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EXPERIMENTAL HYPERKALAEMIA IN RABBITS: EFFECTS OF SALBUTAMOL AND NOREPINEPHRINE TREATMENTS ON BLOOD BIOCHEMISTRY AND ELECTROCARDIOGRAPHY

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The effects of salbutamol and norepinephrine on the electrocardiogram (ECG), serum potassium level and enzyme activities were studied in rabbits with hyperkalaemia; norepinephrine and salbutamol may be therapeutically useful. For induction of hyperkalaemia, 300 mM KCl solution was used and then isotonic saline solution containing 6 μg salbutamol and 3.9 μg norepinephrine per ml were administered. Norepinephrine and salbutamol decreased the serum potassium from 7.36 ± 0.26 and 7.21 ± 0.31 mmol/L to 5.62 ± 0.27 and 4.35 ± 0.33 mmol/L, respectively, and caused the ECG changes (flatness of P wave, widening of QRS complex and bradycardia) to return to the control conditions (time 0). Norepinephrine, but not salbutamol, decreased the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH) to the control levels. These results suggest that monitoring of the enzyme activities might be useful as it yields indexes suitable for evaluating the therapeutic approach with norepinephrine in hyperkalaemia.

Key words: Hyperkalaemia, salbutamol, norepinephrine, biochemistry, electrocardiography, rabbit

Potassium (K^+) is critical because it affects the depolarisation of electrically excitable tissues, such as heart, neurons and skeletal muscle (Hodgkin and Huxley, 1945; Eisner and Lederer, 1979; Rudy, 1988; Hille, 1992; Bal and Oertel, 2001). Hyperkalaemia (HK) (serum K^+ level higher than 5.5 mmol/L) develops when K^+ regulation is disturbed and may have serious cardiotoxic effects with typical changes of electrocardiography (ECG) findings including decreased heart rate, flattened P wave, prolonged QRS complex, and peaked T wave (Chevet, 1998; Kuvin, 1998; Mattu et al., 2000).

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The treatment of HK, a life-threatening condition, is generally directed at stabilising the myocardial conduction system and normalising extracellular and intracellular K^+. Infusion of glucose with insulin has so far been regarded as the standard treatment of choice (Murdoch et al., 1991; Ahee and Crowe, 2000; Mehta et al., 2001). The β_2-stimulatory drug salbutamol (SAL) and epinephrine have been demonstrated to have curative effect by inducing a shift of K^+ into the intracellular medium (Lens et al., 1989; Murdoch et al., 1991; Paterson et al., 1993; Leitch and Paterson, 1994; Darbar et al., 1996; Kemper et al., 1996). Paterson et al. (1992) also presented evidence that norepinephrine (NE) may offset the negative effects of HK.

The aim of this study was to investigate the effects of SAL and NE on ECG, serum K^+ and serum enzyme activities in rabbits with experimentally induced HK.

Materials and methods

Animals

This study was approved by the Ethic Committee of the Faculty of Veterinary Medicine, University of Mustafa Kemal. The experiments were performed on 18 clinically healthy female New Zealand rabbits weighing 2–3 kg and of 10–14 months of age. They were divided into three groups: positive control (PC) (n = 6), NE (n = 6) and SAL (n = 6). Before the experiment, 7 rabbits were used for preliminary studies to establish the dosage of KCl solution to induce HK. The animals were kept in stainless steel cages with 50–60% humidity at room temperature. The rabbits were fed with a pelleted concentrate ration (protein 17%, cellulose 12%, calcium 1–2%, phosphorus 0.5%, sodium 0.1–0.4%, vitamin A 5000 IU/kg, vitamin D_3 600 IU/kg, vitamin E 25 mg/kg, metabolic energy 2600 Kcal/kg), mix grass and carrots, and *ad libitum* access to fresh water was provided.

