Effect of aerosolised salbutamol administration on arterial potassium concentration in anaesthetised horses.

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Highlights

- Aerosolised salbutamol administration is associated with a reduction in arterial potassium concentration in healthy anaesthetised horses.
- Monitoring arterial potassium concentration in anaesthetised horses is important, particularly after the administration of aerosolised salbutamol.
- Arterial potassium and calcium concentration may reduce over time during anaesthesia in healthy horses and monitoring of electrolytes is warranted.

Effect of aerosolised salbutamol administration on arterial potassium concentration in anaesthetised horses.

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Ethical statement

Ethical approval was granted by the Association of Veterinary Anaesthetists (AVA) ethical review committee (2021-003).

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Competing Interests

None

Abstract

Aerosolised salbutamol is associated with hypokalaemia in horses undergoing colic surgery. The objective of this study was to evaluate the effect of aerosolised salbutamol on arterial potassium concentration ([K +]) in healthy anaesthetised horses undergoing elective surgery.

Anaesthetic records were reviewed from healthy adult horses undergoing elective surgery over a 3-year period with two complete sets of arterial electrolyte (sodium [Na +], potassium [K +], chloride [Cl -], calcium [Ca 2+]) concentration measurements. Records were excluded if intra-operative electrolyte supplementation, antimicrobial administration or non-crystalloid fluid administration were documented or if salbutamol was administered prior to electrolyte measurement. Sixty records which fulfilled inclusion criteria were divided into two groups depending on whether or not

aerosolised salbutamol (2 μ g kg -1) (to treat hypoxaemia) was administered after baseline electrolyte measurement and before the second electrolyte measurement. Aerosolised salbutamol was administered (Group S) in 22 horses and not administered (group NS) in 38 horses. There was a significant reduction in [K +] and [Ca 2+] between baseline and the second electrolyte measurement in both groups ($p < 0.001$). The reduction in [K +] between baseline and the second electrolyte measurement was significantly greater in group S (12.3%) compared to group NS (6.9%) ($p = 0.017$) and was significantly associated with salbutamol administration ($p = 0.04$). The results of this study indicate that monitoring [K +] is important in anaesthetised horses, particularly after aerosolised salbutamol administration.

Keywords: equine anaesthesia; hypokalaemia; potassium; salbutamol

1 Introduction

Aerosolised salbutamol, a selective ß$_2$ adrenergic agonist, may be administered intra-operatively to improve arterial oxygen tension (PaO_2) in hypoxaemic horses [1] but its use has been associated with hypokalaemia in horses undergoing colic surgery [2]. In humans, the reduction in serum potassium concentration [K^+] following intravenous (IV) [3] or inhaled [4,5] salbutamol is widely reported. Relatively high doses (16µg kg^{-1}) of aerosolised salbutamol have been investigated as a treatment for hyperkalaemia in humans since a reduction in [K^+] is seen shortly after inhalation [6]. Furthermore, another study demonstrated that the reduction in serum [K^+]could be used as a proxy for lung delivery of inhaled salbutamol in adults [7]. In dogs, IV salbutamol (100µg bolus followed by a 3µg min^{-1}infusion) produced hypokalaemia [8] and the accidental ingestion of albuterol (salbutamol) in one dog resulted in severe hypokalaemia requiring potassium supplementation [9]. Inhaled salbutamol administration has also been associated with other dose-related side effects including tachycardia and tremor in humans [10] and tachycardia and hypotension in anaesthetised horses [11]. Such side effects are thought to be due to both direct stimulation of

cardiac ß$_2$-receptors [10] and skeletal muscle ß$_2$-receptors as well as indirect activation of peripheral ß$_2$-receptors [5,12]. The mechanism by which salbutamol causes hypokalaemia involves stimulation of ß$_2$ adrenoreceptors linked to a membrane-bound Na/K ATPase pump [13]. Stimulation of the membrane bound pump shifts potassium from the extracellular to the intracellular space [14]. Potassium plays a critical role in muscle function. Hypokalaemia leads to cell membrane hyperpolarisation [15] which can result in muscle weakness [16] and have direct implications for anaesthetic recovery in horses. Complications in recovery are directly related to peri-anaesthetic mortality in horses [17] and since musculoskeletal injuries account for the majority of recovery-related complications [18] avoidance of factors which may contribute to muscle weakness is particularly important in this species.

