips 2015); in veterinary medicine accurate information regarding the incidence is lacking.

During the perioperative period, it is often challenging to establish which drug is responsible for an adverse reaction as patients receive numerous drugs (Tomar and others 2012); however, in the current case report the patient received only

buprenorphine as preanaesthetic medication, resulting in easy drug identification.

Buprenorphine is a partial opioid μ -receptor agonist and a semi-synthetic derivate of the morphine alkaloid thebaine (Boggs and others 2013); in small animal practice buprenorphine is widely used because of its analgesic property, the long duration of action and the versatility of administration (Martinez and others 1997, Bell and others 2011).

Buprenorphine, as all opioids, has the potential to cause allergic reactions by activating the opioid receptor present on mast cells in an IgE-independent manner producing release of histamine (Armitage-Chan 2010, Stutius and others 2010, Wang and others 2011, Baldo and Pham 2012).

Many opioids have been described to cause histamine release, with morphine and pethidine being the most likely to cause histamine release when administered intravenously (Guedes and others 2007, Armitage-Chan 2010). With the exception of pethidine, natural compounds such as morphine and codeine appear to be more likely to cause histamine release than the 'synthetic' and 'semi-synthetic' compounds (Pharm 2006). Buprenorphine, being a semi-synthetic compound, is less likely than morphine to cause histamine release (Stellato and others 1992). In vitro studies showed that buprenorphine induces a concentration-dependent release of mediators (histamine and tryptase) selectively from human lung mast cells (Stellato and others 1992).

Reactions to buprenorphine have been described in clinical trials and post-marketing experience: the most common clinical signs include pruritus, rashes and hives (Boggs and others 2013). More severe clinical signs such as angioedema, bronchospasm and anaphylactic shock are reported in human medicine but are considered rare (Stutius and others 2010). Contact allergy dermatitis has been described after application of transdermal delivery system of buprenorphine but other clinical signs including bronchospasm and facial oedema were also reported (Griessinger and others 2005, Hulst and others 2008).

To the author's knowledge this is the first case report of an anaphylactic reaction following buprenorphine administered intravenously in veterinary medicine.

The speed of administration is considered a risk factor for the release of histamine; hence, slow administration of a diluted drug is preferred and is less likely to induce an adverse reaction (Guedes and others 2006, Tomar and others 2012). In this case, buprenorphine was administered quickly as a bolus and this may have been a contributing factor in the development of this reaction.

The initial presentation of anaphylactic reactions may involve different organ systems (Tomar and others 2012): most commonly the cardiovascular system with hypotension, arrhythmias, myocardial depression and cardiovascular collapse; the cutaneous system with flushing and urticaria; the respiratory system with bronchospasm and laryngeal oedema (Laxenaire and Mertes 2001, Tomar and others 2012, Sheldon and Philips 2015). The major cardiovascular features of the anaphylactic reaction are vasodilation and fluid extravasation causing hypovolemic shock: the increased vascular permeability leads to severe fluid shifts of about 35 per cent of the intravascular volume into the extravascular space within 10 minutes from the initial reaction (Fisher 1986, Brown 2005, Shmuel and Cortes 2013).

Due to the young age, the patient was not exposed to previous medications or opioids and did not have a history of atopic dermatitis. Hence, the immune system was not sensitised to a hapten and an anaphylactic non-IgE-mediated reaction was suspected (Lorenz and others 1978, Armitage-Chan 2010, Girard and Leece 2010).

The dog became dyspnoeic and cyanotic five minutes after the intravenous injection of buprenorphine, tachycardia was detected, pulse quality worsened and CRT was prolonged. Furthermore, periorbital and labial oedema were also noted. The dyspnoea was most likely associated with obstruction of the upper airway due to lingual, laryngeal and pharyngeal oedema, whereas the cardiovascular changes may be due to hypotension associated with vasodilation and fluid extravasation (Brown 2005, Girard and Leece 2010, Shmuel and Cortes 2013).

Crystalloids were administered for cardiovascular support and volume expansion; a high fraction of inspired oxygen was provided to support oxygenation during the upper airway obstruction and administration of corticosteroids and histamine receptor antagonists to decrease the airway oedema and to prevent further releasing of mediators respectively.

Epinephrine could have been used to reduce the mast cell and basophils release and for its vasoconstricting, positive inotropic and bronchodilating properties (Girard and Leece 2010).

In this case, after the reaction to buprenorphine, it was decided to use methadone for postoperative pain relief and no adverse reactions were noticed. In IgE-dependent anaphylactic reaction cross-reactivity between structurally different opioids is considered rare; therefore, a different opioid may be administered safely (Ginsberg 1985). Other alternatives for the management of acute pain are non-steroidal anti-inflammatory or regional anaesthesia techniques.

In conclusion, any drugs administered during the perioperative period have the potential to cause an adverse reaction and should be administered as slowly as possible (Mertes and Laxenaire 2000, Armitage-Chan 2010).

Pretreatment with corticosteroids or antihistamines is largely employed in patients with a history of anaphylactic reaction but there is no evidence that this prevents anaphylactic response (Liccardi and others 2008, Armitage-Chan 2010). The most effective measure in case of anaphylactic reaction is prompt detection of clinical signs and readily available equipment for a correct and immediate intervention (Armitage-Chan 2010).

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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Vet Rec Case Rep 2015 3:
doi: 10.1136/vetreccr-2015-000190

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