Protocols

For induction of HK in all the three groups, 300 mM KCl solution (in isotonic NaCl) was infused at 0.5 $ml \cdot kg^{-1} \cdot min^{-1}$ for 15 min via the v. auricularis, which was determined in preliminary studies performed in 7 rabbits. After that, to rabbits of the SAL group isotonic saline solution containing 6 $\mu g \cdot ml^{-1}$ SAL (Sigma) was administered at 0.35 $ml \cdot kg^{-1} \cdot min^{-1}$ for 30 min. To the NE group, isotonic saline solution containing 3.9 $\mu g \cdot ml^{-1}$ NE (Sigma) was administered at 0.35 $ml \cdot kg^{-1} \cdot min^{-1}$ for 30 min. On the other hand, to rabbits of the PC group only isotonic NaCl solution was administered after the first 15 min at 0.35 $ml \cdot kg^{-1} \cdot min^{-1}$ for 30 min.

ECG recordings were performed at every three minutes in the period of the first 45 minutes and then at the 60th and 90th minutes. Blood samples were collected from the other ear vein at 0, 15, 30, 60 and 90 minutes for measurement of enzyme activities including aspartate aminotransferase (AST, EC 2.6.1.1), alanine aminotransferase (ALT, EC 2.6.1.2), lactate dehydrogenase (LDH, EC 1.1.1.27), creatine kinase (CK, EC 2.7.3.2), and levels of creatinine (CRE) and K^+ in the serum and for measuring haematocrit and K^+ in whole blood.

Analysis

The level of whole blood and serum K^+ was measured using flame photometer. The enzyme activities and CRE level were analysed in an autoanalyser (AMS, Roma, Italy) using diagnostic kits (Teco Diagnostics, CA, USA). Haematocrit was measured by a standard method.

ECG recordings

The ECGs were recorded in sternal position without sedation and with minimum of restraint. Recordings were made on a direct writing one channel electrocardiograph (Cardiofax, Nihon Kohden Co., Tokyo, Japan) with the calibration at 1 mV = 20 mm deflection and paper speed of 50 mm·sec^{-1}. Routinely standard bipolar and augmented unipolar limbs leads ECGs were recorded. Heart rate, amplitude of P wave and duration of QRS complex were analysed.

Statistical analysis

Numerical results are given as mean ± SE with *n* being the number of animals. Comparisons of the data between groups were made with Student's *t*-test and group means of each parameter were compared by one-way analysis of variance followed by Duncan's test. All statements of significance are based on the 0.05 level of probability.

Results

Acute HK induced by KCl infusion

Blood serum K^+ concentration varied between 3.10 and 4.80 mmol/L (with a mean of 3.55 ± 0.15) before infusion of KCl (at time 0). Infusion of 300 mM KCl resulted in increases in serum K^+ level to 7.65 ± 0.24, 7.36 ± 0.26 and 7.21 ± 0.31 mmol/L in Groups PC, NE and SAL, respectively, after 15 min.

Effects of NE and SAL on serum K^+ concentration

The level of serum K^+ as a function of time during the experiment in all three groups is displayed in Fig. 1. In Group PC, even though KCl infusion had

been stopped at the 15th minute, the level of serum K^+ continued to increase, peaking at the 30th minute (9.31 ± 0.28 mmol/L). After that it decreased to 8.31 ± 0.22 at the 60th minute and to 7.08 ± 0.30 mmol/L at the 90th minute. On the other hand, serum K^+ levels started to decrease gradually with treatments of NE and SAL after the 15th minute, reaching 5.62 ± 0.27 and 4.35 ± 0.33 mmol/L at the 90th minute in Groups NE and SAL, respectively (Fig. 1). The decreases in K^+ levels in Groups NE and SAL were statistically significant compared with Group PC ($p < 0.05$) at 30, 60 and 90 minutes. Also, the K^+ level of Group SAL was significantly lower ($p < 0.05$) than that of Group NE at 60 and 90 minutes. How NE and SAL lowered the serum K^+ level was studied by measuring haematocrit and the K^+ content of whole blood, as well as serum K^+ level. In this way any possible changes in red blood cell K^+ content could be calculated. However, the infusion of NE or SAL did not statistically change the K^+ level in red blood cells (Table 1).

