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CASE REPORT

Companion or pet animals

A suspected non-allergic anaphylactic reaction to intravenous administration of atracurium in a dog

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Abstract

Hypersensitivity reactions are rare events but have the potential to be life-threatening. They are relatively more common during general anaesthesia. This is potentially due to multiple drugs being administered concurrently. An 8-year-old, female neutered Labrador Retriever with bilateral cataracts was anaesthetised for right phacoemulsification. Soon after atracurium administration, the patient's heart rate (HR) increased, alongside decreases in arterial blood pressure and end tidal carbon dioxide (ETCO2). The dog was treated with clorphenamine and ephedrine intravenously (IV), while receiving a crystalloid fluids bolus. After 20 minutes both HR and blood pressure normalised, and the remainder of anaesthesia and recovery were uneventful. We suspected a non-allergic anaphylactic reaction to atracurium.

BACKGROUND

Most drugs administered during general anaesthesia have the potential to elicit allergic or non-allergic anaphylactic reactions. This current terminology, provided by the European Academy of Allergy and Clinical Immunology,[1] replaces the former distinction between anaphylactic and anaphylactoid reactions.

Allergic anaphylaxis refers to the involvement of the immune system in the reaction of the body to a foreign antigen. The latter stimulates the production of specific immunoglobulin E (IgE) which binds to receptors on mast cell and basophil membranes. At subsequent exposures, the antigen binds to these specific IgE antibodies triggering the activation of a cascade that leads to the release of mediators such as histamine, cytokines, leukotrienes and prostaglandins and to the upregulation of nitric oxide.[2,3] Clinical manifestations may vary in severity and include signs in the skin (oedema, redness, weals, pruritus), gastrointestinal tract (abdominal pain, nausea, vomiting, diarrhoea), cardiovascular system (increased vascular permeability, vasodilation and hypotension) and respiratory system (increased mucous secretion, increased smooth muscle tone and bronchospasm).[4] Classically, these clinical manifestations were thought to occur only after sensitization via a previous exposure to an antigen. However, due to cross-linkages between drugs and other chemical compounds (toothpaste, detergent, nuts, chestnuts, avocado, cough medication),[5,6] severe anaphylaxis can also occur at first exposure. Examples of drugs that can be responsible for allergic reactions in susceptible individuals in the perioperative period are aminosteroid neuromuscular blocking agents (NMBAs), latex, antibiotics (for instance penicillin, cephalosporins),[7] iodinated contrast agents,[6,7] gadolinium-based contrast agents[8] and succinylcholine.[9–11]

Manifestations of non-allergic hypersensitivity reactions are clinically indistinguishable from allergic anaphylactic ones, although the mechanism of action is different; they are also called non-immune reactions because the immune system is not involved. The foreign protein causes histamine release through direct binding to mast cell and basophil membrane receptors, leading to degranulation.[2,3,12] Furthermore, this drug-induced histamine release can be triggered via direct activation of the complement system, comprised of various proteins that, when activated, result in mast cell degranulation, increased vascular permeability and smooth muscle contraction.[2,12] Examples of drugs frequently used by anaesthesiologists that can cause such reactions include opioids (especially morphine and meperdine),[6] colloids (mainly gelatins),[6,9] hyperosmolar solutions such as mannitol,[6,7] benzylisoquinoliniums NMBAs.[10,13]

NMBAs are used in veterinary medicine to facilitate a variety of surgical procedures where muscle relaxation is required.[14] A common use is for those ocular surgeries in which the pupil is required to be central. Multiple NMBAs are available to the anaesthetist, among which non-depolarizing drugs are more commonly used due to their longer duration of action and the improved safety profile compared to depolarizing agents.[15] Hypersensitivity reactions to NMBAs are well documented in human literature,[5,9,10,13,16,17] while few reports exist in veterinary medicine.[2,18]

The aim of the present work is to document a hypersensitivity reaction in an anaesthetized dog likely related to atracurium administration.

CASE PRESENTATION

A 35.8 kg, 8-year-old female neutered Labrador Retriever was presented with bilateral cataracts and scheduled to undergo anaesthesia for right phacoemulsification.

The dog was fully vaccinated, with no allergies reported in the history, and no previous health problems reported by the owners. All haematological and biochemical variables were within normal limits, the dog was not on any medication, and there were no recorded adverse events during previous anaesthetics.

On clinical examination, heart rate (HR) was 116 bpm with a sinus rhythm, no heart murmurs were detected, and the dog was panting. Thoracic auscultation was normal bilaterally with a normal respiratory pattern. Peripheral (dorsal pedal artery) pulses, hydration status and capillary refill time were within normal limits. Body condition score was 7 out of 9,[19] and we allocated an ASA status of II.