An association between hypokalaemia and aerosolised salbutamol administration in horses undergoing colic surgery has been reported [2], but the same relationship in healthy horses undergoing elective surgery has not been assessed, to the author's knowledge. This study aimed to evaluate the effect of aerosolised salbutamol administration on arterial [K^+] in healthy anaesthetised horses undergoing elective surgery. We hypothesised that aerosolised salbutamol administration would be associated with a greater reduction in arterial [K^+] and a higher incidence of hypokalaemia compared to horses under similar anaesthetic conditions when salbutamol was not administered.

1. Materials and Methods

Ethical approval was granted by the Association of Veterinary Anaesthetists (AVA) ethical review committee (2021-003).

2.1 Animals

Anaesthetic records from a 3-year period were examined and records for healthy [American Society of Anesthesiologists (ASA) physical status score I], adult (≥ 2 years of age) horses undergoing elective surgery under isoflurane anaesthesia and containing at least two

complete sets of arterial blood gas and electrolyte measurements were included. Records were excluded if intra-operative electrolyte supplementation, antimicrobial administration or non-crystalloid fluid administration were documented or if aerosolised salbutamol was administered prior to electrolyte measurement. Records meeting inclusion criteria were divided into two groups according to whether aerosolised salbutamol (Group S) was administered (for the treatment of hypoxaemia) or not (Group NS) after baseline electrolyte measurement and before the second electrolyte measurement.

2.2 Anaesthesia

Anaesthetic management was similar but not identical in terms of dose administration. Non-steroidal anti-inflammatories [(phenylbutazone[1] (4.4mg kg^{-1}) intravenously (IV)] and anti-microbials [(procaine penicillin[2] 20mg kg^{-1} intramuscularly (IM) and gentamicin[3] 8.8 mg kg^{-1} IV or oxytetracycline[4] 5mg kg^{-1} IV)] were administered 30-60 minutes prior to induction of general anaesthesia. Premedication using acepromazine[5] (10-20 μg kg^{-1}) IM, romifidine[6] (60-90 μg kg^{-1}) IV and morphine[7] (0.1-0.2mg kg^{-1}) IM was followed by induction of general anaesthesia using ketamine[8] (2.5 mg kg^{-1}) IV and diazepam[9] (0.05 mg kg^{-1}) IV. After induction of general anaesthesia, endotracheal (ET) intubation was performed before hoisting the horse to the operating table where the ET tube[10] was connected to a large animal circle breathing system with the facility for controlled mechanical ventilation[11] (CMV). General anaesthesia was maintained using isoflurane[12] delivered in 100% oxygen and CMV was commenced from the beginning of anaesthesia and tailored to maintain end-tidal carbon dioxide tension ($ETCO_2$) between 4.6 – 6.2 kPa. Crystalloid fluids (Hartmann's solution[13] 5-6 mL kg^{-1} hr^{-1} IV) were administered throughout anaesthesia and IV dobutamine was titrated to maintain mean arterial pressure (MAP) > 70mmHg. A multi-parameter monitor[14] provided electrocardiography (ECG), pulse oximetry, capnography, inspired and end-tidal isoflurane concentration and direct arterial blood pressure measurement via an arterial cannula placed in

a peripheral artery and connected via a saline column to an electrical transducer. The zero reference point for the arterial transducer was the point of the shoulder.

2.3 Arterial electrolyte analysis

Arterial blood sampling was performed by anaerobically withdrawing 2 x 2mL volumes of arterial blood via a 3 way-tap positioned between the arterial cannula and the saline column connected to the blood pressure transducer. The first sample was discarded and the second sample, withdrawn over 2 consecutive inspiratory ventilatory cycles, was immediately introduced into the analyser[15]. Normal ranges for serum electrolytes, arterial blood/gas and acid-base were determined using those reported previously [19]. The time of sample withdrawal was recorded.

