ZOO ANIMALS

Acute hyperkalaemia in a captive Persian leopard (*Panthera pardus saxicolor*) immobilised with a ketamine-medetomidine combination

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SUMMARY

A 12-year-old captive male Persian leopard (*Panthera pardus saxicolor*) required general anaesthesia for examination and treatment of a recurrent oral fistula. Medetomidine (0.065 mg/kg) and ketamine (3.6 mg/kg) administered intramuscularly by blowpipe darting effectively immobilised the animal that was maintained under general anaesthesia with inhaled isoflurane. In absence of clinical signs, acute hyperkalaemia (7.26 mmol/l) was incidentally recognised by the end of anaesthesia. Factors that might have played a role in hyperkalaemia development, such as the use of α2-adrenoceptor agonists, stress response, acidosis or dopamine administration, are discussed. Hyperkalaemia should be considered as a potential complication while anaesthetising large non-domestic felids.

BACKGROUND

Large felids require general anaesthesia for medical interventions because of the potential risk of fatally harming the personnel involved. Medetomidine in combination with ketamine has been successfully used to immobilise a large variety of non-domestic mammals, including large felids, with an apparent wide safety margin.[1]

The Persian leopard (*Panthera pardus saxicolor*), the largest of the leopard subspecies, is considered vulnerable according to the International Union for Conservation of Nature.[2] The present report describes a case involving a captive Persian leopard that developed acute hyperkalaemia after blowpipe remote immobilisation with a ketamine-medetomidine combination and maintenance of anaesthesia with isoflurane. The anaesthetic management of the leopard and possible mechanisms responsible for the increase in serum potassium concentration are presented and discussed.

CASE PRESENTATION

A 12-year-old captive male leopard (*P pardus saxicolor*) required general anaesthesia for examination and treatment of a recurrent oral fistula. The plan was to dart the leopard at the animal park. Thereafter, the animal would be transported under general anaesthesia to the Veterinary Hospital of the University of Bern, where diagnostic tests and adequate treatment would be performed. The main anaesthetic consideration was to assure safety at all stages. Anticipated potential complications were spontaneous arousal, hypoventilation, hypoxaemia, hypothermia, hypotension and bradycardia.

The animal was fasted for 24 hours. It was weighed 69.0 kg once anaesthetised. Drugs were initially administered for an estimated weight of 60.0 kg but are presented here based on its real weight. On the day of the procedure, medetomidine 0.058 mg/kg (Zalopine; 10 mg/ml, Orion Pharma, Espoo, Finland) and ketamine 2.9 mg/kg (Ketasol, 100 mg/ml, Graeub, Switzerland) were administered intramuscularly by blowpipe darting at the animal park facilities. For darting, the leopard was restrained in an isolated room, and quietly approached from the other side of the front grid by two veterinarians (SH and SDB). Both veterinarians had blowpipes pointed to the animal, but only one was charged with the drawn-up dart. The other uncharged blowpipe was used to divert the attention of the leopard. The veterinarians were placed on each corner of the front grid, and the leopard positioned itself approximately 4 m away on the other side of the cage. Once it was distracted and in a good visualisation field, a 3 ml air pressurised dart (Mini-Ject 2000 Nylon syringe cylinder; Dist-inject) was shot into the left hindquarter musculature.

Ten minutes after darting, the leopard was recumbent but ear twitch reflex was still present, therefore ketamine (0.7 mg/kg) and medetomidine (0.007 mg/kg) (Dorbene; 1 mg/ml, Zoetis) were administered intramuscularly by hand into the cervical musculature. Immobilisation period was smooth and uneventful. Physical examination was performed after immobilisation, heart rate (HR) was 68 beats per minute (bpm), respiratory rate (RR) 20 breaths per minute and temperature 37.6°C. Five minutes later, the trachea was intubated with a cuffed endotracheal tube (16 mm internal diameter) via the orotracheal route. Thereafter, isoflurane (Attane; Provet, Lyssach, Switzerland) was administered at 1 per cent in oxygen through a rebreathing system (Matrx VME, Midmark). The animal was then driven to the veterinary university hospital in a secured transport cage in sternal recumbency under permanent observation of the anaesthetist.

