

CASE REPORT

Wildlife

Unanticipated hyperkalaemia and associated perioperative complications in three captive grey wolves (*Canis lupus*) undergoing general anaesthesia

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Abstract

Intraoperative hyperkalaemia has been described in dogs, cats, non-domestic felids and in a calf. This case series reports the occurrence and associated complications in three captive-held grey wolves anaesthetised for root canal treatment. Severe bradyarrhythmia associated with hypotension was detected in two cases before hyperkalaemia was confirmed. These also presented with signs compatible with malignant hyperthermia and rhabdomyolysis. In the third wolf, regular arterial blood gas analysis revealed a progressive increase in plasma potassium exceeding reference values 240 min after premedication. Hyperkalaemia was treated symptomatically with standard protocols, and the recovery was uneventful in all three wolves. The cause of hyperkalaemia in the described cases remains unknown and is most likely multifactorial. Prolonged recumbency, long anaesthetic duration and the administration of α_2 -adrenoceptor agonists are potential influencing factors. Additionally, malignant hyperthermia, rhabdomyolysis, acidaemia and drug effects are discussed for their potential of causing the described intraoperative hyperkalaemia.

KEYWORDS

Anaesthesia, Wolf, Hyperkalaemia

BACKGROUND

Hyperkalaemia, when severe, can be life threatening due to its impact on the resting membrane potential of cardiac myocytes.¹ It is often associated with bradycardia and a variety of changes in the electrocardiogram (ECG), that is, decreased P-wave amplitude, T-wave tenting, prolongation of the PR interval and widening of the QRS complex.^{1,2} The occurrence of atrioventricular (AV) blocks, although less frequent, has also been described in dogs.^{2,3} A sudden decrease in heart rate (HR) may induce a reduction in cardiac output and concurrent systemic hypotension when other compensatory mechanisms fail, for example, during general anaesthesia. Nonetheless, the abovementioned ECG changes may not always occur, making the recognition of hyperkalaemia difficult without measuring potassium plasma concentration.² An acute increase in plasma potassium concentration may be caused by rhabdomyolysis, malignant hyperthermia (MH),

strenuous exercise and toxins and has also been associated with the use of drugs in small animals and people.^{1,4}

Recently, unexpected perioperative hyperkalaemia has been reported in dogs not presenting signs of hyperkalaemia prior to anaesthesia,^{5–10} and its prevalence is suspected to be higher than that reported in this species.⁷ It has also been documented in numerous non-domestic felids,^{11–15} domestic cats^{16,17} and in a calf.¹⁸

In veterinary species, theories about its association with the stress response and depletion of endogenous catecholamines,^{8,9,14} acidaemia,^{6–8,10,14,16,18} use of α_2 -adrenoceptor agonists^{8,10,12–14,16–18} and other drugs,^{6–10,12–14,16–18} duration of anaesthesia,^{5–7,9,10,12,15,17} plasma hyperosmolarity,^{8,10} ischaemia-induced cellular lysis^{10,18} and genetic susceptibility^{6,7,9,17} have been postulated in previous reports.

To the authors' knowledge, this case series is the first to describe peri-anaesthetic hyperkalaemia in grey wolves (*Canis lupus*).

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LEARNING POINTS/TAKE HOME MESSAGES

- Hyperkalaemia may develop in wolves during general anaesthesia.
- The aetiology of the complication is most likely multifactorial, but prolonged anaesthetic time and use of α_2 -adrenoceptor agonists appear to play a particularly important role in its development.
- Regular surveillance of blood electrolyte levels is indicated in wolves undergoing general anaesthesia to promptly diagnose and treat hyperkalaemia.

CASE PRESENTATION

Three captive-held trained grey wolves from the Core Facility Wolf Science Center, Vetmeduni Vienna (WSC, Ernstbrunn, Austria) considered healthy based on examination at a distance by the WSC trainers and veterinarian were anaesthetised for root canal treatment. Variable anaesthetic protocols were used, and details are provided in the specific section for each case. All wolves received intramuscular (IM) premedication before venous catheterisation. When necessary, anaesthesia was induced intravenously (IV) before intubation of the trachea with a cuffed silicone endotracheal tube (ETT). The animals were then transported for approximately 45 min to the veterinary teaching hospital of Vetmeduni Vienna, Austria, under supervision of the WSC trainers. An Ambu bag was available to ventilate them in case of prolonged apnoea. Upon arrival at the teaching hospital, the animals were positioned in dorsal recumbency, connected to a circle breathing system and instrumented. HR and rhythm (ECG), haemoglobin saturation with oxygen (SpO_2), end-tidal carbon dioxide concentration (ETCO_2), end-tidal isoflurane concentration (FEIso) and respiratory rate (fR) were monitored continuously, and non-invasive oscillometric blood pressure was measured at 5-min intervals using a multiparametric monitor (Hewlett Packard CMS 2000, Hewlett Packard, Germany). Intermittent positive pressure ventilation (IPPV), when applied, was performed with an Ohmeda 7800 ventilator (GE Healthcare, Finland). Peak inspiratory pressure (PIP), but not tidal volume, was monitored continuously. Data were recorded every 5 min. Rectal temperature was recorded every 30 min. An isotonic crystalloid solution (Sterofundin ISO, B. Braun Melsungen AG, Germany; 4–10 mL/kg/h) was administered IV. Multimodal analgesia was provided with case-specific locoregional anaesthetic techniques (infraorbital, or infraorbital and maxillary, or inferior alveolar nerve blocks) and meloxicam (Metacam, Boehringer Ingelheim, Germany; 0.2 mg/kg IV or subcutaneously [SC]) to all wolves. A timeline of the anaesthetic events, including complications, treatments, arterial and venous blood gas (vBG) and electrolyte analyses, is depicted in Figure 1.