2.4 Salbutamol

In horses with PaO_2 < 100mmHg, aerosolised salbutamol[16] (2µg kg^{-1}) was administered via the capnograph port positioned on the Y-piece of the breathing system. A purpose-made adaptor allowed connection of the salbutamol cannister directly to the capnograph port. Depression of the canister pump was performed sequentially during the inspiratory phase of mechanical ventilation. According to manufacturer guidelines, each depression of the canister delivers 100µg salbutamol so doses were calculated per kg bodyweight and the desired number of actuations were delivered accordingly.

2.5 Statistics

Retrospective sample size calculations identified that a difference between groups in reduction in $[K^+]$ of 0.25 mmol L^{-1} (or 7% reduction) from baseline could be detected with a β of 0.8 and $\alpha < 0.05$. Data was assessed using the Anderson-Darling test for normality and age, weight, sample timings, electrolyte measurements ($[Na^+]$, $[K^+]$, $[Cl^-]$, $[Ca^{2+}]$, [glucose]), pH, arterial oxygen (PaO_2), carbon dioxide tension ($PaCO_2$) and mean arterial pressure (MAP) were analysed for each group using Student's t-test, paired t-test, Mann-Whitney U

136 test and Wilcoxon signed rank test. Percentage (%) change was calculated for each measured
137 variable using the following equation; [(second measurement – baseline measurement) /
138 baseline measurement] x 100. A 2-way-ANOVA (general linear model) was used to analyse
139 the effect of salbutamol administration on % change in electrolyte concentration and timing
140 of sample collection. Correlation between variables and association between variables and
141 outcome ([% reduction in K^+]) was analysed using Pearson's correlation and logistic
142 regression respectively. A stepwise forward logistic regression analysis was performed for
143 the outcome % reduction in [K^+]. Variables with $p < 0.1$ in the univariate analysis were
144 included in the model. Chi-squared test for association was used for categorical data (sex,
145 breed and procedure type). Parametric data is displayed as median +/- standard deviation
146 (s.d.). Non-parametric data is displayed as median and range. Statistical significance was
147 assigned when $p < 0.05$.

148 **2. Results**

149 Sixty anaesthetic records met inclusion criteria. Aerosolised salbutamol (2μg kg^{-1}) was
150 administered [as a treatment for hypoxaemia (PaO_2 < 13.3 kPa)] in 22 horses (Group S) while
151 38 horses did not receive aerosolised salbutamol (due to the absence of hypoxaemia) (group
152 NS) after baseline electrolyte measurement.

153 *3.1 Demographic data*

154 Horses were significantly older ($p = 0.04$) and heavier ($p < 0.001$) in group S compared to
155 group NS. Breed and procedure type was significantly different between groups (Table 1).
156 There was no difference in sex distribution between groups (Table 1).

157 *3.2 Arterial electrolyte concentration*

158 Baseline [Ca^{2+}] was significantly lower in group NS compared to group S ($p = 0.004$) (Figure
159 1, Table 2). There was no difference between groups in [Na^+], [K^+], [Cl^-] or [glucose] at
160 baseline.

In both groups, $[K^+]$ ($p < 0.001$) and $[Ca^{2+}]$ ($p < 0.001$) were significantly lower at the second electrolyte measurement compared to baseline (Figure 1, Table 2). The % reduction in $[K^+]$ and $[Ca^{2+}]$ was not correlated with the time interval between samples. There was a weak positive correlation between reduction in $[Na^+]$ and $[Cl^-]$ between the two measurements (Pearson's r = 0.3; $p = 0.012$). Percentage reduction in arterial $[K^+]$ from baseline to the second electrolyte measurement was significantly greater in group S compared to group NS ($p = 0.017$) (Figure 1, Table 2). There was no difference between groups in $[Na^+]$, $[Cl^-]$, $[Ca^{2+}]$ or [glucose] % change from baseline to second electrolyte measurements. Univariate logistic regression identified that % reduction in $[K^+]$ was significantly associated with salbutamol administration, $[Ca^{2+}]$ % change, $[Cl^-]$ % change and pH% change ($p < 0.1$). Two-way ANOVA identified that salbutamol administration ($p = 0.017$) but not timing of samples ($p = 0.59$) was associated with % reduction in arterial $[K^+]$. A greater proportion of horses in group S (32%) were hypokalaemic ($[K^+] < 3.05$mmol L^{-1}) at the second measurement compared to group NS (23%) but the difference was not statistically significant ($p = 0.3$). Time of baseline electrolyte measurement was not different between groups but time between samples was shorter in Group S ($p < 0.001$) (Table 2).