Forty minutes after immobilisation, the leopard arrived at the hospital facilities. The animal was disconnected from the anaesthesia machine and rapidly moved into the CT room. Once there, the anaesthesia was continued with isoflurane in oxygen and air mixture (50–50 per cent) (Aespire View, GE Healthcare) and standard monitoring of physiological parameters (ECG, SpO_2, non-invasive

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arterial blood pressure, spirometry, breathing gas analysis) was instituted. An 18 G intravenous catheter was placed in the right cephalic vein and a blood sample was collected immediately after in EDTA and heparin for haematology and biochemistry, respectively. Plasmalyte solution (Plasma-Lyte A, Baxter, Volketswil, Switzerland) was administered intravenously at 10 ml/kg/hour throughout the anaesthesia. After termination of CT, the leopard was transferred to the operating theatre for left mandibular canine extraction. Before surgical incision, a caudal inferior alveolar (mandibular) block was performed transcutaneously with ropivacaine 0.15 mg/kg (Ropivacain 5 mg/ml, Fresenius, Switzerland), and meloxicam 0.2 mg/kg (Metacam 5 mg/ml, Boehringer Ingelheim, Basel, Switzerland) was administered intravenously. During the surgery, the leopard maintained spontaneous breathing at 15 breaths per minute, 1 litre tidal volume, SpO_2 was 98 per cent and $PECO_2$ was 36–43 mmHg. Fifteen minutes after surgery started (120 minutes after immobilisation, 80 minutes after initiating monitoring), the arterial blood pressure (measured by automated oscillometry with the cuff placed over the left radial artery) decreased from 125/75/50 to 100/60/40 mmHg (systolic arterial pressure/mean arterial pressure (MAP)/diastolic arterial pressure, respectively) as confirmed by repeated measurements. The expired isoflurane concentration was judged adequate and a dopamine infusion was started at 7 µg/kg/minute. Ten minutes later, HR decreased from 65 to 55 bpm and MAP was maintained at 70 mmHg. No arrhythmia was recognised on the ECG. The surgical intervention lasted for 45 minutes and a final blood sample (in EDTA and heparin) was then collected from the left jugular vein (150 minutes after immobilisation). Isoflurane was discontinued, all the instrumentation was removed and the leopard was placed on sternal position in the transport secured cage. Once inside, atipamezole 0.33 mg/kg (Antisedan, 5 mg/ml, Orion Pharma) was administered intramuscularly and the leopard was extubated afterwards. At this time point, HR was 65 bpm, RR 18 breaths per minute and temperature 35.9°C. At this stage, no complication had been noticed.

INVESTIGATIONS

Bloodwork was performed twice. The first sample was taken 60 minutes after immobilisation and all measured haematology and biochemistry values were considered unremarkable based on literature. Potassium serum concentration was 4.4 mmol/l. In contrast (incidental finding), the second bloodwork taken 150 minutes after immobilisation revealed biochemical and electrolyte disturbances: elevated plasma potassium (7.26 mmol/l), creatinine (191 µmol/l) and glycaemia (23.55 mmol/l); reduced natraemia (139 mmol/l) and chloraemia (102 mmol/l).

DIFFERENTIAL DIAGNOSIS

Hyperkalaemia

- Drug-induced hyperkalaemia.
- Stress response leading to hyperglycaemia.
- Acidosis.
- Decreased urinary potassium excretion.
- Excessive potassium supplementation.
- Pseudohyperkalaemia.
- Renal insufficiency.
- Acute cell tissue breakdown.

TREATMENT

No treatment was initiated because the results were received after recovery from anaesthesia.

OUTCOME AND FOLLOW-UP

Twenty minutes after atipamezole administration, the leopard recovered uneventfully. Once the animal was bright, responsive and alert, it was transported back to the animal park facilities without incident.

DISCUSSION

Medetomidine (0.065 mg/kg) and ketamine (3.6 mg/kg) administered intramuscularly by blowpipe darting effectively immobilised this captive Persian leopard (*P pardus saxicolor*) that was maintained under general anaesthesia with inhaled isoflurane. However, acute hyperkalaemia developed during anaesthesia.

