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Blood Electrolytes and Metabolites in Rat Model of Acute Metabolic and Respiratory Alkalosis

Shang-Jin Kim, Mun-Young Lee, Jin-Shang Kim*, and Hyung-Sub Kang*,**,***[1]**

*College of Veterinary Medicine, *Korean Zoonoses Research Institute, **Bio-Safety Research Institute, ***Center for the Development of Healthcare Technology, Chonbuk National University, Jeonju 561-756, Korea*

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Abstract : The development of blood ionic changes could be precipitated in acid-base disorder and subsequent treatment. As technology for detecting circulating ionized Mg^{2+} (the most interesting form with respect to physiological and biological properties) is now available in veterinary clinical medicine. This present study investigated the changes of whole blood ionized Mg^{2+} correlated with acute metabolic and respiratory alkalosis in rodent model. Metabolic alkalosis was induced by intravenous infusion with $NaHCO_3$ and mechanical hyperventilation was applied for respiratory alkalosis. We founded that the blood ionized Mg^{2+} could be reversibly decreased by the $NaHCO_3$-induced acute metabolic alkalosis but irreversibly increased by the mechanical hyperventilation-induced respiratory acidosis and respiratory acidosis. We suggested that the potential change in blood suggested that the potential change in blood ionized Mg^{2+} should be counted in treatment of acid-base disorders.

***Key words* :** blood ionized Mg^{2+}, electrolytes, respiratory alkalosis, metabolic alkalosis.

Introduction

Acid-base disorder could evoke ionic unbalance in body (4). For example, chronic alkalosis resulted in a sustained decrement in circulating Mg^{2+} and Ca^{2+} associated with increased fractional renal wasting and metabolic acidosis, which can occur as a result of clinical disorders such as renal failure, distal renal tubular acidosis, or chronic diarrhea, is associated with increased renal Mg^{2+} and Ca^{2+} wasting (13). Interestingly, the infusion of sodium bicarbonate in order to collect metabolic acidosis may potentially cause a clinically significant decrease in blood K^+, Cl^-, ionized and total Ca^{2+} lasted for greater than 2 hours after infusion in cat (3). However, only limited information on blood ionized Mg^{2+} regarding to acid-base disorder per se and subsequent events after apposite treatment is available, although Mg^{2+} is one of the most fundamental ions in the human body with a well-documented physiological and clinical role [maquire]. The ionized Mg^{2+} loss from body and subsequent change in circulating ionized Mg^{2+} may often lead to develop diseases in gastrointerstinal, cardiovascular, neuromuscular and reproductive system, which may also exacerbate the damage caused by the disease (16). Among the fraction of blood Mg^{2+} (ionized, protein-bound and anion complex form, the ionized Mg^{2+} is the most interesting form with respect to physiological and biological properties (9) and is supposed to give more reliable information than total Mg^{2+} (16). A relevant method for measurement of ionized Mg^{2+} was developed in the beginning of the nineties and is now extending in veterinary clinical analysis (1,6,17,19). Accordingly, we investigated the changes of whole blood ionized Mg^{2+} correlated with acute metabolic and respiratory alkalosis in rodent model.

[1]Corresponding author.
E-mail : kang-hs@jbnu.ac.kr

Materials and Methods

All experimental protocols employed herein were approved by the Committee on the Care of Laboratory Animal Resources, Chonbuk National University, and were conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85-23, revised 1996).

Animal preparation

Experiments were carried out on 20 Sprague-Dawley rats (male, 250~350 g, Samtako Biokorea, Daejeon, Korea) housed in a temperature (23 ± 2°C) and humidity (50 ± 5%) with a 12 hours light/12 hours dark cycle. Food and water were available ad libitum.

The rats were anesthetized by 80 mg/kg ketamine puls 8 mg/kg xylazine (i.p.) and were placed on a thermostatically controlled home-made hot plate to keep body temperature constant at 37°C. The right jugular vein and left jugular artery were cannulated for drug administration of drugs and blood collection. A three-way stopcock on the polyethylene catheter allowed flushing of the line with lithium heparin (5 IU/mL of

Table 1. Effects of acute metabolic alkalosis on whole blood pH, lactate, glucose, hemoglobinin, hematocrit, osmolarity and gas composition