3.3 Arterial blood gas measurement

Baseline pH was significantly lower in group S compared to group NS ($p < 0.001$) (Table 2). Percentage change in pH between baseline and second measurement was not different between groups (Table 2). Horses in group S had a significantly lower PaO_2 ($p < 0.001$) and a significantly higher $PaCO_2$ ($p < 0.001$) at baseline. There was a significant increase in PaO_2 between baseline and second measurement in group S ($p = 0.016$). PaO_2 % change between the baseline and second measurements was significantly different between groups ($p = 0.002$) (Table 2). Univariate logistic regression identified that % reduction in [K+] was associated with % change in $PaCO_2$ ($p = 0.002$) and % change in pH ($p = 0.04$). In group S the change in

186 PaO_2 between baseline and second measurement was not correlated with reduction in $[K^+]$.
187 Overall, when data from both groups was pooled, there was a negative correlation between
188 weight and PaO_2 ($r = -0.63$, $p < 0.001$) and between PaO_2 and $PaCO_2$ ($r = -0.49$, $p < 0.001$)
189 at baseline. There was a moderate negative correlation between % change pH and $PaCO_2$
190 from baseline to the second measurement ($r = -0.616$, $p < 0.001$). There was no correlation
191 between change in pH between baseline and second measurement and reduction in [K+].

192 *3.4 Mean arterial pressure measurement*

193 Horses in group S had significantly lower MAP at baseline and second measurements
194 compared to group NS (Table 2). There was no difference in MAP % change between
195 baseline and second measurements between groups (Table 2). Baseline MAP was associated
196 with % reduction in $[K^+]$ ($p = 0.036$) but was not associated with any other measured
197 variable.

198 *3.5 Logistic regression*

199 Factors (salbutamol administration, $[Ca^{2+}]$ % change, $[Cl^-]$ % change, $PaCO_2$ % change and
200 pH % change) significantly ($p < 0.1$) associated with % reduction in $[K^+]$ in the univariate
201 model were selected for inclusion in the multivariate model. Salbutamol administration was
202 the only remaining factor in the model significantly associated with % reduction in $[K^+]$ ($p =$
203 0.044).

204 **3. Discussion**

205 Our study found that the administration of aerosolised salbutamol (2µg kg^{-1}) was associated
206 with a greater % reduction in arterial blood $[K^+]$ compared to when salbutamol was not
207 administered in healthy isoflurane-anaesthetised horses. The effect of inhaled salbutamol
208 administration on serum $[K^+]$ is well known in humans [4,5]. A randomised human cross-
209 over study demonstrated that nebulised salbutamol was associated with a mean decrease in
210 serum $[K^+]$ of 0.33 +/- 0.26 mmol L^{-1} [20] which is slightly less than the mean arterial $[K^+]$

211 reduction seen in our salbutamol-treated horses, however the doses administered were not
212 comparable between studies. Although, the reduction in [K^+] was statistically significant, the
213 clinical relevance remains unknown and no adverse events related to [K^+] occurred in our
214 study population. In human-trials, when compared to saline controls, the salbutamol-
215 associated reduction in [K^+] lasted for 30 – 120 minutes [21] indicating that further work may
216 be warranted to determine the duration of effect on [K^+] in anaesthetised horses. The effect
217 on [K^+] of repeated administration of salbutamol in anaesthetised horses in also unknown and
218 the results from the current study indicate that monitoring [K^+] in salbutamol treated horses is
219 recommended.
220 Adami and colleagues (2020) found that the administration of aerosolised salbutamol was
221 associated with hypokalaemia in horses undergoing colic surgery [2]. Hypokalaemia is a
222 common finding in horses undergoing emergency exploratory laparotomy for colic [2] which
223 may be, in part, due to pre-operative electrolyte deficiencies resulting from altered
224 gastrointestinal tract absorption and losses [22]. Therefore, it is possible that horses
225 undergoing colic surgery are at a greater risk of developing hypokalaemia as a result
226 salbutamol administration due to the presence of pre-existing deficits. The magnitude of the
227 decline in [K^+] was not documented by Adami and colleagues (2020) so limited comparisons
228 can be made with our results. However, both studies reported a significant effect of
229 aerosolised salbutamol administration on [K^+] which suggests that the effect is relevant to
230 both systemically healthy and compromised horses.
231 To account for electrolyte alterations as a result of fluid administration and general
232 anaesthesia, analysis of [Na^+], [Cl^-] and [Ca^{2+}] was also performed in this study. Intravenous
233 crystalloid fluid administration may have a dilutional effect on one or more component of
234 blood [23] which may explain the reduction in [Ca^{2+}] and [K^+] in both groups. However,