The selection of the drug protocol used was based on review of the published literature and experience from colleagues. Chemical immobilisation of leopards (*P pardus*) has been previously described using xylazine and ketamine at a dose of 1.4–1.5 and 5 mg/kg, respectively.[3 4] Effective combinations of ketamine and medetomidine have been reported in other non-domestic felid species including snow leopards (*Panthera uncia,* 2.5–3.0 mg/kg ketamine and 0.06–0.08 mg/kg medetomidine),[5] Sunda clouded leopards (*Neofelis diardi,* 3–4.39 mg/kg ketamine and 0.039–0.054 mg/kg medetomidine),[6] jaguars (*Panthera onca,* 4.4 mg/kg ketamine and 0.04 mg/kg medetomidine)[1] and lions (*Panthera leo,* 1.0–5.7 mg/kg ketamine and 0.048–0.058 mg/kg medetomidine).[7] The present leopard had also been effectively anaesthetised previously with this combination.

Acute perianaesthetic hyperkalaemia has been reported in non-domestic large felids including lions, tigers, cheetahs, cougars and jaguars, but not yet in leopards.[8–11] In all the former reports, α2-adrenoceptor agonists and ketamine have been used to immobilise the felids and isoflurane for anaesthesia maintenance. A progressive increase in plasma potassium and glucose concentrations with a decrease in plasma insulin concentration was observed in eight tigers and three lions.[9] Hyperkalaemia (6.5 mEq/l) was reached in one tiger only 150 minutes after induction of anaesthesia. Common features between these cases including the leopard presented here are the drugs used (α2, ketamine, isoflurane) in large felids and the slow development of hyperkalaemia. It was hypothesised that the increase in plasma potassium concentration occurred as a result of a decrease in plasma insulin concentration caused by medetomidine.[9] However, the causes and mechanisms are still unclear.

Hyperkalaemia is a potentially life-threatening condition. Main clinical consequences are muscle weakness, and severe cardiac rhythm abnormalities secondary to prolonged depolarisation and repolarisation of the myocardial conduction. However, clinical suspicion often arises while high potassium concentrations have already been reached. The severity of the manifestations depends on the potassium serum concentrations and on the speed of onset of hyperkalaemia.[12] Identification of patients at risk is essential to suggest routine perianaesthetic monitoring of electrolytes and allows for early recognition of the condition. This appears to be necessary in large felids requiring chemical immobilisation.

Hyperkalaemia can result from increased intake or supplementation, translocation from the intracellular to the extracellular space, decreased renal excretion or pseudohyperkalaemia.[13] In the present case, pseudohyperkalaemia was not considered

because the haematological values were unremarkable for both blood samples. Moreover, excessive intake was also unlikely because potassium was solely supplemented through balanced fluid therapy with physiologic concentration of potassium (Plasma-Lyte A, 5 mEq/l of potassium) at a rate of 10 ml/kg/hour. More probably, translocation of potassium from the intracellular to extracellular space and a reduced urinary excretion both contributed to the development of hyperkalaemia in the present case.

Stress response is a complex neuroendocrine response that implies important metabolic changes through the activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, leading to increased catecholamines and cortisol, reduced insulin and hyperglycaemia, among others.[14] Hyperglycaemia occurs in proportion to the intensity of the stressor as a result of low insulin concentration, high glucagon concentration and the antiinsulin effects of catecholamines and cortisol.[14] Stress response can be triggered by physical and psychological stressors like fasting, capture anxiety or nociceptive stimulation. There are evidences that stress response is elicited under anaesthetic conditions in humans as well as in animal species.[15–18] Plasma concentrations of cortisol, noradrenaline and insulin may inform on the amplitude of this stress response, but were not analysed in the present case. Although the approach was planned in order to reduce stress and anxiety, the stressors of capturing a wild animal are not avoidable. Stress response may have contributed to the increase in plasma glucose leading to hyperkalaemia in the leopard.

