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# Brief Reports

# NO ASSOCIATION BETWEEN HYPONATREMIA AND RHABDOMYOLYSIS IN RATS

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☐ **Abstract—Background: Rhabdomyolysis is an uncommon complication of hyponatremia, reported previously only in case reports and small retrospective studies, and its underlying mechanism is controversial. Some studies support the hypothesis that the rapid correction of hyponatremia is responsible for rhabdomyolysis, whereas others emphasize the severity of the hyponatremia as a predisposing factor for rhabdomyolysis. Objectives: To test the association between hyponatremia and rhabdomyolysis and to demonstrate a causal association. Methods: Hyponatremia was induced by administration of water and desmopressin acetate in rats during 3 days, followed by its rapid correction, using animal models established for the evaluation of central pontine myelinolysis. The plasma creatine phosphokinase levels, a marker for rhabdomyolysis, were monitored, and hematoxylin and eosin sections of the quadriceps and gastrocnemius muscles were evaluated for signs of rhabdomyolysis. Results: The induction of hyponatremia and its correction were accompanied by the previously reported neurological sequelae, including signs of central pontine myelinolysis. However, no increase in plasma creatine phosphokinase levels was found, and histopathological examination of the quadriceps and gastrocnemius muscles revealed no sign of rhabdomyolysis. Conclusions: The present study, which is the first to test the association between hyponatremia and rhabdomyolysis in an animal model, does not support any causal association between hyponatremia and rhabdomyolysis. Thus, other factors might be necessary for an association between hyponatremia and rhabdomyolysis, such as genetic factors or convulsions that are known to be associated with both hyponatremia and rhabdomyolysis. Further research in this important physiologic and clinical question is needed.** © **2014 Elsevier Inc.**

☐ **Keywords—hyponatremia; rhabdomyolysis; rat; convulsion; desmopressin**

## INTRODUCTION

Hyponatremia, defined as a sodium serum level of < 135 mEq/L, is a commonly encountered electrolyte abnormality associated with a 60-fold increase in morbidity and mortality compared to patients without documented hyponatremia (1,2). Although correction of hyponatremia is indicated to prevent the well-known neurologic sequelae, including disorientation, confusion, obtundation, and seizures, excessive rapid correction should be avoided because it can lead to irreversible neurological complications, including central pontine myelinolysis (CPM) (3,4). CPM syndrome is a demyelinating disease in the central nervous system caused by rapid correction of hyponatremia (5). This disorder begins with lethargy, followed by dysarthria, spastic quadriparesis, pseudobulbar palsy, and may eventually lead to death. To prevent CPM, the recommended limitation on the rate of correction of hyponatremia is 12 mEq/L per 24 h.

Rhabdomyolysis is a syndrome that is characterized by muscle necrosis and the release of intracellular muscle

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constituents into the circulation, which, in turn, can induce renal failure. Various causes of rhabdomyolysis have been reported, such as trauma, convulsions, drug abuse, infections, and abnormal electrolyte levels such as hyponatremia (6). Rhabdomyolysis is an uncommon complication of hyponatremia, and the underlying mechanism is controversial (7). Although the association between hyponatremia and CPM is well established, with a demonstrated causality in animal models, the association between rhabdomyolysis and hyponatremia has only been reported in case reports and one small retrospective study (4,8). It was found that the increase in the serum sodium level in the initial 24 h, for patients treated for severe hyponatremia that suffered from rhabdomyolysis, was significantly higher when compared with patients who did not suffer from rhabdomyolysis. Thus, a hypothesis was proposed stating that the rapid correction of hyponatremia is responsible not only for CPM but also for rhabdomyolysis. Several case reports have also supported this hypothesis (9–11).

To test this hypothesis, hyponatremia was induced in rats, followed by its rapid correction, using animal models that are established for the research of CPM (4,12). The plasma creatine phosphokinase (CPK) levels, a marker for rhabdomyolysis, were monitored throughout the experiment (13). Hematoxylin and eosin sections of the quadriceps and gastrocnemius muscles were evaluated for signs of rhabdomyolysis.