since fluid administration rates were not analysed, the findings assume that there were no differences in fluid administration rates between groups.

Potassium uptake from the extracellular space can also be influenced by insulin concentration [24] and acidosis [25]. Glucose concentration was not different between measurements or between groups which indicates that the change in [K+] seen was unlikely to be related to insulin concentration. At baseline, $PaCO_2$ and pH were statistically different between groups which is consistent with the effects of different gas exchange indices. It is likely that horses in group S and therefore exhibiting hypoxaemia, had poorer gas exchange efficiency, leading to higher $PaCO_2$ and therefore lower pH. It is unlikely that this difference between groups is clinically significant. There was no difference in pH or $PaCO_2$ before and after salbutamol administration in group S and there was no difference between groups in pH or $PaCO_2$ % change. Change in $PaCO_2$ and pH were significantly associated with reduction in [K+] in the univariate model, but were no longer significant in the multivariate model indicating that acidosis was not the primary cause of the reduction in [K+]. To identify whether $PaCO_2$ represents a confounding factor, a prospective controlled clinical study with a standardised approach to ventilation in both groups would be required. Baseline PaO_2 is also likely to be a confounding factor, since salbutamol was only administered to hypoxaemic horses. A true control group would be required to clarify this, however, this would contradict our normal clinical approach to the treatment of hypoxaemia and to the author's knowledge, there is no known relationship between hypoxaemia and $[K^+]$.

Salbutamol is an effective bronchodilator in horses with recurrent airway obstruction [26] and improves PaO_2 in hypoxaemic anaesthetised horses [1], however the measurement of serum $[K^+]$ after salbutamol administration is rarely discussed. In humans, $[K^+]$ has been used as a proxy for salbutamol lung delivery, however, in our study there was no correlation between PaO_2 and $[K^+]$ which may be due to the small sample size or the use of different doses used

in man and horses. It could be argued that salbutamol administration should be limited to horses with PaO_2 < 8 kPa rather than the higher value (13.3 kPa) used by the author. Absolute hypoxemia is arbitrarily defined as a PaO_2 < 8 kPa [27] however, suboptimal PaO_2 (< 13.3 kPa) during general anaesthesia reflects an inadequacy of ventilation and still represents a therapeutic challenge and the implementation of salbutamol therapy at PaO_2 < 13.3 kPa is shared by other authors [11]. Arterial oxygenation is negatively influenced by increased body mass indices [28] which is supported by the findings of this study. Horses in group S were significantly older than those in group NS but the difference is unlikely to be of clinical significance.

Adverse effects associated with aerosolised salbutamol administration include sweating [1] and tachycardia and hypotension [11]in anaesthetised horses. We did not find any significant changes in MAP associated with salbutamol administration in our study. Horses in group S had a significantly lower MAP at baseline and second measurement compared to horses in group NS. There was no association between MAP and bodyweight in this study, however, the analysis may have been underpowered to detect more subtle differences. Baseline MAP was significantly associated with reduction in $[K^+]$ which is likely to reflect the lower baseline MAP values in group S.