	Time after $NaHCO_3$ administration (n=8)		
	0 min	10 min	60 min
pH	7.41 ± 0.02	7.54 ± 0.01***	7.49 ± 0.03***
Lactate, mM/L	4.0 ± 0.7	3.2 ± 0.7	3.4 ± 0.4
Glucose, mM/L	231 ± 17	258 ± 15	283 ± 19*
Hb, mM/L	14.8 ± 0.3	13.4 ± 0.2**	13.7 ± 0.2**
Hct, %	45 ± 1	40 ± 1**	40 ± 1***
Osmolality, mM/kg	287 ± 2	296 ± 2**	295 ± 1**
PCO_2, %	39.8 ± 2.7	41.2 ± 0.6	40.0 ± 1.3
PO_2, %	95.6 ± 10.4	93.8 ± 5.9	93.4 ± 5.7
O_2sat, %	97.4 ± 0.7	97.6 ± 1.0	97.0 ± 0.6

Hb, hemoglobin;Hct, hematocrit; PCO_2, partial CO_2 tension; PO_2, partial O_2 tension; O_2sat, CO_2 saturation. The data are reported as the mean ± SEM. *P < 0.05, **P < 0.01 and ***P < 0.001; Bonferroni *post hoc* test following one-way ANOVA versus 0 min.

Table 2. Effects of acute metabolic alkalosis on whole blood electrolytes

	Time after $NaHCO_3$ administration (n=8)		
	0 min	10 min	60 min
Na^+, mM/L	140 ± 1	144 ± 1**	142 ± 1*
HCO_3^-, mM/L	25.3 ± 1.0	34.9 ± 2.0***	32.5 ± 0.8***
K^+, mM/L	4.5 ± 0.3	3.8 ± 0.1*	3.8 ± 0.1*
Ca^{2+}, mM/L	1.20 ± 0.02	1.10 ± 0.02**	1.21 ± 0.02
Mg^{2+}, mM/L	0.51 ± 0.01	0.45 ± 0.02*	0.51 ± 0.02
Ca^{2+}/Mg^{2+}	2.37 ± 0.04	2.42 ± 0.10	2.39 ± 0.08

Ca^{2+}, ionized Ca^{2+} normalized to pH; Mg^{2+}, ionized Mg^{2+} normalized to pH; Ca^{2+}/Mg^{2+}, the ration of Ca^{2+} per Mg^{2+}. The data are reported as the mean ± SEM. *P < 0.05, **P < 0.01 and ***P < 0.001; Bonferroni *post hoc* test following one-way ANOVA versus 0 min.

isotonic saline, Sigma Chemical Co). To prevent blood clot, 0.1 mL of isotonic saline with lithium heparin (1000 IU/mL, Sigma Chemical Co) was administrated into the polyethylene catheter as required. Tracheostomy was made to enable artificial ventilation. The ventilation rate was initially set at 80 breath per min (bpm) and the ventilation volume ranged from 2.0 to 2.5 mL depending on size of the rat.

Induction of acute metabolic and respiratory alkalosis

Metabolic alkalosis was induced by intravenous infusion with sodium bicarbonate ($NaHCO_3$, 300 mg/kg) dissolved in 0.5 mL of warm saline at a rate of 0.1 mL/min as previously described (3,7,12). In order to induce acute respiratory alkalosis, mechanical hyperventilation was applied with the ventilation rate increased to as high as 160 bpm and volume increased up to 5.0 mL as described in previous reports (14,15). And then the rate and volume went back to normal for recovery test.

Measurement of whole blood ions and metabolites

In experiment of metabolic alkalosis, arterial blood samples were collected at 0, 10 and 60 min after administration of $NaHCO_3$. In experiment of respiratory alkalosis, arterial blood samples were collected before and after mechanical hyperventilation and 30 min after changing to normal ventilation. 250 uL of blood was drawn from the cannulated arterial catether into a lithium heparin syringe and immediately measured for whole blood ions and metabolites using Nova Stat Profile® 8 CRT (NOVA Biomedical Corp, Waltham, MA, USA) including the plasma pH, blood gas compositions and the concentrations of ionized Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+} and lactate$^-$. Hematocrit (Hct) was measured by conductivity. The concentration of HCO_3^- was calculated using the Henderson-Hasselbach equation. The anion gap values were calculated by the formula; $[Na^+-(Cl^-+HCO_3^-)]$.

Statistical analysis

The results were expressed as the means ± standard error of the mean (SEM). The data was analyzed via analysis of variance (ANOVA) followed by a Bonferroni post hoc test using Prism 5.03 (GraphPad Software Inc, San Diego, CA). A p value of < 0.05 was considered to significant.