In this study we aimed to examine, using a rat model, whether a rapid correction of hyponatremia, compared with hyponatremia alone or no electrolyte change, can induce rhabdomyolysis. The primary outcome of the present study is an increase in plasma CPK levels, used as an indicator of rhabdomyolysis.

## METHODS

### *Experimental Animals*

Studies were performed on male Wistar rats weighing 240–260 g (Harlan, Israel). The rats were maintained on standard rodent diet with free access to water until the induction of hyponatremia. Rats were housed in a standard animal facility under conditions of constant temperature (23°C) and a 12-h light/12-h dark cycle. The study was approved by the institutional committee of ethics in animal experiments.

### *Induction of Hyponatremia*

Our experimental protocol is summarized in Figure 1. Hyponatremia was induced, as previously described, by simultaneous water loading (2.5% dextrose in water solution) and 8-deamino-arginin vasopressin (human desmopressin acetate [DDAVP] solution for injection, 4 $\mu$g/mL) administration as follows: 12 animals (groups 1–3) received intraperitoneal (i.p.) injections of 10 mL (4% body weight) dextrose solution twice daily on days 1 and 3 (9 AM and 5 PM), and once daily on day 2 (4 PM) (12). Two micrograms of DDAVP in 0.5 mL solution was administered subcutaneously (s.c.) twice daily on days 1 to 3 (9 AM and 5 PM). Four animals (group 4) served as control and were saline injected, both i.p. and s.c., with a schedule similar to that above.

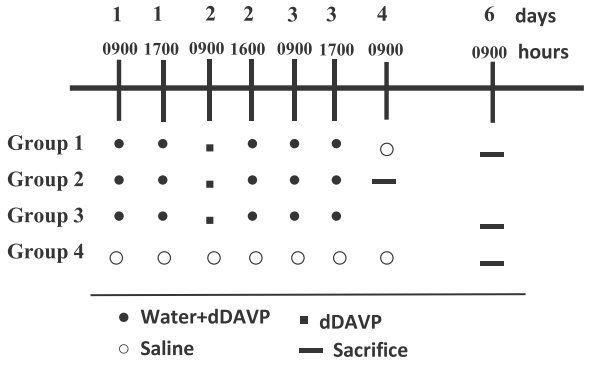


**Figure 1. Experimental protocol. Rats were rendered hyponatremic by intraperitoneal (i.p.) water loading (2.5% dextrose in water) and subcutaneous (s.c.) injection of human desmopressin acetate (DDAVP) (Groups 1–3). Four animals (group 4) served as control and were saline injected, both i.p. and s.c., with a similar schedule. Four days after the beginning of the induction of hyponatremia, serum sodium levels were rapidly corrected by a bolus injection of 0.9% NaCl administered i.p. in group 1 (n = 4), or without any further injections in group 3 (n = 4). Four animals (group 2) were sacrificed on day 4, without correction of hyponatremia. Rats in groups 1, 3, and 4 were sacrificed 2 days after correction (day 6 of the experiment).**

### *Correction of Hyponatremia*

Four days after the beginning of the induction of hyponatremia, rats were given free access to normal chow and water, and serum sodium levels were rapidly corrected by a bolus injection of 0.9% NaCl (1 mL/100 g body weight) administered i.p. in group 1 (n = 4), or without any further injections in group 3 (n = 4), serving as a control to test the effect of a slower increase in plasma sodium levels on muscles. The correction of hyponatremia in group 3 was based on the fact that both water and DDAVP administration were stopped on day 4. Four animals (group 2) were sacrificed by $CO_2$ inhalation on day 4, without correction of hyponatremia, and their quadriceps and gastrocnemius muscles were taken for histological examination, serving as a control to show that any observed histological changes in the muscles are the consequence of rapid correction of hyponatremia