4.1 Limitations

Since different anaesthetists were responsible for aerosolised salbutamol administration, it is possible that dose delivery was not consistent for all horses due to differences in delivery technique and synchronisation with CMV cycling. Delivery of salbutamol to the lung was assumed since there was a significant improvement in PaO_2 in most horses, however, since pulmonary delivery was not measured, successful delivery in all horses cannot be confirmed. Penicillin and gentamicin can induce hypokalaemia [24] and since this was not adjusted for in the analysis, antimicrobial administration may present a confounding factor. However since

the difference in [K^+] was analysed rather than absolute values alone, and cases involving intra-operative anti-microbial administration were excluded from the analysis, it is unlikely that this would significantly bias our results. Intravenous fluid administration was not precisely measured or recorded in individual horses which may also represent a confounding factor.

Conclusion and clinical relevance

Aerosolised salbutamol administration was associated with a reduction in [K^+] in healthy isoflurane-anaesthetised horses undergoing elective surgery. Monitoring [K^+] is important during general anaesthesia, particularly after salbutamol administration.

Manufacturers list

1. Equipalazone; Dechra. UK
2. Depocillin; Intervet. UK
3. Genta-Equine; Dechra. UK.
4. Engemycin; Intervet. UK.
5. Acesedate; Jurox. UK
6. Sedivet; Boehringer-Ingelheim. UK
7. Morphine; Wockhardt, Wrexham, UK.
8. Ketamidor; Richter Pharma, Austria.
9. Ziapam; TVM Animal Health, Lempdes, France.
10. Endotracheal tube, Kruuse.
11. LAVC-2000 JD Medical; Arizona, USA.
12. Isofane; Priamal Healthcare Ltd, Morpeth, UK
13. Hartmann's solution Aqupharm 11; Animalcare, UK.
14. Datex-Ohmeda S/5; GE Healthcare, UK.
15. EPOC; Woodley, UK.

16. Ventolin Evohaler; GlaxoSmithKline, Middlesex, UK.

Ethical statement

Ethical approval was granted by the Association of Veterinary Anaesthetists (AVA) ethical review committee (2021-003).

Conflicts of interests

There are no competing interests.

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385 arterial oxygenation in anaesthetized horses and ponies. Vet Anaesth. Analg. 35, 392-399.

386

387 Table 1. Demographic data for 60 healthy adult horses undergoing elective surgery under isoflurane-
388 anaesthesia for which arterial blood gas analysis and electrolyte concentrations were measured on two
389 or more occasions. Group S received aerosolised salbutamol (2μg kg^{-1}) between electrolyte

Variable	Group S	Group NS
Age (years)[a]	9.5 (6 – 19)[a]	8 (2 – 16)[a]
Weight (kg)[a]	611 (485 – 700)[a]	503 (373 – 663)[a]
Sex	Mare (n=5), Gelding (n=17).	Mare (n = 15), Gelding (n =21), Stallion (n =2)
Breed [a]	Warmblood (n = 9), Irish Sports Horse (n = 9), Cob (n = 2), Connemara (n = 2).	Thoroughbred (n = 15), Warmblood (n = 8), Irish Sports Horse (n = 4), Cob (n = 4), Welsh pony (n = 3), Arabian (n =1), Icelandic (n =1), Highland (n = 2).
Surgical procedure [a]	Tenoscopy (n = 2), bursoscopy (n = 3), arthroscopy (n = 9), perineal urethrostomy (n =2), neurectomy (n = 3), cervical surgery/ stabilisation (n=3).	Tenoscopy (n = 10), bursoscopy (n = 1), arthroscopy (n = 13), perineal urethrostomy (n =2), neurectomy (n = 2) cervical surgery/stabilisation (n=1), arthrodesis (n = 2), fracture repair (7).

390 measurements (for the treatment of hypoxaemia (arterial oxygen tension < 13.3 kPa) and Group NS
391 did not receive salbutamol between electrolyte measurements (due to the absence of hypoxaemia).

392 [a] significant difference between groups ($p < 0.05$).

393

394

395

396 Table 2. Sampling timing, arterial electrolyte, blood gas and mean arterial pressure measurements on
397 two occasions during elective surgery under isoflurane anaesthesia in 60 healthy adult horses. The
398 difference between measurements is calculated as second measurement – first measurement. Group S
399 received aerosolised salbutamol (2μg kg^{-1}) between electrolyte measurements (for the treatment of
400 hypoxaemia (arterial oxygen tension < 13.3 kPa) and Group NS did not receive salbutamol between
401 electrolyte measurements (due to the absence of hypoxaemia).