CASE ONE

A 6-year-old, 47 kg, vasectomised, hand-raised captive grey wolf was anaesthetised by hand injection with IM butorphanol (Alvegesic vet, Alvetra & Werfft, Austria; 0.1 mg/kg),

medetomidine (Narcostart, Richter Pharma, Netherlands; 22 $\mu\text{g}/\text{kg}$), ketamine (Ketamidol, Richter Pharma AG, Austria; 5 mg/kg) and IV midazolam (Midazolam-Hameln, Hameln Pharma Plus, Germany; 0.35 mg/kg). After orotracheal intubation with a 57-French cuffed ETT, the animal was transported to Vetmeduni Vienna. On site, general anaesthesia was maintained with isoflurane in an oxygen–air mixture (fraction of inspired oxygen [FiO_2] ≥ 0.6). An isotonic crystalloid solution (Sterofundin ISO; 5–10 mL/kg/h) was administered IV. Anaesthetic monitoring was performed as described above. Besides the development of hypercapnia ($\text{ETCO}_2 \geq 60$ mmHg), leading to the initiation of IPPV (PIP 11 cmH_2O , fR 10 breaths per minute), anaesthesia was uneventful for 2 h. However, 270 min after premedication, HR abruptly decreased from 100 to 50 beats per minute (bpm), Mobitz type II second-degree AV blocks started occurring, and mean arterial blood pressure (MAP) decreased from 80 to 58 mmHg. Atropine (Atropine sulfuricum 'Nycomed', Takeda Austria, Austria; 10 $\mu\text{g}/\text{kg}$) was administered IM twice at 15-min intervals and IV after 20 min with no effect on HR or MAP. The crystalloid infusion rate was increased from 5 to 10 mL/kg/h. Venous blood was sampled and sent for analysis. While waiting for the results, glycopyrrolate (Robinul, Riemser Pharma, Germany; 12.5 $\mu\text{g}/\text{kg}$) was administered IV, and a dopamine (Dopamine HCl, Fresenius Kabi Austria, Austria) constant rate infusion (CRI) initiated at a dose of 2.5 $\mu\text{g}/\text{kg}/\text{min}$, which was progressively increased to a maximum infusion rate of 5 $\mu\text{g}/\text{kg}/\text{min}$. Neither treatment was effective (HR 54 bpm, MAP 55 mmHg). The results of vBG and electrolyte revealed mixed respiratory and metabolic acidosis (pH 7.1, reference range: 7.35–7.46; venous partial pressure of CO_2 [PvCO_2] 80 mmHg, reference range: 32–49 mmHg; bicarbonate [HCO_3^-] 22.8 mmol/L, reference range: 18–24 mmol/L; base excess [BE] -9 mmol/L, reference range: 0 ± 3 mmol/L) as well as severe hyperkalaemia (8.8 mmol/L, reference range: 3.5–5.1 mmol/L). Additionally, an increase in rectal body temperature (from 38.9°C to 39.7°C) over a 40-min period was noted. MH was suspected. Therefore, isoflurane was immediately discontinued, and anaesthesia was instead maintained with a propofol CRI (Propofol 'Fresenius' 1%, Fresenius Kabi Austria; 0.15–0.4 mg/kg/min). The anaesthetic machine was replaced, and a new non-rebreathing system used to provide 100% oxygen. Manual ventilation was performed (PIP 14–16 cmH_2O , fR 10–16 breaths per minute). Despite manual ventilation, ETCO_2 progressively augmented to values of 92 mmHg and less. Concurrently, a bolus of 2.5% glucose (Glucose 50%, Landesapothek Salzburg, Austria; 75 mg/kg) diluted in Sterofundin ISO was administered IV slowly. Active cooling was instigated with ice packs placed on the femoral arteries and jugular veins and alcohol repeatedly applied to the paws. Following the glucose bolus, HR and MAP rapidly increased to values ≤ 110 bpm and 108 mmHg, respectively. Temperature progressively normalised. Electrolytes and vBG were measured again 495 min after premedication; plasma potassium concentration had decreased to 6.9 mmol/L. A second bolus of 2.5% glucose (75 mg/kg) was administered IV slowly. Once the procedure was terminated, the wolf was allowed to breathe spontaneously. A final vBG and electrolyte measurement, 520 min after premedication, revealed persisting mixed acidosis (pH 7.12, PvCO_2 84 mmHg, HCO_3^- 24.6 mmol/L, BE -7.3 mmol/L) and an improvement in

TABLE 1 Results of venous and arterial blood gas analysis and physiological parameters measured and recorded during general anaesthesia of three wolves (*Canis lupus*) undergoing anaesthesia for root canal treatment.