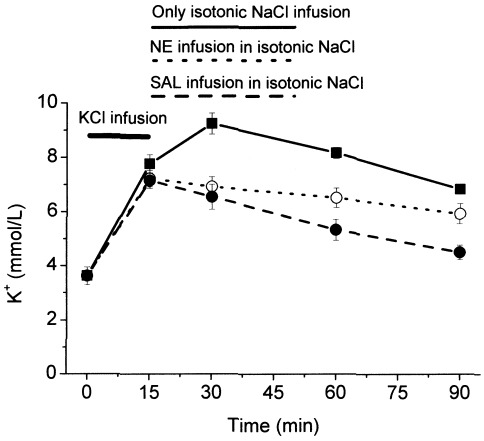

Fig. 1. Serum K^+ levels as a function of time in Groups PC, NE and SAL. The time and duration of KCl infusion and the time and duration of NE and SAL application are shown at the top of the figure

Table 1

K^+ levels in erythrocytes as a function of time in Groups PC, NE and SAL*

	Time (min)	Groups		
		PC	NE	SAL
K^+ (mmol/L)	0	96.72 ± 4.55	94.33 ± 5.33	101.66 ± 3.65
	15	100.50 ± 5.70	103.17 ± 4.28	98.50 ± 5.36
	30	98.33 ± 2.11	100.62 ± 2.14	102.67 ± 3.89
	60	99.50 ± 4.27	105.83 ± 3.27	104.50 ± 2.75
	90	99.17 ± 5.36	104.17 ± 3.62	105.12 ± 3.97

*No significant ($P > 0.05$) differences were detected between means within the same row according to Duncan's multiple range tests

Changes in some blood serum parameters

In Groups PC, SAL and NE, AST activities were measured to be 227.33 ± 19.1 IU/L, 228.66 ± 23.7 IU/L and 214.33 ± 24.7 IU/L, respectively, before infusion of KCl. After infusion of KCl (at the 15th minute), the activities of blood serum AST significantly increased ($p < 0.01$), reaching 449.5 ± 76.6 IU/L, 387.83 ± 35.2 IU/L and 311.33 ± 124.0 IU/L in Groups PC, SAL and NE, respectively. At the end of the experiments (90th minute), in Groups PC and SAL the activity levels of AST dramatically increased to 1017.25 ± 188.5 IU/L and 1005.5 ± 72.9 IU/L, respectively. On the other hand, in Group NE, the level of AST was significantly lower ($p < 0.05$) (489.83 ± 157.4 IU/L) than in Groups PC and SAL (Fig. 2A). With the induction of HK (at the 15th minute), serum ALT activity steadily increased in all the three groups, as seen in Fig. 2B. At the end of the experiments, the increase in ALT activity of Group NE (33.66 ± 5.6 IU/L) became significantly ($p < 0.05$) lower than that in Group PC (49.0 ± 6.6 IU/L) (Fig. 2B). Induction of HK (at the 15th minute) caused the control level of LDH (120 ± 18.1 IU/L, 129.0 ± 15.3 IU/L and 121.6 ± 9.8 IU/L in Groups PC, SAL and NE, respectively) to increase significantly ($p < 0.05$) by about ten times (1450.75 ± 470.4 IU/L, 1469.0 ± 109.4 IU/L and 923.33 ± 43.9 IU/L, respectively). At the end of the experiments (90th minute), the activity of LDH in Group NE was significantly ($p < 0.05$) lower (359.75 ± 160.6 IU/L) than in Groups PC (762.66 IU/L) and SAL (1340.4 ± 196.3 IU/L) (Fig. 2C). Interestingly, the levels of CK and CRE increased from 300.5 ± 11.6 IU/L and 191.83 ± 3.54 μmol/L at the beginning of experiment to 1077.0 ± 187.0 IU/L and 306.75 ± 26.52 μmol/L, respectively, at the end of experiment, whereas the values of these parameters did not change in Groups PC and SAL (Fig. 2D and Fig. 2E).