Premedication consisted of acepromazine (ACP injection 2 mg/ml, Novartis) 20 μg/kg IM and methadone (Comfortan 10 mg/ml, Dechra Veterinary Products) 0.2 mg/kg IM. A 20 gauge intravenous catheter (Biovalve safe, Vygon) was placed in the right cephalic vein 30 minutes after premedication. The dog was pre-oxygenated for 5 minutes, and anaesthesia was induced with propofol (PropoFlo plus 10 mg/mg, Abbot) intravenously (IV) to effect (65 mg administered in total) until the eye rotated ventromedially and the jaw tone was relaxed. Following endotracheal intubation with a straight silicone tube 12 mm i.d. (51 Fr silicone endotube w/cuff, Jorvet, Jorgensen Laboratories) and inflation of the tube cuff until no leaks were detected at a pressure of 15 cmH2O, the patient was positioned in left lateral recumbency and connected to a circle breathing system. Anaesthesia was maintained with isoflurane (IsoFlo 100%, Zoetis) in 100% oxygen. The patient was connected to a multi-parameter monitor (Datex Engstrom compact, AS/3) and HR, respiratory rate (RR), ETCO2, SpO2 (arterial saturation of oxygen via a pulse oximeter), end tidal anaesthetic agent (ETAA) were recorded every 5 minutes. A size four blood pressure cuff was placed on the left antebrachium to monitor non-invasive blood pressure via an oscillometric method. Hartmann's solution (Aqupharm 11, Animalcare) was administered intravenously at 5 ml/kg/h. The dog was moved into the operating theatre 15 minutes after induction of anaesthesia, and propofol 30 mg (PropoFlo plus 10 mg/mg, Abbot) was administered during the transfer onto the operating table due to return of brisk spontaneous blinking. The patient was connected to an anaesthetic machine (Aestiva/5 Datex Ohmeda workstation with S/5 monitor) via an integrated circle breathing system, and anaesthesia continued with isoflurane (IsoFlo 100%, Zoetis) in 100% oxygen. Intermittent positive pressure ventilation was started (Datex Ohmeda 7900 software-driven, pneumatically powered ventilator). Lungs were mechanically ventilated at an RR of 10 breaths per minute, with a tidal volume (Tv) of 350 ml (approximately 10 ml/kg) and peak inspiratory pressure (PIP) of 12 cmH2O. Physiological variables were manually recorded every 5 minutes throughout the anaesthetic period. A peripheral nerve stimulator (Microstim DB3, supramaximal nerve stimulator, Viamed, UK) was placed over the superficial peroneal nerve on the lateral aspect of the head of fibula of the right hindlimb to monitor the neuromuscular blockade during surgery by visual and tactile assessment of the train-of-four (TOF) stimulation. Position of conducting electrodes was checked, and four contractions without fade of the digital extensors were obtained. Two minutes before surgery started (35 minutes after induction of anaesthesia), HR was 72 bpm, systolic arterial pressure was 101, with diastolic (DAP) and mean arterial pressures (MAP) of 55 and 75 mm Hg, respectively. ETCO2 was 5.4 kPa, ETAA was 1.3% (vaporiser setting 2%), and the dog was deemed at an adequate depth of anaesthesia (ventromedially rotated pupils, absent palpebral reflex, relaxed jaw tone). Atracurium (Atracurium besilate 10 mg/ml, Hameln) 0.3 mg/kg (total volume 1 ml) was administered IV over 1 minute. One minute after atracurium injection, HR increased to 116 bpm, MAP dropped to 30 mm Hg, and ETCO2 decreased to 3.8 kPa.

LEARNING POINTS/TAKE-HOME MESSAGE

- Anaphylaxis is a rare event but potentially life threatening.
- In the presence of an anaphylactic reaction, prompt recognition and initiation of appropriate treatment are crucial for a positive outcome.
- Allergic and non-allergic anaphylaxis associated with neuromuscular blocking agents' administration remain likely under-reported in veterinary medicine due to the multiple drugs administered during general anaesthesia and the perioperative period which can contribute to an adverse reaction.
- Slow administration of diluted solutions is highly recommended for potential histamine-releasing drugs.

TREATMENT

Clorphenamine (Clorphenamine maleate 10 mg/ml, MaCarthys Laboratories Ltd T/A Martindale Pharma, UK) 0.3 mg/kg IV was administered immediately, a crystalloid fluid bolus initiated (10 ml/kg over 20 min), and the vaporiser setting decreased to 1.5% (ETAA 1.1% within 10 minutes, further decreasing to 0.94% by the end of the surgical procedure). Over the next 10 minutes, HR reached a peak of 128 bpm and then started decreasing mildly, while MAP gradually increased to 55 mm Hg, and ETCO2 returned to 5.3 kPa. However, peripheral pulses were still weak. A decision was made to administer ephedrine (Ephedrine Hydrochloride 30 mg/ml, MaCarthys Laboratories Ltd T/A Martindale Pharma, UK) 0.042 mg/kg IV. Five minutes later, MAP was 70 mm Hg with an HR of 101 bpm, and peripheral pluses were good.

