COMPANION OR PET ANIMALS

Severe bradycardia after hypoxaemia and endotracheal intubation and cardiac arrest following glycopyrrolate in a dog

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SUMMARY

A nine-year-old neutered male Yorkshire terrier with history of chronic cough underwent bronchoscopy and bronchoalveolar lavage; general anaesthesia was maintained with a variable rate infusion of propofol, and oxygen was insufflated via a urinary catheter in the trachea. At the end of the procedure, desaturation occurred; endotracheal intubation was performed and was immediately followed by severe bradycardia and respiratory arrest. Glycopyrrolate (5 µg/kg) was administered leading to cardiac arrest. Apnoea and asystole were quickly treated with manual positive pressure ventilation, external chest compressions and intravenous administration of 0.04 mg/kg of atropine. This case describes vagally induced bradycardia after intubation, possible predisposing factors and its treatment/prevention with antimuscarinic drugs.

BACKGROUND

To the author's knowledge, this is the first report of severe bradycardia during intubation followed by cardiac arrest after glycopyrrolate administration in dogs. In veterinary medicine, vagally mediated arrest as an adverse effect of endotracheal intubation is only briefly mentioned in some anaesthesiology textbooks (Dugdale 2010), whereas, in human medicine, bradycardia and asystole during laryngoscopy and tracheal intubation are well-recognised complications (Jones 2016). Due to the vagal origin of this reflex bradycardia, antimuscarinic drugs are commonly used as a treatment or prevention (Dyson and James-Davies 1999, Lerche 2015). The aim of this report is to warn clinicians of the possible development of bradycardia during endotracheal intubation and to alert them that care should be taken when glycopyrrolate is administered to counteract vagally mediated bradycardia.

CASE PRESENTATION

A nine-year-old, 7.2 kg, neutered male, Yorkshire terrier was referred for investigation of chronic cough. Haematology was unremarkable, biochemistry blood tests revealed moderately elevated urea (12.6 mmol/l Reference Intervals (RI): 3.5–6.0), alkaline phosphatase (338 U/I RI: 0–100) and cholesterol (8.1 mmol/l RI: 3.2–6.5) and mild hyperalbuminemia (35 g/l RI: 23–31); all other values were within normal limits. Cardiac troponin I was mildly elevated (0.165 ref <0.15 ng/ml) and systolic blood pressure, measured by a Doppler flow detector, was 155 mm Hg.

A six-lead electrocardiogram (ECG) was performed showing sinus arrhythmia with occasional premature supraventricular complexes and P pulmonale; P waves of variable morphology were also present, consistent with wandering pacemaker. Doppler echocardiography identified degenerative myxomatous mitral valve disease with no evidence of significant left side volume overload, cardiac remodelling or congestive heart failure and normal systolic function.

General anaesthesia was requested for thoracic and neck radiographs, bronchoscopy and bronchoalveolar lavage (BAL).

At preoperative examination, the dog was bright, alert and responsive, panting, heart rate (HR) was 120 beats per minute (bpm), mucous membranes were pink and moist and capillary refill time was less than two seconds. The dog was premedicated with butorphanol (Dolorex; MSD Animal Health) 0.3 mg/kg intramuscularly and acepromazine (ACP; Novartis) 0.02 mg/kg intramuscularly. Fifty minutes later, an intravenous catheter was placed in the right cephalic vein and neck, and thoracic radiographs were taken under sedation. Radiographs showed a generalised bronchial pattern, particularly apparent in the caudal lung lobes and tracheal collapse.