Variables	Reference range	Case one			Case two					Case three					
		Time (min ^a)			Time (min ^a)					Time (min ^a)					
		395	495 ^b	520	300	330 ^b	375	540	570	105	180	240	270	330 ^b	350
pH	7.35–7.46	7.1	7.1	7.12	7.25	7.23	7.26	7.33	7.33	7.26	7.26	7.23	7.21	7.25	7.22
PaCO ₂ (mmHg)	36–44	–	–	–	–	–	–	47.3	47.8	57.3	55.7	64.5	67.5	58.8	69.9
PaO ₂ (mmHg)	85–100	–	–	–	–	–	–	348	207.8	355.7	351.4	289.3	281.5	313.5	320
PvCO ₂ (mmHg)	32–49	80	84	84	63.4	64.5	58	–	–	–	–	–	–	–	–
PvO ₂ (mmHg)	24–48	–	–	–	43	61.7	75.9	–	–	–	–	–	–	–	–
HCO ₃ ⁻ (mmol/L)	18–24	22.8	23.7	24.6	27.1	26.2	25.7	24.7	24.5	25.5	24.9	26.6	26.2	25.2	27.9
BE (mmol/L)	0 ± 3	-9	-8.1	-7.3	-1.58	-2.87	-2.35	-1.53	-1.91	-2.9	-3.4	-2.86	-3.62	-3.22	-1.97
Na ⁺ (mmol/L)	140–152	156	154	156	149.1	147	150.9	148.3	145.9	148.4	151.1	147.9	148.3	147.8	149.6
K ⁺ (mmol/L)	3.5–5.1	8.8	6.9	5.4	7.88	6.65	4.55	4.63	4.39	3.69	4.44	7.86	7.67	6.7	6.83
Cl ⁻ (mmol/L)	98–107	117	116	116	119.6	117.8	120.9	120.3	120.2	116.8	119.3	119.3	119.1	120.3	118.7
Ca ⁺⁺ (mmol/L)	1.15–1.33	–	–	–	1.32	1.57	1.57	1.48	1.4	1.48	1.4	1.37	1.39	1.4	1.48
Glu (mg/dL)	74–101	–	–	–	153	203	56	60	90	108	99	152	144	163	182
Lac (mmol/L)	1–1.8	–	–	–	1.4	1.1	<1	<1	<1	<1	<1	<1	<1	<1	<1
EtCO ₂ (mmHg)	–	60	78	75	50	50	46	35	35	50	49	57	58	50	59
T (°C)	–	39	38.5	38.2	37.1	37.3	37.7	38	37.9	36.4	36.9	36.9	36.8	37	37
Arrhythmias	–	Yes	–	–	Yes	–	–	–	–	–	–	Yes	Yes	–	–

Abbreviations: BE, base excess; Ca⁺⁺, calcium; Cl⁻, chloride; ETCO₂, end-tidal carbon dioxide tension; Glu, blood glucose; HCO₃⁻, bicarbonate; K⁺, potassium; Lac, lactate; Na⁺, sodium; PaCO₂, arterial carbon dioxide partial pressure; PaO₂, arterial oxygen partial pressure; PvCO₂, venous carbon dioxide partial pressure; PvO₂, venous oxygen partial pressure; T, rectal body temperature.

^aMinutes after premedication.

^bAfter initiation of goal-directed therapy for hyperkalaemia.

plasma potassium concentration (5.4 mmol/L) (Table 1). IV butorphanol (0.2 mg/kg), medetomidine (5 µg/kg) and ketamine (5 mg/kg) were administered for safe transportation back to the WSC, where the wolf recovered uneventfully. The anaesthesia time (from IM immobilisation to IV bolus prior to transport) was 9 h. A PCR assay for the canine RYR1 gene defect, typical of MH, was negative.

CASE TWO

A 7-year-old, 45.4 kg, vasectomised, hand-raised captive grey wolf was anaesthetised at the WSC with IM butorphanol (0.1 mg/kg), medetomidine (22 µg/kg) and ketamine (4.4 mg/kg). After IV administration of an additional quarter dose of the described premedication protocol, its trachea was intubated with a 57-French cuffed ETT, and the animal transported to Vetmeduni Vienna. On site, anaesthesia was maintained with isoflurane in an oxygen–air mixture (FiO₂ ≥ 0.6, FeISO 0.7%–0.9%). The animal was mechanically ventilated (PIP 9–13 cmH₂O, 6–10 breaths per minute) to maintain ETCO₂ between 45 and 55 mmHg. Additional boli of propofol (1 mg/kg IV) and midazolam (0.2 mg/kg IV) as well as a medetomidine CRI (0.5 µg/kg/h IV) were administered to maintain the desired anaesthetic plane. An isotonic crystalloid solution (Sterofundin ISO; 4–5 mL/kg/h) was administered IV. Anaesthetic monitoring was performed as described above. Three hundred minutes following premedication, HR suddenly decreased from 80 to 30 bpm, Mobitz type II second-degree AV blocks occurred, and MAP decreased from 80 to 55 mmHg. Body temperature was 37.1°C.

Medetomidine CRI was discontinued, and atropine (22 µg/kg IM) was administered with no effect. A vBG and electrolyte analysis revealed respiratory acidosis (pH 7.25, PvCO₂ 63 mmHg, HCO₃⁻ 27.1 mmol/L, BE -1.58 mmol/L), hyperkalaemia (7.88 mmol/L) and hyperglycaemia (153 mg/dL, reference range: 74–101 mg/dL). Boli of 10% calcium gluconate (Calcium Gluconat 10%, B. Braun; 40 mg/kg) and 2.5% glucose (200 mg/kg) were administered IV slowly over 10 min. Human insulin (Huminsulin 'Lilly' Normal, Eli Lilly, Austria; 0.1 IU/kg IV) was additionally administered. HR and MAP immediately increased to 90 bpm and 110 mmHg, respectively. A vBG and electrolyte analysis performed 330 min after premedication revealed similar respiratory acidosis (pH 7.23, PvCO₂ 64.5 mmHg, HCO₃⁻ 26.2 mmol/L, BE -2.87 mmol/L) and improved hyperkalaemia (6.65 mmol/L), hypercalcaemia (1.57 mmol/L, reference range: 1.15–1.33 mmol/L) and hyperglycaemia (203 mg/dL). Body temperature steadily increased, but never exceeded 38.0°C throughout the perioperative period. A vBG and electrolyte analysis performed 375 min after premedication revealed normokalaemia (4.55 mmol/L) and hypoglycaemia (56 mg/dL) but unchanged hypercalcaemia. A 10% glucose infusion was started: the rate of 1–2 mL/kg/h was continuously adapted according to venous glucose concentrations measured at 15-min intervals. Only mild respiratory acidosis (pH 7.33, PaCO₂ 47.8 mmHg, reference range: 36–44 mmHg; HCO₃⁻ 24.5 mmol/L, BE -1.91 mmol/L) and hypercalcaemia (1.43 mmol/L) persisted when the decision was made to transport the wolf back to the WSC 570 min after premedication; both potassium and glucose plasma concentrations were now within normal limits (4.39 mmol/L and 90 mg/dL, respectively);