OUTCOME AND FOLLOW-UP

The last 30 minutes of the anaesthetic were uneventful. Neostigmine (Neostigmine methylsulfate 2.5 mg/ml, Hameln) 0.05 mg/kg and glycopyrronium (Glycopyrronium bromide 200 μg/ml, Martindale Pharmaceuticals Ltd, UK) 10 μg/kg were administered slowly IV at the end of surgery (which lasted 42 minutes), and anaesthesia continued until the patient recovered spontaneous ventilation with a normal tidal volume and thoracic excursion, and the TOF and double burst stimulation showed no signs of residual neuromuscular blockade. A mild swelling and redness of eyelids were noticed when surgical drapes were removed. Tracheal extubation was performed 5 minutes after discontinuation of the inhalant anaesthetic (total anaesthesia time was 100 minutes) once the dog swallowed. Recovery was calm and the patient was moved to the ICU unit. The cutaneous reactions persisted for approximately 15 minutes after recovery from anaesthesia, then resolved completely. MAP measured through an oscillometric device (Cardell 9401, Midmark Animal Health) every 10 minutes for 30 minutes was always above 75 mm Hg. The patient was discharged from the hospital 24 hours later with no further complications.

DISCUSSION

This case report describes cardiovascular complications and cutaneous signs in a dog, likely related to a non-allergic hypersensitivity reaction caused by the intravenous administration of atracurium.

Atracurium is a benzylisoquinoline non-depolarising NMBA which exerts its action via binding to nicotinic acetylcholine receptors of the motor endplate, thus inhibiting neurotransmission. The quaternary ammonium structure of these compounds, very similar to that of d-tubocurarine (especially atracurium), is responsible for the propensity of this class of drugs to cause direct histamine release without involvement of the immune system. Due to these factors and the absence of known allergies in the patient's history, we hypothesized a non-allergic hypersensitivity reaction was responsible for the events described.

Cases of hypersensitivity reaction following atracurium administration are well documented in human medicine,[9,11,20–22] but no reports exist in veterinary medicine. Numerous other drugs administered in the perioperative period can be responsible for an acute non-allergic hypersensitivity reaction or allergic anaphylaxis, among which antibiotics,[23–26] opioids,[27,28] iodinated[29] and gadolinium-based contrast media,[8,30] thiopentone,[31–33] acepromazine,[34,35] dexamethasone,[36] xylazine-ketamine[37] and rocuronium,[18] just to mention a few. Particularly during the perioperative period, many of these drugs are likely to be administered concurrently, thus making it difficult for the clinician to identify the agent responsible for the adverse reaction. This may account for the paucity of published reports of documented hypersensitivity reactions to NMBAs encountered in veterinary patients.

In the present case, acepromazine and methadone had both been administered 78 minutes before the adverse event, and no complications developed after administration. Antibiotics had not been administered yet, and the last dose of propofol (30 mg, when the patient was moved onto the operating table) was injected 13 minutes prior to the cardiovascular changes, which occurred 1 minute after the end of intravenous injection of atracurium. Hence, we hypothesized that the sudden hypotension and increased HR observed were due to vasodilatation related to histamine release associated with atracurium administration.

The use of acepromazine in the premedication may have worsened hypotension during general anaesthesia due to its α1-adrenoceptor antagonistic properties,[38–40] exacerbating vasodilation. Moreover, acepromazine has also been demonstrated to have the potential itself to release histamine.[34,35] In this case, blood pressure was within normal limits before atracurium administration, even though it is impossible to establish how much acepromazine contributed to the subsequent hypotension. Nevertheless, the use of acepromazine may have been of benefit for its antihistaminic properties due to H1 receptor blockade,[6,39] which could have limited the subsequent histamine release and complications.

The manifestations we detected, likely associated with a hypersensitivity reaction, were hypotension, increased HR and localized cutaneous swelling and rash. This clinical response, according to the Ring and Messmer clinical severity scale, can be classified as grade 2.[41] Grade 1 response comprises only cutaneous signs, increasing to grade 2 when non-life-threatening tachycardia, hypotension, dyspnoea and gastrointestinal signs occur. Life-threatening cardiovascular and respiratory compromise are categorized as grade 3, with cardiocirculatory arrest characterizing the most severe reaction (grade 4). This classification may be useful to guide the most appropriate patient management.[2]

Recommendations for anaphylaxis drills in the human literature[42,43] provide guidelines for immediate and secondary management. Primary treatment involves discontinuation of the suspected causative agents, maintenance of the airway and oxygen supplementation, seeking help, and administration of epinephrine and crystalloids. While secondary treatment is based on antihistamines and corticosteroid administration.