Results

Effect of acute metabolic alkalosis on arterial blood metabolites, electrolytes and gas composition

The administration of $NaHCO_3$ produced a significant increase in blood pH, accompanied with an increase in Na^+, HCO_3^-, osmolality and the ration of Ca^{2+} per Mg^{2+} (Ca^{2+}/Mg^{2+}). However, Hb, Hct, K^+, Ca^{2+} and Mg^{2+} were decreased after the administration. There were no significances of change in lactate, glucose, PCO_2, PO_2, O_2 saturation (O_2sat), Ca^{2+} and

Table 3. Effects of acute repiratory alkalosis on whole blood pH, lactate, glucose, hemoglobinin, hematocrit, osmolarity and gas composition

	Serial change in ventilation (n=12)		
	Control (2 mL, 80 bpm)	Hyperventilation (5 mL, 160 bpm)	Recovery (2 mL, 80 bpm)
pH	7.43 ± 0.01	7.61 ± 0.02***	7.42 ± 0.01
Lactate, mM/L	3.2 ± 0.2	7.5 ± 0.2***	3.6 ± 0.4
Glucose, mM/L	255 ± 14	419 ± 31**	448 ± 28***
Hb, mM/L	14.2 ± 0.3	13.4 ± 0.4**	13.4 ± 0.4**
Hct, %	43 ± 1	40 ± 1**	40 ± 1**
Osmolality, mM/kg	296 ± 2	292 ± 2	295 ± 1
PCO_2, %	35.0 ± 2.5	13.1 ± 1.3***	33.3 ± 2.6
PO_2/FI	555 ± 60	761 ± 27***	524 ± 61
O_2sat, %	97.0 ± 0.9	99.7 ± 0.1	95.9 ± 1.4

Hb, hemoglobin;Hct, hematocrit; PCO_2, partial CO_2 tension; partial O_2 tension/fraction of inspired O_2 (PO_2/FI); O_2sat, oxygen saturation. The data are reported as the mean ± SEM. **P < 0.01 and ***P < 0.001, Bonferroni *post hoc* test following one-way ANOVA versus control.

Table 4. Effects of acute respiratory alkalosis on whole blood electrolytes

	Serial change in ventilation (n=12)		
	Control (2 mL, 80 bpm)	Hyperventilation (4 mL, 160 bpm)	Recovery (2 mL, 80 bpm)
Na^+, mM/L	139 ± 2	137 ± 1	137 ± 1
K^+, mM/L	4.2 ± 0.4	4.2 ± 0.1	4.2 ± 0.1
Ca^{2+}, mM/L	1.20 ± 0.03	1.31 ± 0.01**	1.23 ± 0.02
Mg^{2+}, mM/L	0.54 ± 0.02	0.65 ± 0.03***	0.67 ± 0.03***
Ca^{2+}/Mg^{2+}	2.24 ± 0.07	2.04 ± 0.08**	1.87 ± 0.06***
HCO_3^-, mM/L	23.2 ± 1.2	13.3 ± 1.1***	21.3 ± 1.2
Cl^-, mM/L	106 ± 1	109 ± 1*	107 ± 1
Anion gap	10.0 ± 1.5	14.7 ± 1.6*	8.7 ± 1.6

Ca^{2+}, ionized Ca^{2+} normalized to pH; Mg^{2+}, ionized Mg^{2+} normalized to pH; Ca^{2+}/Mg^{2+}, the ration of Ca^{2+} per Mg^{2+}; anion gap, [Na^+-(Cl^- +HCO_3^-)]. The data are reported as the mean ± SEM. The data are reported as the mean ± SEM. *P < 0.05, **P < 0.01 and ***P < 0.001; Bonferroni *post hoc* test following one-way ANOVA versus control.

Mg^{2+}. Until 60 min after the administration, the changes in Na^+, HCO_3^-, K^+, pH, Hb, Hct and osmolality were not recovered. But Ca^{2+} and Mg^{2+} went back to normal in 60 min.

Effect of acute respiratory alkalosis on arterial blood metabolites, electrolytes and gas composition

The mechanical hyperventilation produced a significant increase in blood pH, accompanied with an increase in lactate, glucose, partial oxygen tension/fraction of inspired oxygen (PO_2/FI), Ca^{2+} and Mg^{2+}. Cl^- and anion gap. However, Hb, Hct, PCO_2, Ca^{2+}/Mg^{2+} and HCO_3^- were decreased after the hyperventilation. There were no significances of change in osmolality, O_2sat, Na^+ and K^+. Until 30 min after changing to normal ventilation, the changes in glucose, Hb, Hct, Mg^{2+} and Ca^{2+}/Mg^{2+} were not recovered. But lactate, PCO_2, PO_2/FI, Ca^{2+}, HCO_3^- and Cl^- went back to normal.