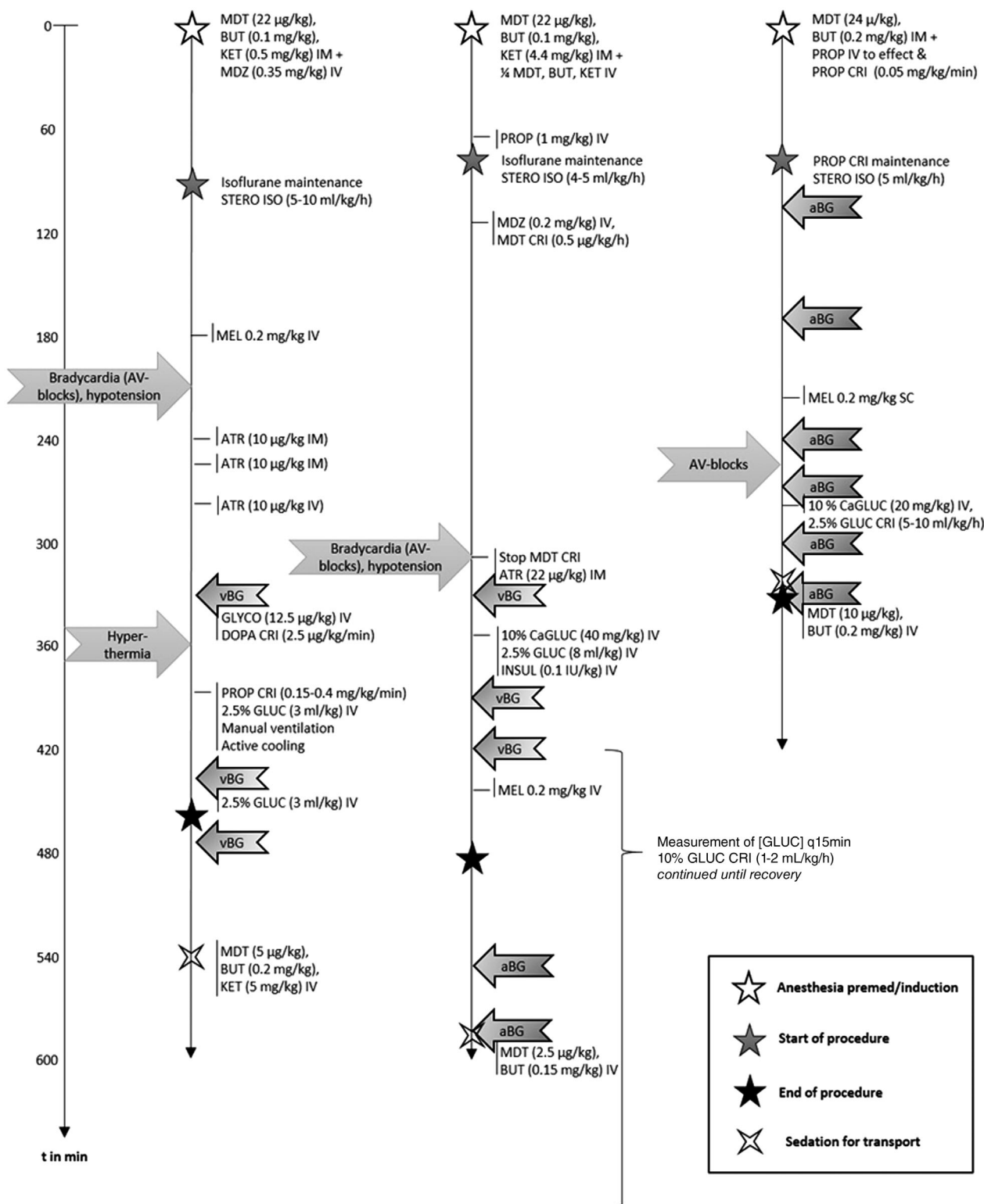


FIGURE 1 Timeline of the anaesthetic events, including complications, arterial and venous blood gas and electrolyte analyses and treatments in three grey wolves (*Canis lupus*) undergoing general anaesthesia for root canal treatment. Abbreviations: ATR, atropine; BUT, butorphanol; CaGLUC, calcium gluconate; CRI, constant rate infusion; DOPA, dopamine; GLUC, glucose; GLYCO, glycopyrrolate; IM, intramuscular; INSUL, insulin; IV, intravenous; KET, ketamine; MDT, medetomidine; MDZ, midazolam; MEL, meloxicam; PROP, propofol; SC, subcutaneous; STERO ISO, Sterofundin ISO.

Table 1). The wolf received IV butorphanol (0.15 mg/kg) and medetomidine (2.5 µg/kg) for safe transport back to the WSC. An anaesthetist continuously monitored its HR and fR during transport and administered 2–3 mL/kg/h of 5% glucose until its uneventful recovery. The total anaesthesia time was 10 h. Urine and blood samples collected at the end of anaesthesia were analysed. The sampled urine was coloured brown and

contained a moderate amount of bilirubin and blood (50 µL). Apart from increased creatinine kinase (CK) (2192 U/L, reference range: <250 U/L) and creatinine (1.5 mg/dL, reference range: 0.4–1.2 mg/dL), blood chemistry results were within reference values. Blood and urine were repeatedly sampled, and all the parameters returned within the reference range 11 days after the procedure (Table 2).

TABLE 2 Results of post-operative blood chemistry of the second wolf, who developed severe hyperkalaemia and bradyarrhythmias during anaesthesia, sampled on five occasions for 11 days following his anaesthesia for root canal treatment.