In the present case report, an endotracheal tube was in place, and the patient was receiving 100% oxygen; a senior anaesthetist was called in the operating theatre for help, and the surgeon was informed of the complications. No additional doses of atracurium were administered.

Epinephrine is the drug of choice in anaphylaxis, due to both α agonistic effects (vasoconstriction) and β effects (relaxation of smooth muscle and bronchodilation, positive inotropy and suppression of inflammatory mediators such as histamine).[3,42] Multiple studies and reviews recommend early administration of epinephrine in severe cases, that is, grade 3 and 4 of the Ring and Messmer classification,[2,6,44] particularly in the light of the common association of significant bronchoconstriction with cardiovascular signs in severe reactions.[44] We decided not to administer epinephrine because cardiovascular signs were moderate and were improving in our patient. Furthermore, unlike various other case reports in the veterinary literature[18,23,26,29,30] where respiratory signs (bronchospasm and decreased chest compliance) were associated with cardiovascular ones, no signs of severe bronchoconstriction were evident in our patient (Tv and PIP did not show any changes during the episode). Nonetheless, peripheral pulses were still weak 15 minutes after the onset of hypotension.

A decision was made to administer ephedrine to promote an increase in cardiac output in order to improve tissue perfusion. Ephedrine is a naturally occurring sympathomimetic amine, synthesized for medical use, that acts both indirectly (inducing norepinephrine release from the sympathetic nerve terminals) and directly on α and β adrenoceptors. At lower doses it acts predominantly on β adrenergic receptors,[45] resulting in increased myocardial perfusion, cardiac contractility, cardiac output and blood pressure. A single bolus proved sufficient in our patient to increase blood pressure and improve pulse quality.

In our patient, clorphenamine was administered promptly in an attempt to prevent further histamine release. The role of H1 antihistaminic drugs in anaphylaxis is controversial, as there is no consensus regarding the benefits related to their use,[44,46] especially once cardiovascular collapse has occurred.[47] Muraro et al[17] conducted a systematic review which produced the guidelines from the European Academy of Allergy and Clinical Immunology in anaphylaxis. The authors' recommendations (with a level of evidence I) are to employ antihistamines only as a third line intervention, because their benefits have been demonstrated to relieve solely cutaneous signs such as pruritus and urticaria.[48–50] Indeed, a few case reports described hypotension related to intravenous administration of antihistamines potentially associated with the speed of injection.[51] Improved outcomes have been observed when H1 antagonists were combined with H2 antagonists (for example ranitidine),[49] which were not administered in this case. However, the use of H1 blockers in the early phases of anaphylaxis is still recommended by many other authors and included in the guidelines for management of anaphylaxis during anaesthesia and the perioperative period.[3,42,43]

Administration of aggressive intravenous crystalloid replacement is advised as part of immediate treatment in anaphylaxis to compensate for the large fluid shifts associated with vasodilation and capillary leakage.[3,6,42,44] We administered a volume of Hartmann's solution of approximately 350 ml (10 ml/kg) over 20 min, which does not represent a large total volume compared to shock rates (60–90 ml/kg). However, less aggressive fluid replacement may be sufficient for grade 2 reactions[2] and led to an improvement in our patient. Despite the enhancement we observed, it is not possible to rule out whether a higher speed of administration, achievable through a second intravenous catheter or fluids administered with a pressure bag, would have led to a better circulatory volume thus increasing blood pressure faster and more consistently.

The speed of injection and the allergen concentration are considered the primary factors in non-allergic hypersensitivity reactions, and they are positively correlated with the severity of signs.[2,3] Other determining factors are the patient's sensitivity and the route of administration, with the IV injection potentially triggering the most rapid and severe responses.[3] While even a small amount of allergen can trigger a fatal response,[3] a recent veterinary case report also possibly suggests a role of the total dose administered in the severity of clinical signs.[26] Histamine release may be avoided/blunted by slow administration of diluted solutions,[6,7,14,44] thus allowing early discontinuation of the suspected allergen if an adverse reaction is detected. In this case, atracurium was administered intravenously undiluted over 1 minute. Considering the total volume administered, a slower speed of injection and a dilution with saline might have potentially prevented the development of the hypersensitivity reaction.

In conclusion, to the authors' knowledge, this is the first report of a suspected non-allergic hypersensitivity reaction to atracurium in a dog. Prompt recognition of the adverse event and initiation of appropriate therapy are of utmost importance.[6,42,44] Where large volumes of potentially allergenic substances are to be administered, a slow speed of injection and possible dilution with saline are recommended.

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