To perform tracheobronchoscopy and bronchoalveolar lavage, general anaesthesia was induced with propofol (Vetofol 1.0 per cent; Norbrook) slowly to effect (total dose 2 mg/kg intravenously) without preoxygenation due to non-cooperation of the dog. Oxygen was administered at 4 l/minute via a dog urinary catheter inserted into the trachea and general anaesthesia was maintained with a variable rate infusion of propofol (0.4–0.56 mg/kg/minute). Throughout the procedure the dog was panting, HR was between 100 and 116 bpm, mean arterial pressure (MAP), measured with an oscillometric device (Datex Engstrom Compact; Datex Ohmeda) was between 70 and 100 mm Hg and oxygen saturation (SpO_2) was 98 per cent. Twenty-five minutes after induction, immediately after BAL was performed, SpO_2 decreased to 85 per cent and crackles were audible on both sides at lung auscultation, mainly in the cranial area. To attempt to improve oxygenation, the urinary catheter was removed and the trachea was intubated with a 5.5 mm cuffed endotracheal tube. Immediately after tracheal intubation, apnoea and severe bradycardia developed; occasional

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TABLE 1: Results of arterial blood gas performed at the end of cardiopulmonary—cerebral resuscitation

Parameter	Result	Reference range	Unit
pH	7.073	7.350–7.450	
pCO2	82.2	34.0–40.0	mm Hg
pO2	74.6	85.0–100.0	mm Hg
cHCO3	24.0	20.0–24.0	mmol/l
BE (ecf)	−6.1	−5.0–0.0	mmol/l
cSO2	86.5	90.0–100.0	per cent
Na^+	144	139–150	mmol/l
K^+	4.9	3.4–4.9	mmol/l
Ca^{++}	1.35	1.12–1.40	mmol/l
Cl^-	117	106–127	mmol/l
cTCO2	26.5	17.0–25.0	mmol/l
AGapK	8	8–25	mmol/l
Hct	33	35–50	per cent
cHgb	11.4	12.0–17.0	g/dl
Glu	9.9	3.4–6.4	mmol/l
Lac	4.54	0.60–2.90	mmol/l
Crea	132	44–115	µmol/l

BE, Base Excess (extracellular fluid).

normal complexes could be seen on the monitor's screen but a reading of the HR was unavailable (<30 bpm). Manual intermittent positive pressure ventilation was immediately started at 10 breaths per minute (brpm), HR increased to 70 bpm with sinus rhythm, spontaneous ventilation was resumed two minutes later and SpO_2 was 90 per cent. Propofol infusion was stopped and glycopyrrolate (glycopyrronium bromide; Martindale Pharmaceuticals) 5 µg/kg was administered intravenously as a bolus due to the presence of marked sinus arrhythmia. Two minutes after glycopyrrolate administration, a sudden cardiopulmonary arrest occurred. Cardiopulmonary resuscitation (CPR) was started: external chest compressions (with hands positioned directly over the heart) and manual ventilation were applied at 120 bpm and 10 brpm, respectively. Atropine (Atrocare 600 µg/ml; Animalcare) 0.02 mg/kg was administered intravenously immediately after starting chest compressions but no response was noticed; therefore, two minutes later, a second dose of 0.02 mg/kg intravenously was administered leading to a return of sinus rhythm (HR of 81 bpm) in two minutes, and spontaneous ventilation was resumed. MAP was 84 mm Hg at the first reading after resuscitation and $EtCO_2$ was 30 mm Hg. Arterial blood gas analysis, performed with the dog breathing 100 per cent of oxygen, showed respiratory and metabolic acidosis with severe hypercapnia, mild hypoxia and hyperlactatemia (Table 1). Twenty-five minutes postresuscitation, the dog was blinking and swallowing so the trachea was extubated; no blood or secretions were present on the endotracheal tube. The dog was recovered in the intensive care unit and oxygen at 3 l/minute was administered via nasal prongs until the dog no longer tolerated them (30 minutes). The dog had returned to normal behaviour after 4 hours.