Discussion

$NaHCO_3$ infusion has been used to treat metabolic and respiratory acidosis by induction of metabolic alkalosis (10) Also, $NaHCO_3$ ingestion had beneficial effects on exercise performance in human (20) and racing horse (19), since extracellular alkalosis alters skeletal muscle intracellular ionic composition and increases lactate efflux from skeletal muscle (8). As expected, we found that single IV $NaHCO_3$ infusion produced a rapid metabolic alkalosis. By 10 minutes, blood K^+, Ca^{2+} and ionized Mg^{2+} were less than those in the control. Our results are in coincidence with previous report showed that a single IV injection of 40 mg/kg $NaHCO_3$ to awake cats decreased serum K^+ and ionized and total Ca^{2+} lasted for greater than 2 hours after infusion (3). The adding of $NaHCO_3$ in human neonatal serum caused significant decrease in ionized Mg^{2+} suggesting a hypothesis that $NaHCO_3$ infusion into the circulation system of body may potentially cause immediately and clinically significant decrease in ionized Mg^{2+} (21) independent from decrease in renal wasting. Although $NaHCO_3$ infusion to acidotic neonatal calves did not have any adverse effects on plasma concentrations of several commonly measured electrolytes or enzyme activities (2), it may

be helpful to keep blood ionized Mg^{2+} because the increased urinary Mg^{2+} excretion secondary to an acute acid load has been reported (13) and $NaHCO_3$ infusion per se could decrease the absolute and fractional excretion of urinary Mg^{2+} and Ca^{2+} in animals (2). In our study, we observed the $NaHCO_3$ infusion-induced lower ionized Mg^{2+} and Ca^{2+} could go back to normal within 60 min, even though the decreased K^+ was not recovered. Another potential area of interest could be the possible effect on blood ionized Mg^{2+} of the postprandial alkaline tide (metabolic alkalosis), which develops in regularly and intermittently feeding animals (11)

In contrast to metabolic alkalosis, we founded that the mechanical hyperventilation-induced respiratory alkalosis produced a sustained irreversible increase in blood ionized Mg^{2+} that could be wasted into urinary excretion. It had been reported that chronic respiratory alkalosis resulted in a sustained decrement in plasma ionized Ca^{2+} associated with increased fractional renal excretion of Ca^{2+} (13). Artificial ventilation-dependent respiratory alkalosis accompanies the clinical syndrome of tetany (15,19) and also precipitates cardiac arrhythmias and predisposes to coronary vasoconstriction which could be induced by Mg^{2+} deficiency (16). The hyperventilation-induced respiratory alkalosis for 30 min reduced the circulating ionized Mg^{2+} and the extracellular Mg^{2+} deficiency maybe at least a subsidiary cause of the syndrome of tetany and the cardiac complications precipitated by hyperventilation in human (5).

In view of the above arguments and the new data presented herein, we strongly propose that blood iMg^{2+} could be reversibly decreased by the acute metabolic alkalosis but irreversibly increased by the respiratory acidosis so that that the potential change in blood ionized Mg^{2+} should be counted in treatment of acid-base disorders.

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흰쥐 급성 대사성 알칼리증과 호흡성 알칼리증 모델에서 혈액 전해질 및 대사산물

김상진 · 이문영 · 김진상*·** · 강형섭*·**·***[1]

전북대학교 수의과대학, *인수공통전염병연구소, **생체안전성연구소, ***헬스케어기술개발사업단

요 약 : 산염기 불균형과 수반되는 치료과정에서 혈액 이온들은 변동되어 질 수 있다. 생리적 그리고 생물학적 활성을 가진 순환 이온화 Mg^{2+} 측정이 수의 임상분야에도 적용되고 있다. 실험동물모델에서 급성 대사성 알칼리증 및 호흡성 알칼리증에 수반하는 혈액 이온화 Mg^{2+} 변동을 관찰하였다. 대사성 알칼리증은 $NaHCO_3$ 정맥투여로 그리고 호흡성 알칼리증은 과호흡에 의해 유도하였다. 혈액 이온화 Mg^{2+}은 $NaHCO_3$에 의해 유도된 대사성 알칼리증에서는 가역적인 감소를 보인 반면, 과호흡에 의해 유도된 호흡성 알칼리증에서는 비가역적인 증가를 보였다. 따라서 산염기 불균형 치료에 있어 혈액 이온화 Mg^{2+}의 잠재적 변동 가능성을 고려하여야 한다고 판단된다.

주요어 : 혈액 이온화 Mg^{2+}, 전해질, 호흡성 알칼리혈증, 대사성 알칼리혈증