Effects of NE and SAL on ECG parameters

The effects of NE (Fig. 3) and SAL (not shown) on ECG parameters including heart rate, amplitude of the P wave and duration of QRS complex were analysed. Induction of HK increased the width of QRS complex by 51%, decreased the amplitude of the P wave by 70% and decreased the heart rate by 32% (Figs 3 and 4). After infusion of NE and SAL, the amplitude of P wave, the width of QRS complex and the heart rate returned to the control values. At the same time, in Group PC the amplitude of P wave further decreased by 10%, and the width of QRS complex also increased by 130%.

Clinical signs

As hyperkalaemia developed, the animals showed weakness, increased respiration, mild to moderate tremors and occasionally urination. Two rabbits in the positive control group died after suddenly developing severe convulsions

with ventricular fibrillation seen in ECG following KCl infusion at around the 20th minute. These animals were not used for the statistical analysis.

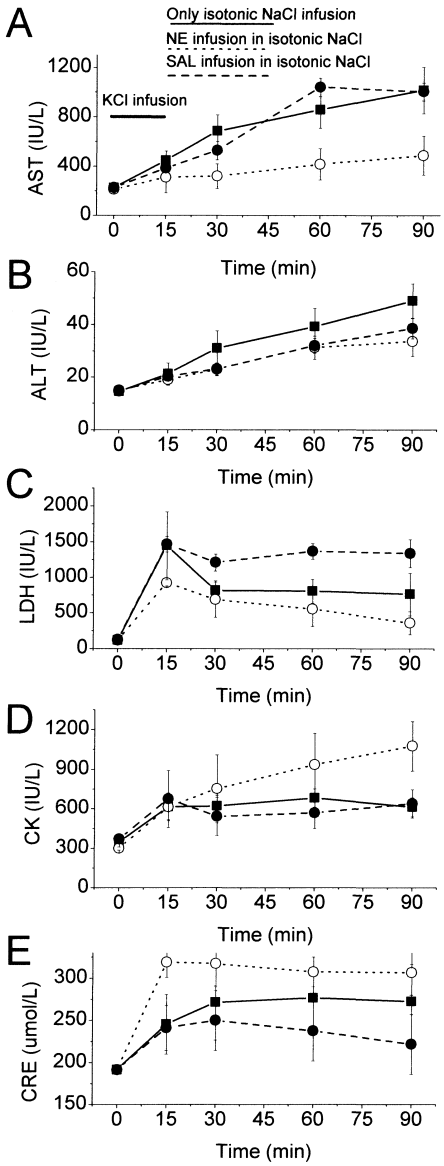

Fig. 2. The activities of blood serum AST (A), ALT (B), LDH (C), CK (D) and the level of CRE (E) in Groups PC, NE and SAL. The time and duration of KCl infusion and the time and duration of NE and SAL application are shown at the top of the figure

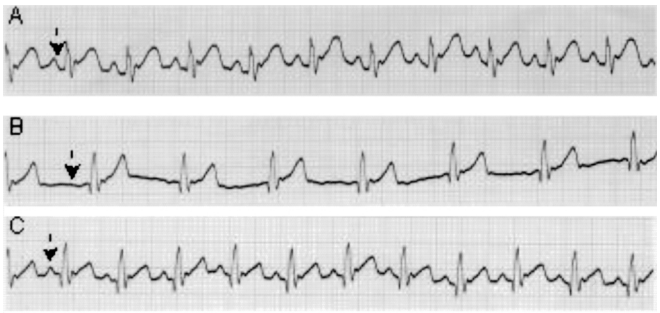

Fig. 3. ECG traces taken from a rabbit in Group NE. A: Before starting the experiment, B: HK stage (15th minute), C: After NE application (90th minute). The arrows show the P waves. Note that P wave in B is not clearly seen. This figure was taken from the preliminary study by Bal et al. (2003)