DISCUSSION

In human medicine, paediatric and adult patients with high vagal tone are particularly at risk of bradycardia and asystole at tracheal intubation (Sutera and Smith 1994). There are two sources of vagal reflex bradycardia during intubation. The first occurs when hypoxia is sensed by the aortic bodies and transmits via an afferent branch of the vagus nerve to the medulla oblongata which in turn uses an efferent branch of the vagus nerve to lower the HR. The second source of reflex bradycardia during intubation is the manipulation of the laryngopharynx which provokes efferent vagal nerves activation (Jones and others 2012, Jones and others 2014). This bradycardia is accompanied by peripheral vasoconstriction with the aim of redistributing blood flow to the vital organs while reducing myocardial oxygen consumption (Jones and others 2012). This mechanism is similar to the diving reflex which produces bradycardia, peripheral vasoconstriction and apnoea; this reflex is particularly developed in diving mammals but is present also in humans, particularly in infants (Lumb and Pearl 2010), in birds (Ludders 2015) and in dogs (Gandevia and others 1978).

In the veterinary literature, Mathews and others (2011) reported a case of cardiopulmonary arrest in a French bulldog after extubation and administration of hydromorphone: the author concluded that extubation was the more likely responsible for the cardiac arrest. The typical high vagal tone of brachycephalic dogs was considered by the author to be a possible predisposing factor.

The dog in this case report experienced a severe bradycardia immediately after tracheal intubation; although not a brachycephalic dog, the ECG performed the day before anaesthesia showed marked sinus arrhythmia with a wandering pacemaker, both signs of dominance of parasympathetic tone (Moïse 1998). Moreover, immediately after the BAL, the SpO_2 decreased to 85 per cent revealing severe hypoxaemia (Haskins 2015) which may have enhanced the vagal response to intubation. Respiratory arrest and subsequent cardiac arrest might have developed as a consequence of hypoxaemia independent of intubation; however, the sudden onset of bradycardia immediately after endotracheal intubation may suggest that this was a triggering factor. At this point, as the HR was relatively low compared with preprocedure and intraprocedure values, marked sinus arrhythmia was still present and SpO_2 was only 90 per cent, therefore, glycopyrrolate was administered. Two minutes later, the dog developed cardiac arrest. Considering the effects obtained with the administration of glycopyrrolate, the use of atropine may have been a better option.

Among anticholinergic drugs, atropine is the most commonly used to treat bradycardia following tracheal intubation in children (Jones and others 2012, Jones and others 2014) and has been commonly used in dogs to treat anaesthesia-related bradycardia. Disadvantages of using atropine are short duration of action, especially if given intravenously, tachycardia and arrhythmias (Richards and others 1989). In paediatric human patients, the use of glycopyrrolate has been suggested as a preferable alternative to atropine as it induces less sinus tachycardia; in fact, when tachycardia is too pronounced, ventricular filling is limited and myocardial oxygen consumption is increased (Jones 2016).

In a clinical study (Watney and others 1987) including 100 dogs undergoing elective procedures, the effects of atropine, hyoscine and glycopyrrolate administered for premedication, together with acepromazine, were evaluated; a control group, not receiving antimuscarinic agents, was also included. Both atropine and glycopyrrolate were effective maintaining higher HR compared with the control group but the dogs receiving atropine developed more severe tachycardia than the dogs receiving glycopyrrolate, particularly in the time period between premedication and induction and during recovery phase. The authors concluded that the effects of glycopyrrolate were much more desirable than the effects of atropine. Conversely, Richards and others (1989) showed that the rise in HR following intravenous glycopyrrolate was of the same order of magnitude as

that produced by atropine. Moreover in the latter study, both dogs receiving glycopyrrolate and atropine experienced the same degree of bradycardia and second degree atrioventricular blocks, mainly when low doses of drugs were used. These 'paradoxical' effects after administration of anticholinergic drugs result from initial blockade of presynaptic peripheral postganglionic M1 receptors that normally inhibit the acetylcholine (Ach) release. This causes a transient increase in Ach prior to the onset of competitive antagonism at postsynaptic M2 receptor (Lerche 2015). Richards and others (1989) suggested caution when using antimuscarinics to treat bradycardia due to increased vagal tone as there may be further parasymphatomimesis prior to the desired anticholinergic effect.