Variables	Reference range (dogs)	Days post-anaesthesia				
		1	3	4	6	11
Creatinine (mg/dL)	0.4–1.2	1.5	1.9	1.7	2	1.3
Potassium (mmol/L)	3.6–5.6	3.8	4	4	4.3	4.5
Creatinine kinase (U/L)	<250	2192	464	297	149	–
Urea (mg/dL)	20–40	–	64.4	85.5	78.3	43.1

CASE THREE

A 3-year-old, 29.5 kg, female, hand-raised captive wolf was anaesthetised at the WSC with IM butorphanol (0.2 mg/kg) and medetomidine (24 µg/kg) and IV propofol to effect. Orotracheal intubation was performed with a 51-French cuffed ETT, and the animal was transported to Vetmeduni Vienna. During transport, anaesthesia was maintained with a propofol CRI (0.05 mg/kg/min). On site, the animal was connected to a circle breathing system to receive an oxygen air mixture ($\text{FiO}_2 > 0.7$), and anaesthesia was maintained with a propofol CRI (0.05–0.15 mg/kg/min). The wolf was allowed to breathe spontaneously. An isotonic crystalloid solution (Sterofundin ISO; 5 mL/kg/h) was administered IV. Anaesthetic monitoring was performed as described above, but an arterial catheter was additionally placed in the right dorsal pedal artery for continuous measurement of invasive blood pressure and arterial blood sampling, which was conducted repeatedly during the procedure. The first and second aBG revealed respiratory acidosis (pH 7.26, PaCO_2 57.3 mmHg, HCO_3^- 25.5 mmol/L, BE -2.9 mmol/L and pH 7.26, PaCO_2 55.7 mmHg, HCO_3^- 24.9 mmol/L, BE -3.4 mmol/L, respectively) with hypercalcemia (1.48 and 1.4 mmol/L, respectively) and hyperchloremia (116.8 and 119.3 mmol/L, reference range: 98–107 mmol/L, respectively). A progressive increase in arterial potassium (3.69 and 4.44 mmol/L, respectively) within the reference range was also noted (Table 1). Hyperkalaemia (7.86 mmol/L) and hyperglycaemia (152 mg/dL) were diagnosed during the third routine aBG and electrolyte screening 240 min after premedication and 10 min prior to the first apparition of occasional Mobitz type I second-degree AV blocks. Blood work was repeated 270 min after premedication and revealed similar findings (Table 1). An infusion of 2.5% glucose was started at a rate of 10 mL/kg/h for 10 min and reduced to 5 mL/kg/h for the rest of the anaesthetic period. Concurrently, 10% calcium gluconate (20 mg/kg) was administered IV slowly over 20 min.

Urine and blood samples were taken for later analysis. Blood chemistry revealed severe hyperglycaemia (212 mg/dL), persisting hyperkalaemia (7.8 mmol/L) and a mild increase in CK (158 U/L). All other blood values were within the reference ranges. At the end of the dental procedure, 350 min after premedication, potassium plasma concentration had decreased to 6.83 mmol/L (Table 1). After the procedure, the wolf received IV butorphanol (0.2 mg/kg) and medetomidine (10 µg/kg) for safe transportation back to the WSC. Transport went smoothly, and the wolf recovered uneventfully. The anaesthesia time was 5.5 h.

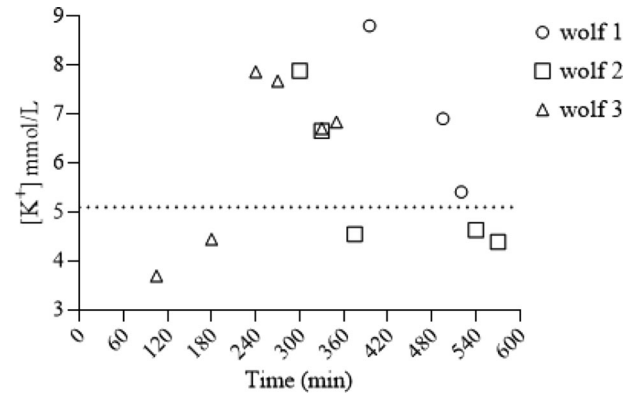


FIGURE 2 Potassium serum concentration (mmol/L) measured from venous or arterial blood at different time points during general anaesthesia in three captive-held grey wolves (*Canis lupus*). The dashed line represents the upper reference limit of potassium serum concentrations in dogs.

A graphical representation of the relationship between time and plasma potassium concentration in the three wolves is depicted in Figure 2.

INVESTIGATIONS

Electrolyte and blood gas analyses were performed during general anaesthesia in all wolves (Table 1). Additional performed blood and urine analyses are detailed in the individual case descriptions.

DIFFERENTIAL DIAGNOSIS

- Increased potassium load (e.g., iatrogenic due to inappropriate potassium supplementation)
- Decreased renal potassium excretion (e.g., renal failure, hypoadrenocorticism)
- Transcellular potassium shift (e.g., acidaemia, insulin deficiency, acute cell tissue breakdown, α -adrenergic mediated effect)

In case one, MH was suspected due to presentation of hyperthermia associated with severe hypercarbia and acidaemia. In case two, rhabdomyolysis was considered due to the qualitative alterations of the urine and the increased plasma concentrations of CK, urea and creatinine. In case three, neither hyperthermia nor signs of muscular damage were noticed.

Common causes of hyperkalaemia, such as endocrinopathies (hypoadrenocorticism and diabetes) and acute renal impairment, cannot be excluded in the present report as potential causes of hyperkalaemia. No preoperative blood work (e.g., biochemistry including cortisol levels) was performed. The animals had also never undergone routine health checks that included blood analysis prior to their anaesthetic event. Nevertheless, the absence of noticeable clinical signs before and after the anaesthetic events make this diagnosis unlikely.

In the discussion, the authors will address the most likely causes of hyperkalaemia in the described cases, notably MH, rhabdomyolysis, the use of medetomidine and other drugs, isotonic crystalloid infusions, the occurrence of acidaemia and the duration of anaesthesia. It is possible and probable, although, that multiple factors contributed to the hyperkalaemic events described in our report.