Variable	First Sample		Second sample		Difference (2^{nd} – 1^{st}) *(percentage change)	
Mean +/- standard deviation Median (range)	Group S	Group NS	Group S	Group NS	Group S	Group NS
Time of sampling (minutes after induction)	28.5 (20 – 45)	30.0 (20 - 65)	80 (48 – 155)[a]	110 (70 – 185)[a]	50 (23 - 120)[a]	70 (30 - 120) [a]
Sodium [Na^+] mmol L^{-1}	140.55 +/- 2.48	140.97 +/- 2.64	141.05 +/- 2.9	141.42 +/- 2.15	0.50 +/- 1.74 (0.36 +/- 1.25%)	0.45 +/- 2.11 (0.33 +/- 1.50%)
Potassium [K^+] mmol L^{-1}	3.66+/- 0.46	3.60 +/- 0.48	3.22 +/- 0.53[b]	3.35 +/- 0.46[b]	-0.45 +/- 0.21[a]	-0.25 +/- 0.30[a]

					(-12.46 +/- 6.5 %)[a]	(-6.58 +/- 7.8%)[a]
Chloride [Cl^-] mmol L^{-1}	98.05 +/- 2.15	98.32 +/- 3.22	97.59 +/- 2.65	97.93 +/- 3.35	-0.45 +/- 1.53 (-0.46 +/- 1.56%)	-0.39 +/- 1.79 (-0.39 +/- 1.81%)
Calcium [Ca^{2+}] mmol L^{-1}	1.55 +/- 0.04[a]	1.50 +/- 0.08[a]	1.48 +/- 0.08[b]	1.45 +/- 0.07[b]	-0.07 +/- 0.05 (-4.8 +/- 3.55%)	-0.05 +/- 0.06 (-3.33 +/- 3.84%)
Arterial oxygen tension (PaO_2) kPa [mmHg]	10.91 (6.7 – 13.2)[a] [81.85 (50 – 99)]	63.3 (15.6 – 90.5)[a] [474.7 (117 - 679)]	13.7 (7.3 - 38.3)[ab] [102.65 (55-287)]	51.1 (12.2-84.9)[a] [383.2 (91.5–636.7)]	3.1 (-4.7 – 27.2)[a] [23 (-35 – 204)] (25.6%)[a]	-4.3(-40.8 – 8.0)[a] [-32] [(-306 – 60)] (-19%)[a]
Arterial carbon dioxide tension ($PaCO_2$) kPa [mmHg]	8.7 +/- 0.9[a] [65.22 +/- 7.02]	7.8 +/- 0.8[a] [58.8 +/- 6.2]	8.9 +/- 0.8 [66.84 +/- 6.14]	8.45 +/- 0.8[b] 63.4 +/- 6.0	0.08 +/- 0.9 [0.6 +/- 6.6] (1.5 +/- 9.77%)	0.72 +/- 0.7 [5.39 +/- 5.02] (8.71 +/- 9.55)
pH	7.32 +/-	7.36 +/-	7.33 +/-	7.34 +/-	0.01 +/-	-0.02 +/-