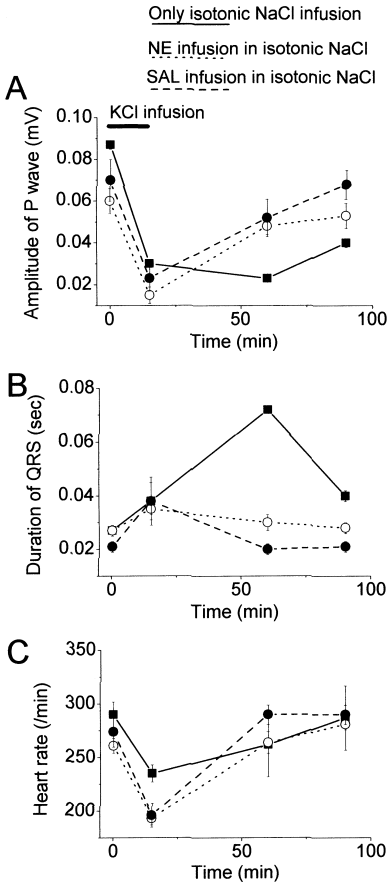

Fig. 4. Analysis of ECG parameters including amplitude of P wave (A), duration of QRS complex (B) and heart rate (C) in Groups PC, NE and SAL. The time and duration of KCl infusion and the time and duration of NE and SAL application are shown at the top of the figure. This figure was taken from the preliminary study by Bal et al. (2002, 2003)

Discussion

We report in this paper the hypokalaemic effect of NE and the effects of SAL and NE on blood serum enzyme activities and CRE in experimentally induced HK. NE as well as SAL substantially reduced the serum K^+ level and reversed the changes in ECG induced by HK.

Potassium is an important element in electrical conduction, and the association of high K^+ concentrations with arrhythmias, ventricular tachycardia and fibrillation has been well known for a long time (Pick, 1966; Bashour et al., 1975; Wishnitzer and Caspi, 1981; Ng et al., 1994; Mehta et al., 2001). Very high concentrations of serum K^+ have long been associated with the risk of cardiovascular morbidity and mortality (Fang et al., 2000).

Induction of HK

Serum K^+ levels above 5.5 mmol/L have traditionally been regarded as HK (Chevet, 1998; Mattu et al., 2000; Hummel and Chauveau, 2001). In the present study, infusion of 300 mM KCl solution for 15 min resulted in a more than 7 mmol/l increase in serum K^+ level (Fig. 1). This confirms that experimentally HK was induced in these animals.

Effects of NE and SAL on serum K^+ level

Paterson et al. (1992) demonstrated that NE can offset the negative effects of HK in whole animals and in isolated heart, an effect that is mimicked by stimulation of cardiac sympathetic nerves. However, there is no study reporting about the effect of NE on serum K^+ level. In this study, it is seen that NE significantly ($p < 0.001$) reduced the serum K^+ level (Fig. 1), which is consistent with our previous report (Bal et al., 2003). On the other hand, it has been known for some years that the β_2-stimulatory drug SAL may be an effective agent to treat HK in humans by inducing a shift of K^+ into the intracellular compartment (Lens et al., 1989; Murdoch et al., 1991). However, few studies have been conducted in laboratory animals to investigate the effects of SAL on experimentally induced HK (Du Plooy, 1994; Mahmoudian and Damankeshideh, 1996). The present study showed that SAL decreased the serum K^+ level in rabbits with experimental HK, which is consistent with the findings of our previously published work (Bal et al., 2002) and with the references given above. However, it has to be noted that SAL was found to induce a more pronounced reduction in the serum K^+ level than NE.