OUTCOME AND FOLLOW-UP

All the wolves recovered uneventfully.

DISCUSSION

This case series describes the development of hyperkalaemia in three captive-held wolves anaesthetised with a combination of medetomidine, butorphanol, ketamine, isoflurane, midazolam, propofol (case one, case two) and a combination of medetomidine, butorphanol and propofol (case three). The first two wolves developed intraoperative bradycardia with morphological changes in the ECG, second-degree AV blocks and hypotension at 270 and 360 min, respectively, after premedication. Bradycardia was unresponsive to anticholinergic treatment and motivated the realisation of blood gas and electrolyte analysis, which revealed acidaemia and hyperkalaemia. In case three, hyperkalaemia was detected during routine blood screening 240 min after premedication.

Treatment of severe hyperkalaemia usually includes the administration of calcium gluconate, glucose with or without insulin and fluid therapy with a balanced crystalloid solution.^{1,19} Calcium gluconate is used as an emergency treatment to normalise cardiac function by restoring the resting and threshold potential difference in the cardiac myocytes. However, its administration does not resolve the underlying cause (no effect on plasma potassium concentration), and further treatment with glucose and insulin is therefore commonly initiated.²⁰ Glucose uptake into the cells promotes the intracellular shift of potassium and stimulates endogenous insulin release. Its effect can be potentiated by the concomitant administration of insulin.^{1,20} The administration of a balanced crystalloid solution (infusion and/or boli) is generally indicated in all cases of hyperkalaemia due to its dilutive effect, which helps to reduce plasma potassium concentration.^{1,21}

It is relevant to mention that hyperkalaemia-induced bradycardia is often unresponsive to anticholinergics (e.g., atropine, glycopyrrolate), as seen in our report. This is due to the depressant effect of high extracellular potassium levels on myocardial excitability and on conduction of action potentials by the myocytes.^{22,23} More precisely, biphasic changes

in myocardial function are described according to the degree of hyperkalaemia. Moderate elevation of potassium shifts the resting potential of the myocytes closer to the threshold potential, and the activation of voltage-gated sodium channels causes increased excitability and conduction velocity, resulting in a shortened action potential. A further increase in extracellular potassium, instead, inactivates the voltage-gated sodium channels, causing decreased excitability and conduction velocity and ultimately leading to a refractory status of the myocytes.^{24,25} Therefore, the current literature suggests to consider hyperkalaemia in all cases in which bradycardia is unresponsive to the administration of anticholinergic drugs.^{22,23}

In the first wolf (case one), hyperkalaemia was associated with hypercarbia, mixed respiratory and metabolic acidosis, hypotension, bradyarrhythmia and hyperthermia, all of which are indicative of a hypermetabolic state. MH was, therefore, suspected. MH is a syndrome that combines the distinct pathological signs of cardiac arrhythmia, acidosis, hypercarbia, elevated body temperature and muscle rigidity, three of which must be present for it to be diagnosed.²⁶ A genetic test for the mutation of the RYR1 locus may be diagnostic of MH in dogs and wolves.^{27–29} The onset of MH in response to inhalant anaesthetic administration is often quick, within the first hour of exposure.²⁹ However, in sensitive patients, the clinical signs may arise several hours after exposure, suggesting a potential dose-dependent triggering effect of inhalant anaesthetics.^{30,31}

In absence of dantrolene, the state-of-the-art treatment for MH,²⁹ supportive treatment consisting of discontinuation of inhalation anaesthesia, replacement of the anaesthetic machine and rebreathing circuit, manual IPPV providing 100% O₂ and active cooling techniques was initiated. Additionally, boli of glucose were administered to normalise potassium levels. Both bradycardia and hypotension resolved in response to treatment. Postoperatively, the wolf's blood was tested for the canine RYR1 locum mutation. The test result was negative and, in addition to the animal's smooth recovery after anaesthesia, suggests that MH, most likely, did not cause the observed hyperkalaemia. However, other causes of acute cellular breakdown, such as rhabdomyolysis triggered by hyperthermia, may also be considered in this case.³²

In the second wolf (case two), hyperkalaemia was associated with bradyarrhythmia, hypercarbia, respiratory acidosis, hypotension and hyperglycaemia. After treatment with boli of calcium gluconate, glucose and insulin, normokalaemia was quickly restored, and the observed cardiovascular abnormalities resolved. However, the administration of insulin caused hypoglycaemia, the stabilisation of which took several hours, ultimately prolonging the anaesthetic period since the facilities were not equipped for on-site recovery of the wolf. In hindsight, the authors believe that SC insulin administration could have had less detrimental effect on the glycaemic state of the patient^{33–35} but, at the time, the critical state of the wolf motivated this treatment approach.

Aforementioned symptoms of the second wolf in addition to brown-coloured urine, elevated intraoperative levels of plasma CK and urea concentrations, together with the complications that had occurred in the first wolf raised a strong suspicion of rhabdomyolysis. Rhabdomyolysis is a muscular disorder characterised by high levels of myoglobin, CK and other intracellular components (e.g., potassium in the blood

as a consequence of ruptured muscular fibres and myocytes) that may occur in the perioperative period.³⁶ In wild animals, capture myopathy (CM) is a well-known disease triggered by stress and exertional activity causing high morbidity and mortality.³⁷ In humans, myopathies following prolonged periods of recumbency have been reported. In these cases, ischaemia and reperfusion injury led to muscular cell lysis. Prolonged duration of surgery (more than 5–6 h) and obesity, among others, have been identified as risk factors.³⁸ In horses, post-anaesthetic myopathy is a well-known complication.³⁹ Diagnostic criteria for rhabdomyolysis in humans are the occurrence of tetraparesis, hyperkalaemia, myoglobinuria, coagulopathy and a 10-fold increase above the higher reference limit of CK.⁴⁰ In contrast, in grizzly and American black bears (showing clinical signs of CM), any CK level above the reference limit is considered diagnostic.⁴¹ The clinical signs and diagnostic findings during the perioperative period, the prolonged recumbency during anaesthesia and size and weight of the animals are compatible with rhabdomyolysis. Nonetheless, the good quality recoveries and absence of severe musculoskeletal signs in the post-operative period make rhabdomyolysis questionable as the sole cause for the observed peri-anaesthetic hyperkalaemia.