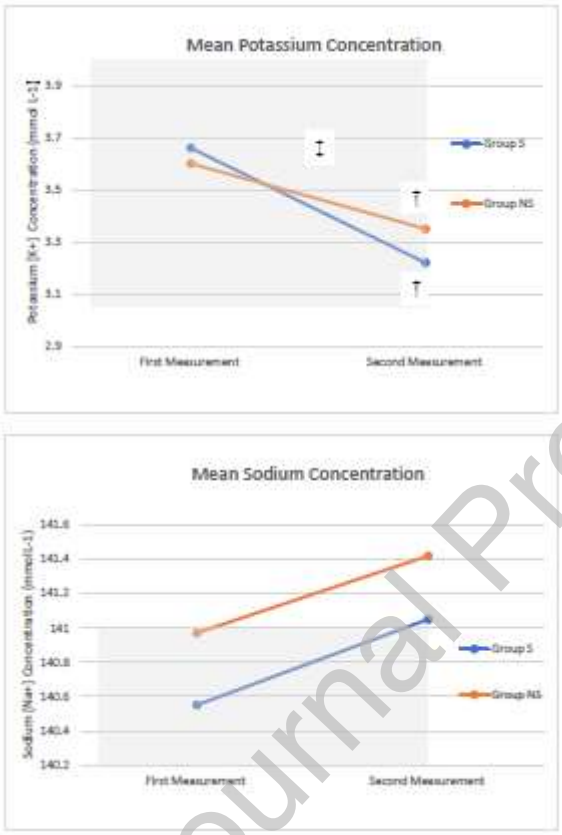
	0.037 [a]	0.042[a]	0.036	0.048[b]	0.04 (0.145 +/- 0.552)	0.04 (-0.27 +/- 0.6%)
Glucose (mmol L^{-1})	12.99 +/- 3.15	12.4 +/- 2.6	13.03 +/- 3.58	11.9 +/- 2.5	0.03 +/- 2.55 [1.2 (-25.8 – 29.7) %]	-0.48 +/- 2.55 [-8.2 (-32.8 – 91.7)%]
Mean arterial pressure (mmHg)	69 (58 – 92)[a]	78 (68 – 110)[a]	73 (62 – 105)[a]	79 (71 – 105)[a]	2.5 (-10 – 15) [3.6 (-12.5 – 23.1) %]	3 (-18 – 25) [4.0 (-16.4 – 31.3)%]

[a] difference between groups ($p<0.05$) [b] difference between samples within group ($p < 0.05$)

*Percentage change between measurements is calculated as [(second measurement – first measurement)/ first measurement] x 100.

414 Figure 1. Arterial electrolytes concentrations in 60 healthy adult horses undergoing elective surgery
415 under isoflurane-anaesthesia at baseline and second measurements. Group S received aerosolised
416 salbutamol (2μg kg^{-1}) between electrolyte measurements (for the treatment of hypoxaemia (arterial
417 oxygen tension < 13.3 kPa) and Group NS did not receive salbutamol between electrolyte
418 measurements (due to the absence of hypoxaemia).

419



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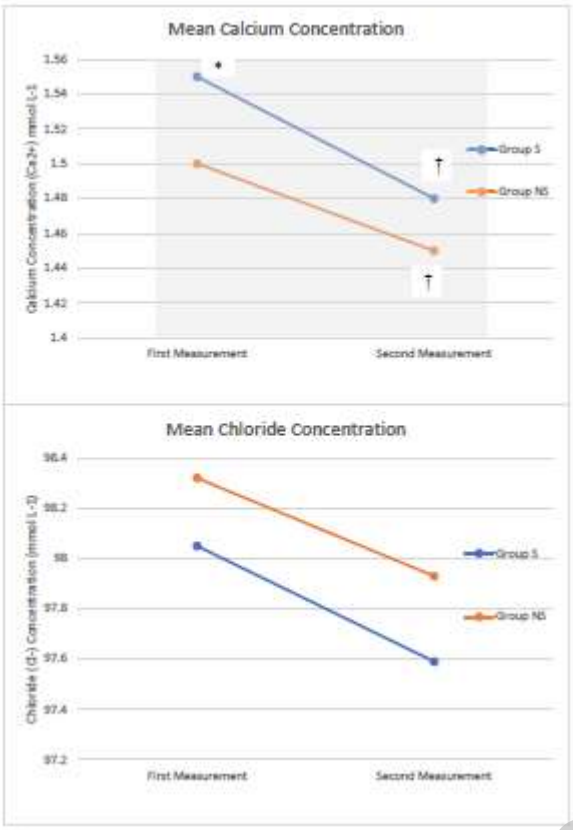

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424 ¶Grey shaded area delineates the normal range [19]. Na^+ (133–141 mmol L^{-1}),

425 K^+ (3.05–4.65 mmol L^{-1}), Ca^{2+} (1.34–1.72 mmol L^{-1}), Cl^- (100–110 mmol L^{-1}) [19].

426 * Significant difference between groups

427 †Significant difference between measurements within group

428 ‡ Significant difference between groups in % change in electrolyte concentration between

429 measurements.

430