The experiments carried out for this study suggest that the reduction of serum K^+ induced by infusion of NE and SAL might not be associated with the influx of K^+ into red blood cells but other cells possessing beta-adrenergic receptor on their membranes, since NE and SAL did not increase the K^+ level of red

blood cells (Table 1). This is consistent with reports by Rosa et al. (1980) that the decrease of serum potassium level is due to potassium uptake by liver and muscle cells and is mediated by β_2-adrenergic receptors. The intimate mechanism shifting K^+ from the extracellular to the intracellular compartment after stimulation of β_2-adrenergic receptor probably involves stimulation of the enzyme adenylate cyclase, to increase the conversion of adenosine triphosphate to 3'5'-cyclic AMP, which then acts on the sodium-potassium ATPase pump, facilitating intracellular uptake (Wang and Clausen, 1976; Clausen and Flatman, 1977; Clausen and Flatman, 1980; Rosa et al., 1980).

Levels of enzyme activities and CRE

The levels of enzyme activities including CK, LDH and AST are well known to increase in animals with myocardial injuries (Johnson et al., 1981; Bush, 1994). A number of studies carried out in humans (Moss and Henderson, 1999) as well as in cats and dogs (Visser et al., 1981; Bush, 1994) have shown that ALT activity marginally increased in uncomplicated myocardial infarction and injuries, because the concentration of ALT activity in heart muscle is only a fraction of that of AST activity. There are few studies presenting evidence that ECG changes resembling an acute myocardial infarction occurs in HK (Chawla et al., 1978; Pastor et al., 2001), possibly indicating an existence of myocardial injuries. Consistently with the references given above, in the present study induction of HK in rabbits led to increases in the levels of enzyme activities including AST, ALT, LDH and CK, and in the level of CRE (Fig. 2).

In the present study, the activities of serum enzymes including AST, ALT and LDH induced by HK returned to the control (time 0) levels upon application of NE. This is partially consistent with the report by Rabkin (1986) that the cumulative amount of AST is inversely related to the extent of recovery of contractile function. It is conceivable that a similar notion may be valid for ALT and LDH. On the other hand, SAL did not affect enzyme activities and CRE level (Fig. 2). These differential effects of NE and SAL on enzyme activities may be due to the fact that these two pharmacological agents appear to have different mechanisms of action. On one hand, SAL reduced the serum K^+ level to a marked extent, which reportedly results from shifting K^+ into the intracellular compartments (Lens et al., 1989; Mahmoudian and Damankeshideh, 1996). On the other hand, it did not affect the enzyme activities. This may indicate that SAL cannot improve the myocardial injuries induced by HK, since the enzyme activities, used as indexes for cell damage, continued to be high after application of SAL. Whereas, NE appeared to offset the negative effects of HK on myocardial cell damage, since the enzyme activities including AST, ALT and LDH returned to the control levels.

Effects of NE and SAL on ECG parameters

The changes of ECG parameters including widened QRS complex, decreased P wave amplitude and bradycardia found in this study (Figs 3 and 4) are common findings in HK, which is entirely consistent with early reports (Kuvin, 1998; Mattu et al., 2000; Mehta et al., 2001). O'Neill and Paterson (1995) demonstrated in the anaesthetised pig that cardiac sympathetic nerve stimulation or NE infusion both corrected the cardiovascular parameters disturbed by HK. This is consistent with our findings. Similarly, many studies carried out in humans have shown that SAL treatment normalises the hyperkalaemic ECG changes (Lens et al., 1989; Murdoch et al., 1991), which are confirmed by our findings. NE might exert its effects through both stimulating cardiac sympathetic nerves and shifting K^+ into the intracellular medium, whereas SAL exerts its therapeutic effects by shifting extracellular K^+ into the intracellular compartment (Lens et al., 1989; Mahmoudian and Damankeshideh, 1996).

In conclusion, our results confirm the protective role of NE in HK and suggest that NE may be effective in reducing extracellular K^+ concentration. It has to be noted that NE appeared to be effective in correcting the serum enzyme activities increased by HK; on the other hand, SAL seemed to be working well to reduce the serum K^+ level. Infusion of NE and/or SAL may be therapeutically useful in HK. Furthermore, monitoring of the enzyme activities might be useful as it yields indexes suitable for evaluating the therapeutic approach with NE in HK.

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