In the third wolf (case three), only occasional second-degree AV blocks were noted 10 min after repeated screening of aBG and electrolytes had revealed hypercarbia, respiratory acidosis, hyperglycaemia and hyperkalaemia. Observed hyperkalaemia was treated with glucose. Additionally, calcium gluconate was administered to preserve cardiac function. This treatment alone did not resolve hyperkalaemia; plasma potassium concentration decreased from 7.86 mmol/L at 240 min to 6.83 mmol/L at 350 min. This may, in part, have been because the animal was already hyperglycaemic when glucose treatment was initiated. To date, available literature only shows a benefit of glucose administration without insulin in the treatment of hyperkalaemia in euglycaemic patients.⁴² However, elevated plasma glucose concentrations show an almost linear relationship with insulin secretion levels.⁴³ Nevertheless, the administration of medetomidine may have reduced insulin secretion, influencing glucose uptake in the cells.⁴⁴ Despite this, the wolf in case three never developed alarming bradyarrhythmia or hypotension; therefore, this treatment certainly mitigated the effects of hyperkalaemia. Additionally, the peri-anaesthetic period was considerably shorter than in the other cases and the wolf's recovery was smooth.

Common factors seen in all three wolves included acidaemia, administration of butorphanol, a competitive μ -receptor antagonist and κ -receptor agonist, meloxicam, a non-steroidal anti-inflammatory drug (NSAID), Sterofundin ISO, a crystalloid isotonic solution, medetomidine, an α_2 -adrenoceptor agonist and propofol, a phenol compound used as a hypnotic agent. Since only little scientific evidence on the influence of butorphanol on potassium homeostasis exists,^{45,46} only the influence of the other factors will be discussed in detail.

Acidaemia may induce an increase in potassium plasma concentration because potassium moves out of cells when intracellular hydrogen ion concentration increases.^{1,20} The scientific literature offers conflicting evidence regarding the degree of change in plasma potassium levels in response to pH alteration, describing values from 0.3 to 1.3 mmol/L per

0.1 unit fall in pH in anaesthetised domestic animals and people.^{47,48} Nevertheless, respiratory acidosis appears to have less impact on potassium movement compared to metabolic acidosis.^{1,20,47,48} Also, it is consistently proven that mineral metabolic acidosis causes the greatest increase in potassium concentration in the blood.⁴⁷ Frequently cited studies in human medicine report a plasma potassium level increase of 0.3–0.4 mmol/L per 7.5 mmHg increase in PCO₂ during respiratory acidosis.^{49,50} To distinguish the impact of acidosis on plasma potassium levels in the described wolves, corrected potassium values were calculated. All three animals presented acute acidosis, respiratory or mixed, but corrected potassium values allowed to exclude acidaemia as the sole cause of the detected hyperkalaemia. It is possible, although, that it may have contributed to or triggered the observed hyperkalaemia. This is further supported by the observation that in the third wolf, respiratory acidosis remained almost unchanged, while potassium plasma levels continuously increased over time.

The effect of NSAIDs on potassium homeostasis has been reported in humans.^{51,52} It is associated with the inhibition of the production of specific renal prostaglandins that ultimately impair the secretion of aldosterone and renin, two hormones essential to the regulation of renal blood flow and renal excretion of potassium.^{51–53} Nevertheless, the hyperkalaemic effect of NSAIDs is only clinically relevant in patients with severe renal disease.⁵³ All wolves in the present report received meloxicam as part of a multimodal analgesic treatment. However, in case two, meloxicam was administered hours after the occurrence of hyperkalaemia. Moreover, no evidence of NSAID-induced hyperkalaemia exists in the veterinary literature. Nonetheless, a contribution of meloxicam to the hyperkalaemic episodes cannot be ruled out in two of the described wolves, since a subclinical renal impairment may have been present prior to anaesthesia.

The veterinary literature regarding isotonic crystalloid solutions and the development of intraoperative hyperkalaemia has been controversial. Various studies associated isotonic crystalloid administration with a decrease in serum potassium concentration^{54,55} whereas two other studies observed a mild⁵⁶ and a severe increase in serum potassium concentration.⁵⁷ Interestingly, the most recent randomised prospective study performed in healthy dogs undergoing general anaesthesia reported an unexpected increase in serum potassium concentrations using three different crystalloid solutions at a rate of 10 mL/kg/h over a 2-h period.⁵⁷ However, West et al.⁵⁷ were unable to find an explanation for their atypical finding and argued that the antibiotic administration might have played a role. Additionally, dogs included in that study received different anaesthetic protocols, which may have affected potassium homeostasis in different ways. Furthermore, administration of a balanced crystalloid solution is recommended in the treatment of hyperkalaemia.^{1,21} In our report, all wolves received an isotonic crystalloid infusion (Sterofundin ISO) containing potassium (4 mmol/L) at a rate lower (case two and case three) or equal (case one) to the rate of the abovementioned study. Although considered unlikely by the authors, it is still possible that the crystalloid solution administered may have increased the potassium load in the wolves, thereby contributing to the development of hyperkalaemia.

