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The effect of hypernatraemia on ketamine anaesthesia in male rats

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Summary

We studied the effects of a single ketamine injection in an experimental model of chronic hypernatraemia in rats. Three groups, each of 20 male Wistar rats were chosen for the experiment; the control group was given water and the test groups were given 1% (group 1) and 2% (group 2) NaCl solutions for two weeks. All groups were fed with the same diet, containing about 0.5% salt. Other living conditions for all groups were similar. Before using saline in the test groups and before induction of anaesthesia, blood samples were drawn to measure the serum sodium level. A single ketamine injection (125 mg/kg, IP) was used in all groups. Latency times to inhibit the righting reflex and to inhibit the response to painful stimulus, re-appearance time of response to painful stimulus and recovery time from anaesthesia were measured; mortality rates during anaesthesia were also recorded. During consumption of salt solutions and before induction of anaesthesia, we had no animal death. The serum sodium level in group 2 was significantly higher than group 1 and the control group. The required time to inhibit the righting reflex and the response to painful stimulus in group 2 was significantly shorter than group 1 and the control group. These parameters in group 1 were also significantly shorter than the control group. The required time for re-appearance of response to painful stimulus and for recovery from anaesthesia in group 2 was significantly longer than group 1 and the control group. We observed severe pulmonary complications in the test groups during anaesthesia. Mortality rate in group 2 was 60% and in group 1 was 20%; the control group had no significant problems during anaesthesia. Hypernatraemia decreased the induction time of anaesthesia. The duration of ketamine anaesthesia increased and the recovery from anaesthesia was associated with significant delay.

Key words: Anaesthesia, Hypernatraemia, Ketamine, Rat

Introduction

Disorders of body fluids are among the most commonly encountered problems in the practice of clinical medicine (Verbalis, 2003). Disorder of water imbalance manifests as hypo- and hypernatraemia (Lin *et al*., 2005). Sodium is regulated within narrow limits in human (137–141 mEq/L) (Dickenmann and Brunner, 1998). Physiologic serum sodium ranges in rat is 135–146 mEq/L like human serum sodium ranges (Van Reeth and Decaux, 1989). Sodium imbalances are commonly encountered in clinical practice and can have a substantial impact on the prognosis of the patient (Tareen *et al*., 2005). Hypernatraemia is defined as an increase in extracellular sodium concentration above 145 mEq/L which is a common electrolyte disorder. Hypernatraemia is an uncommon condition that can be life-threatening when it is severe (serum sodium >160 mEq/L) (Adrogué and Madia, 2000). Hypernatraemia is one of the most common electrolyte disorders with an incidence of 1–3% in non-hospitalized patients (Metheny, 2000). The increase in the plasma osmolality by hypernatraemia, results in water movement from out of the cells into the extracellular space. Dehydration of brain cells is responsible for the dominant neurological symptoms such as lethargy, seizures and coma (Hans *et al*., 2001). In many instances patients are asymptomatic, but they may also present with neurologic alterations, severe muscle weakness, disorientation, nausea, vomiting or

cardiovascular emergencies (Weiss-Guillet *et al*., 2003).

Hypernatraemia is associated with significant morbidity and mortality, especially in children. In experimental animals, there is a significant correlation between the extent of hyperosmolality and the severity of the symptoms (Greco and Jacobson, 1996). Hypernatraemia can result from water loss or Na retention (Rose, 1994). Hypernatraemia can occur with normal, increased, or decreased total body sodium content (Chan and Wang, 2000). Hypernatraemia could be hypovolaemic, hypervolaemic or euvolaemic (Alpern *et al*., 1990). Ingestion of seawater (approximately 350 to 500 mEq/L Na) not only leads to hypernatraemia but also leads to water loss from solute diuresis or osmotic diarrhoea (Ellis, 1997). For every litre of seawater drunk, two litres of urine volume would be required to get rid the body of solute ingested (Guyton and Hall, 2006). In animal models of hypernatraemia, hypovolaemic hypernatraemia was induced in rats by hypertonic salt loading and water deprivation (Heilig *et al*., 1989).

The function of internal systems can be influenced significantly during the hypernatraemia; even anaesthesia may be affected by this electrolyte imbalance. Anaesthesiologists have problems with anaesthesia complications during hypernatraemia (Wong *et al*., 1998). As hypernatraemia affected anaesthesia significantly and because the incidence of hypernatraemia is approximately high, we decided to study the effects of a single dose ketamine injection at an anaesthetic dose on rats with chronic hypernatraemia.

Materials and Methods

We received the necessary consents for performing our study from the animal experimentation committee of University of Medical Sciences of Zanjan. The principles of laboratory animal care (National Institutes of Health publication No. 86-23, revised 1985) were followed in this study.

The animals were obtained from Iranian Razi Institute and ketamine hydrochloride was purchased from Sankyo Co. (Tokyo, Japan). NaCl was purchased from Merck Co. (Darmstsdt, Germany). Sixty male Wistar rats, with a mean ± SD weight of 200 ± 20 g were allocated randomly to three groups. Animals were housed five per cage under a standard 12 hrs light/dark cycle; food was available *ad libitum*. The temperature of the testing room was kept at 24°C.