Medetomidine is an α2-adrenoceptor agonist, and has been reported to attenuate the stress response directly through sympatholytic activity, as well as indirectly through sedative and antinociceptive activity.[18–21] Nevertheless, medetomidine may have contributed to development of hyperkalaemia. Agonists of the α2-adrenergic receptor (α2-AR) inhibit insulin secretion from pancreatic β cells ($\alpha2_A$-AR subtype),[22] which results in hyperglycaemia. Medetomidine has been reported to cause hyperglycaemia in rats, cattle, dogs and cats[23–27]; among them the greatest elevation in plasma glucose was found in cats.[28] Both insulin deficiency (leading to a decreased cellular uptake of potassium) and hyperglycaemia (leading to hyperosmolality and cellular water loss) can lead to hyperkalaemia.[12] This is in agreement with observations from Reilly *et al* in lions and tigers.[9] Still, it appears unclear why hyperkalaemia develops hours later after medetomidine administration.

Other drugs have been reported for chemical immobilisation of large felids and may help to limit occurrence of hyperkalaemia. Tiletamine-zolazepam combination has been reported in cheetahs and small non-domestic felid immobilisation.[29 30] The use of potent opioids as etorphine or carfentanil has also been reported to immobilise other non-domestic mammals,[31 32] however neither its effectiveness nor safety is documented in non-domestic felids. According to the literature, despite the risk for hyperkalaemia, combinations of an α2-adrenoceptor agonist and ketamine remain the most recommended choice of drugs. Further investigations would be required to find an alternative drug for immobilising these species.

Acidosis is another potential cause of hyperkalaemia. With lowering pH, potassium is shifted from the intracellular space into the extracellular in exchange for hydrogen ions.[13] In the present case, no blood gas analysis was run and occurrence of acidaemia cannot be excluded. The $PECO_2$ was maintained between 36 and 43 mmHg under spontaneous ventilation throughout the anaesthesia such that respiratory acidosis is unlikely, but metabolic acidosis was not tested.

Impaired urinary excretion can also lead to hyperkalaemia. Urinary potassium excretion is mediated by aldosterone hormone, which increases sodium reabsorption and potassium secretion in the distal nephron.[12] In case of hyperkalaemia, aldosterone secretion is stimulated in order to facilitate excretion and normalise blood potassium concentration. In addition, stress response can also promote aldosterone secretion through adrenocorticotropic hormone. However, in this case dopamine administration may have impaired excretion as shown in vivo in human beings.[33 34] Dopamine inhibits aldosterone production via D2 receptors in the adrenal cortex affecting the late phase of aldosterone biosynthesis as shown in vitro.[35] How quick this mechanism can lead to significant hyperkalaemia is unknown and other cases of hyperkalaemia were not associated with dopamine. It remains unclear if the administration of dopamine for approximately 30 minutes may have partially contributed to the development of hyperkalaemia. Adrenaline, noradrenaline and dobutamine are alternatives to dopamine for cardiovascular support and may limit impairment of potassium excretion,[36] but they might affect serum potassium levels through their adrenergic activity.[37]

In the present case, no specific treatment was administered for managing hyperkalaemia because biochemistry results were received after recovery and no clinical signs developed. Due to the possible contribution of α2-adrenoceptor agonists to the development of hyperkalaemia in non-domestic felids, atipamezole administration might be an effective treatment. Nevertheless, caution should be taken if administered during anaesthesia as arousal and consequent risk for the personnel might occur. Other therapeutic options include drugs that promote potassium shift into the intracellular space, like insulin, dextrose and bicarbonate. Measuring blood pH is indicated to treat acidaemia and adjust bicarbonate administration. Fluid therapy will help restore electrolyte imbalance and support kidney function. It appears sensible to ensure availability of these treatment options when anaesthetising non-domestic felids, together with ECG monitoring.

In conclusion, a combination of ketamine (3.6 mg/kg) and medetomidine (0.065 mg/kg) was effective to immobilise a captive Persian leopard, however hyperkalaemia developed during the anaesthesia. This report, together with previous reports in other large felid species, suggests that hyperkalaemia is an important consideration while anaesthetising these species and must be monitored. Further research is needed to confirm the causing mechanisms and find alternative drug protocols for preventing hyperkalaemia.

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