The effectiveness of diverse combinations of sedatives and anaesthetics, including α_2 -adrenoceptor agonists, is well documented and considered safe for wolf immobilisation.^{58–61} Interestingly, α_2 -adrenoceptor agonists were administered to most veterinary patients, particularly in large felids, in which hyperkalaemia was reported.^{8,11–14,17} Medetomidine inhibits endogenous insulin, cortisol and catecholamine release.^{44,62,63} A single bolus of medetomidine has been shown to suppress the sympathetic outflow of catecholamines for 180 min in dogs.^{62,64} As previously discussed by other authors, the low circulating catecholamine levels might produce an imbalance in α - and β -adrenoceptor activation, which over time may lead to a pronounced α -adrenoreceptor stimulation, which in turn pushes potassium out of the cells.¹⁰ These processes, in combination or alone, have been suspected of causing hyperkalaemia in anaesthetised felids,^{11–15,17} dogs^{8,10} and in a calf.¹⁸ In other case reports, describing an aggressive dog and a captive Persian leopard, the adrenoceptor imbalance was considered to be exacerbated or directly triggered by exaggerated stress with depletion of endogenous catecholamines.^{8,14} In this context, it is possible that the high prevalence of hyperkalaemia encountered in Greyhound dogs under general anaesthesia^{5,9} may be related to their anxious and fearful behaviour. Additionally, medetomidine-induced insulin deficiency and hyperglycaemia are associated with a reduction in cellular potassium uptake and an increase in water elimination, both of which may contribute to the development of hyperkalaemia.^{1,20} A prospective study in large felids showed that alterations in blood insulin and glucose concentrations occurred concurrently to an increase in potassium plasma concentration.¹² Another recent study demonstrated that the administration of atipamezole, an α_2 -adrenoceptor antagonist, helped to mitigate the severity of hyperkalaemia in felids and that the length of anaesthesia was a predictive factor for hyperkalaemia.¹⁵ All wolves reported in our case series received medetomidine as part of a balanced anaesthetic protocol. It is, therefore, possible that medetomidine favoured the development of hyperkalaemia. However, unexpected hyperkalaemia has also been described in Greyhound dogs not receiving α_2 -adrenoceptor agonists during anaesthesia.^{5,9} Furthermore, an average of six wolves are anaesthetised for prolonged procedures yearly at our institution. Their anaesthetic protocols always include α_2 -adrenoceptor agonists, and the occurrence of reported complications is rare. It is thus presumable that other factors are involved in the development of this electrolyte disturbance. Based on the recent literature, atipamezole administration might have been beneficial in restoring normal potassium plasma concentrations in the described wolves.¹⁵ Atipamezole was not administered for multiple reasons. Firstly, it was necessary to maintain the wolves anaesthetised for safe transport back to the WSC, making a balanced anaesthetic protocol particularly important. Secondly, the first symptoms observed in two wolves (case one and case two) were acute bradyarrhythmia occurring 4 h or more after the administration of medetomidine. In absence of blood gas and electrolyte values, anticholinergic treatments were therefore privileged. Thirdly, since hyperkalaemia with or without hyperglycaemia was only diagnosed several hours after medetomidine administration, it was questionable whether atipamezole would have counteracted the observed hyperkalaemia as McEntire et al.¹⁵ only demonstrated a benefit of early atipamezole administration (within 150 min of

sedation) on the progression of hyperkalaemia. Lastly, safe transport back to the WSC required that wolves would remain anaesthetised for an additional period of approximately 45 min.

A rare but deathly condition commonly referred to as propofol infusion syndrome consists of a sudden onset of hyperkalaemia after propofol administration. It has been described in humans⁶⁵ and in a dog.⁶⁶ Clinical signs include hyperkalaemia, rhabdomyolysis, lactic acidosis, as well as acute renal and cardiac failure. Sometimes hyperkalaemia is the only symptom presented.^{65,67} Interestingly, it has also been described after short infusions and low doses of propofol.^{65,68} All wolves in this report received propofol, two prior to the onset of hyperkalaemia. Therefore, propofol cannot be excluded as a potential trigger for hyperkalaemia in two of the three wolves.

Finally, since wolves one and two were blood relatives, a genetic component cannot be ruled out. A hereditary or breed-specific component has been considered in the onset of hyperkalaemia in Greyhound dogs.^{6,9}

In summary, hyperkalaemia and other blood gas and electrolyte disturbances were recognised in all wolves. Administered treatments were successful in resolving associated cardiovascular abnormalities. Under different circumstances, adjunctive treatment with atipamezole could have been considered. A conservative ventilatory approach allowing for permissive hypercapnia ($\text{ETCO}_2 < 60$ mmHg) entrained the development of marked respiratory acidosis in two of the wolves due to an unexpectedly high arterio-alveolar gradient in PCO_2 , which most probably was caused by dead space ventilation. Therefore, more efficient ventilatory support should have been instituted, especially considering the already discussed impact of acidaemia on the increased extracellular concentration of potassium. Causes for perioperative hyperkalaemia in the three wolves were most likely multifactorial. A common feature of all wolves was that hyperkalaemia always occurred several hours after the start of anaesthesia. This was best seen in case three, where aBG analysis was regularly performed during the procedure. The scientific evidence suggests that the long duration of anaesthesia^{5–7,9,12,17} and use of medetomidine^{8,10,12–14,17,18} were potential influencing factors. The process may have been aggravated or triggered by acidaemia,⁷ cell lysis,^{10,14} stress^{7,8} or other unaddressed causes. Further research is warranted to elucidate the aetiology of hyperkalaemia during general anaesthesia in animals and to establish a solid relationship between hyperkalaemia and the use of α_2 -adrenoceptor agonists in wolves.

AUTHOR CONTRIBUTIONS

Case management, manuscript writing and editing: Giorgio Mattaliano. *Supervision of the cases management and manuscript writing, editing and revision:* Inga-Catalina Cruz Benedetti. *Case management and manuscript revision:* Marianne Heberlein.

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The authors declare no conflicts of interest.

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ETHICS STATEMENT

The Austrian legislation does not require ethical review and approval when data are obtained during a medically necessary intervention. Therefore the redaction of this case series, being retrospective in nature, was exempt from ethical approval.

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