In order to produce hypernatraemia, l and 2% salt solutions in distilled water were used. Distilled water was used as the solvent, 10 and 20 g salt was dissolved in one litre of distilled water. One percent salt solution contains about 172 mOsm Na and 172 mOsm Cl; the 2% salt solution has about 342 mOsm Na and 342 mOsm Cl. Osmolalities of 1% salt solution is about 342 mOsm and that of 2% salt solution is about 684 mOsm.

During the experiment, the control group used potable water and the test groups were deprived of potable water; group 1 used 1% salt solution and group 2 used 2% salt solution as the sole source of drinking fluid for two weeks. All groups were fed with the same diet, containing approximately 0.5% salt, other living conditions were similar for all groups. We considered the time of water deprivation in the test groups as the beginning of the experiment. After commencement of the experiment, physical examinations were performed daily, and physical status, neurological signs and vital signs of each rat were evaluated and recorded carefully. Blood samples were taken via tail vein to measure the serum sodium level at the beginning of the experiment and before induction of anaesthesia by flame photometry.

Ketamine hydrochloride was selected as an anaesthetic drug at a dose of 125 mg/kg intraperitoneally (IP) (Saranteas *et al*., 2005). To prevent anaesthetic complications, the rats were deprived of food and water for six hrs before anaesthesia. Before induction of anaesthesia, the animals were weighed and the ketamine was calculated as 125 mg/kg for each rat. Ketamine was dissolved in 0.9% saline and injected IP. Righting reflex latency and the required time to inhibit the response to painful stimulus were measured. When the signs of deep anaesthesia appeared in the animals, the painful test was induced by two click

squeezing of the haemostat on the right ear of animal. During anaesthesia, vital signs were observed carefully. When the signs of recovery from anaesthesia appeared in the animals, we repeated the above painful test on the animals again. The appearance time of the response to painful stimulus was recorded. Complete re-establishment of the righting reflex considered as full recovery time from anaesthesia (when animals could spontaneously move through the table). The number of dead animals and the death time were also recorded. In dead animals, craniotomy was performed to look for intra-cranial haemorrhage. All the remaining animals in the test groups were treated with tap water gradually. Data were analysed by different groups Kruskal-Wallis non-parametric test and results were presented as mean ± SD. A p-value <0.05 was considered statistically significant.

Results

We had no death in the control and test groups during consumption of salt solutions. No serious problems in group 1 during consumption of salt solutions were observed. But consumption of 2% salt solution led to a continuous water loss, dehydration and weight loss. Meanwhile, typical neurological signs appeared in group 2. Physical status of group 2 was not suitable for anaesthesia before induction. The mean ± SD serum sodium levels were 140.1 ± 2.2 mEq/L in group 1, 139.9 ± 2.6 in group 2 and 140.6 ± 2.5 mEq/L in the control group at the beginning of the experiment (P>0.05). The mean ± SD serum sodium levels were 148.4 ± 2.1 mEq/L in group 1 and 156.8 ± 4.3 in group 2, two weeks after consumption of salt solutions and it was 141 ± 3.2 mEq/L in the control group. The mean ± SD serum sodium level in group 2 was significantly higher than group 1 and the control group (P = 0.045 and P = 0.009, respectively). The mean ± SD serum sodium level in group 1 was also significantly higher than the control group (P = 0.045).

The mean righting reflex latency in group 2 was significantly shorter than that in group 1 (P = 0.009) and the control group (P = 0.008). This time in group 1 was significantly shorter than that in the control group (P = 0.006). The mean required time to inhibit the response to painful stimulus in group 2 was significantly shorter than that in group 1 (P = 0.008) and the control group (P = 0.009). This time in group 1 was significantly shorter than that in the control group (P = 0.009). Adversely, the mean required time for recovery from anaesthesia and appearance of the response to painful stimulus in group 2 was significantly longer than that in group 1 (P = 0.014) and the control group (P = 0.042). This time in group 1 was also longer than that in the control group (P = 0.039). The mean full recovery time from anaesthesia in group 2 was significantly longer than that in group 1 (P = 0.014) and the control group (P = 0.04). This time in group 1 was significantly longer than that in the control group (P = 0.04) (Table 1). The mortality rate during anaesthesia was 20% in group 1 and 60% in group 2. The control group had no complications during anaesthesia. The mean time of death after ketamine injection was 20 ± 3 min in group 1 and 15 ± 2 min in group 2. We observed intracranial haemorrhages in different forms in most of hypernatraemic rats.