In their study in 1999, Dyson and others underlined two important aspects about the use of glycopyrrolate in dogs. First of all, glycopyrrolate increases oxygen demand so its use in presence of hypoxia could result in significant sequelae such as premature ventricular contraction and cardiac arrest; secondly, dogs of body weight less than 10 kg are more resistant to glycopyrrolate and are more likely to require higher doses (>10 μg/kg) to reverse bradycardia. Hypoxia and the use of low-dose (5 μg/kg) glycopyrrolate could have contributed to cardiac arrest in our case.

In the past, the addition of a muscarinic anticholinergic drug to anaesthetic premedication for preventing harmful vagal reflexes (and for decreasing secretions) was mandatory in people, but with modern anaesthetic drugs, it is less important (Glick 2015) and its indiscriminate use is often not justified (Dyson and James-Davies 1999, Jones and others 2012). Sutera and Smith (1994) suggested that preoperative predetermination of autonomic nervous system reflex activity may help identify patients at risk of developing bradycardia at anaesthesia induction/intubation; in these patients, a pretreatment with anticholinergic agents may prevent or attenuate vagal-mediated cardiac arrhythmias. In this case, ECG before anaesthesia was indicative of high vagal tone; possibly the administration of antimuscarinics in the premedication could have been beneficial. However in a recent case report (Jang and others 2015), glycopyrrolate 10 μg/kg administered in premedication was unable to prevent fentanyl-induced asystole in one case and to treat fentanyl-induced bradycardia in a second one. Although not a vagal reflex, glycopyrrolate was still unable to prevent this parasympathetically mediated bradycardia. Further studies are warranted to investigate the usefulness of anticholinergic drugs in premedication for dogs with previously diagnosed increased vagal tone.

When cardiac arrest developed, atropine was administered. Atropine has been widely used in patients with cardiopulmonary arrest; the reported dose range for atropine in dogs and cats is 0.02–0.04 mg/kg intravenously (Lerche 2015) but a dose of 0.04 mg/kg intravenously has been recommended for CPR in case of asystole associated with high vagal tone (Fletcher and others 2012). In this case, a first dose of 0.02 mg/kg was administered, and only after the second administration a response was noticed; a full dose of 0.04 mg/kg intravenously should have been administered and should be considered the standard dose in case of CPR.

In human medicine, bronchoscopy and BAL are considered safe procedures but hypoxaemia and bradycardia are reported as possible complications (Milman and others 1994, Hasdiraz and others 2006, Gao and Cui 2014). In small animals, bronchoscopy and BAL are generally reported as safe procedure if the animal can tolerate general anaesthesia. Oxygen supplementation is recommended in the perioperative period to prevent/treat hypoxaemia (Hawkins and others 1990). In small-sized patients, however, the procedure potentially carries a greater risk due to the increased technical challenges of providing oxygen during the procedure itself. In a retrospective study (Johnson and Drazenovich 2007) evaluating the safety of bronchoscopic BAL in 68 cats, complications occurred in 38 per cent of animals; 12 of 68 cats experienced haemoglobin desaturation, four had prolonged anaesthetic recovery and two had pneumothorax; all cats, however, survived to discharge from the hospital.

Based on human literature, cardiac monitoring is also suggested during tracheal bronchoscopy in small animals because arrhythmias can occur, generally during oxygen desaturation or during manipulation of the larynx (Roudebush 1990). Bronchoconstriction is another possible complication, such as that some clinicians advocate premedication with a bronchodilator before the procedure (Creevy 2009). To the authors' knowledge, there are no reports of cardiac arrest after BAL or bronchoscopy in veterinary species.

In conclusion, severe vagal reflex bradycardia should be considered a possible complication after intubation in dogs, and care should be taken when administering low doses of glycopyrrolate to counteract vagally mediated bradycardia.

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