Table 1: Comparison of different anaesthesia parameters in the experimental groups

	Groups		
	Control group	Test group 1	Test group 2
(Mean±SD) time needed for inhibition of the righting reflex(min)	10 ±1.55[a]	5 ±1.55[b]	3 ±1[c]
(Mean±SD) time needed to inhibit response to painful stimulus(min)	15 ±1.58[a]	8 ±1.22[b]	4 ±1.41[c]
(Mean±SD) time needed for re-appearance of the righting reflex(min)	100 ±11.6[a]	120 ±6.7[b]	150 ±4.7[c]
(Mean±SD) time needed for complete recovery from the anaesthesia(min)	115 ±7.9[a]	150 ±4.7[b]	180 ±7.1[c]

Note: Different letters in each row represent the significant difference (P<0.05)

Discussion

The present study produced several key findings in hypovolaemic hypernatraemic

rats. Firstly, there was a direct correlation between serum sodium levels and the rate of salt concentration in distilled water. Serum sodium level in group 2 was higher than group 1, because group 2 consumed a solution with a higher salt concentration. Secondly, there was an inverse correlation between hypernatraemia and the required time to inhibit the righting reflex and the required time to inhibit the response to painful stimulus in the test groups. The two above-mentioned parameters in group 2 were shorter than those in other groups. Deficits in extracellular fluid volume may adversely affect cardiovascular function, central nervous system function, and metabolic and temperature regulation (Wilmore, 2002). Since hypovolaemia reduces the volume of distribution for intravenous drugs, dose reduction should be considered (Bissonnette and Dalens, 2002).

We did not reduce the ketamine dosage in the test groups, thereby, the volume of distribution of ketamine was decreased in the test groups, hence ketamine effects appeared faster in the test groups as compared with the control group. Thirdly, there was a direct correlation between hypernatraemia and the time needed for appearance of the response to painful stimulus and full recovery from anaesthesia in the test groups. The two above-mentioned parameters in group 2 were longer than those in other groups.

Acute manipulation of daily sodium intake dose alter renal function and hepatic cytochrome P450 isoforms and should be considered when using these rat models (Liu *et al*., 2003). Due to hepatic and kidney tissue changes, the processes involving in ketamine metabolism may be slower in the test groups in comparison to the control group. Reduction in the volume of distribution of ketamine increases anaesthetic drug concentration in body fluid. Furthermore, slower ketamine metabolism increases the duration of action of ketamine in the test groups. However, the mechanisms of how hypernatraemia leads to hepatocellular damage are not still clear (Jawan *et al*., 2002). Hayek *et al*. (1983) suggested that hypernatraemia *per se* leads to hyperlipaemia and fatty liver. Hypernatraemia may be associated with brain death, which is a more complex process producing profound alterations of the endocrine system and electrolyte imbalance affecting all organ systems in a complicated way (Jawan *et al*., 2002). Fourthly, there was a direct relationship between hypernatraemia and anaesthesia disorders and mortality rate. The rate of anaesthesia-induced disorders and mortality rate in group 2 was higher than other groups. Hypernatraemia *per se* can be life-threatening during anaesthesia; some effects of the anaesthetic drugs can contribute to animal death.

Hypernatraemia primarily affects the central nervous system function by causing cellular dehydration (Jawan *et al*., 2002). Maintenance of brain cell volume is essential for normal central nervous system functioning. In adult rats, when plasma osmolality increases, water flows across the blood-brain barrier from brain to plasma and results in a decrease in brain volume (Stonestreet *et al*., 2003). This change is associated with rupture of cerebral veins, resulting in intracerebral or sub-arachnoids haemorrhage which is responsible for neurological symptoms. Ketamine is considered as a potent cerebral vasodilator. Cerebral blood flow increases greatly, by as much as 60 to 80%. Ketamine should be avoided in patients with known intracranial pathology (Collins, 1993). Rupture of cerebral veins and intracerebral or sub-arachnoids haemorrhage is a common phenomena and use of a cerebral vasodilator leads to aggravation of the hypernatraemic sequelae.

Diabetes insipidus is one of the causes of hypernatraemia. Diabetes insipidus is an uncommon complication of pregnancy (Sherer *et al*., 2003). Pre-existing central diabetes insipidus is unmasked after successful kidney transplantation, leading to rapid dehydration and hypernatraemia (Henne *et al*., 2001). Hypernatraemia in the donor organ is one of the most dangerous risk factors that may cause primary graft loss after orthotropic liver transplantation (OLT) (Jawan *et al*., 2002). Recipients of hepatic allograft from donors with uncorrected hypernatraemia had a significantly greater incidence of graft loss as compared with recipients of hepatic allograft from

normonatraemic donors (Totsuka *et al*., 1999). A great deal of controversies has been generated regarding the effects of donor hypernatraemia on liver function in recipients of hepatic allograft. Although further studies are pending, these findings suggest that a moderate rather than a severe approach to the management of donor hypernatraemia may be preferred (Van da Walker, 1998). The results of our study are in agreement with other findings. As our experimental model of chronic hypernatraemia was a hypovolaemic hypernatraemia, the results of our study limited to this kind of chronic hypernatraemia.

In conclusion, ketamine anaesthesia in hypernatraemic rats is associated with faster induction time, prolonged recovery from anaesthesia and higher mortality rate during anaesthesia. Therefore, it seems necessary to correct hypernatraemia before induction of anaesthesia in affected animals.

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