The Journal of International Medical Research
2008; 36: 648 – 655

Natriuretic Peptides, Antidiuretic Hormone and Hyponatraemia after Acute Craniocerebral Injury

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We investigated the physiological mechanisms involved in central hyponatraemia in patients with acute craniocerebral injury (ACI). We measured blood concentrations of natriuretic peptides, antidiuretic hormone (ADH), and endogenous digitalis-like substance (EDLS), blood and urine sodium concentrations, and the plasma and urine osmolality in 68 patients with ACI and 24 healthy control subjects. A total of 27 ACI patients were hyponatraemic and the majority of these had grievous or severely grievous craniocerebral injuries. Blood concentrations of EDLS and ADH in hyponatraemic ACI patients were significantly higher compared with normonatraemic ACI patients and control subjects. Blood EDLS and sodium concentrations were negatively correlated with each other, whereas EDLS was positively correlated with urine sodium concentration and with urine osmotic pressure. Hyponatraemic ACI patients require different treatment based on the cause of their central hyponatraemia, so it is important to undertake a comprehensive analysis of each patient's physiological status.

KEY WORDS: Acute craniocerebral injury (ACI); Hyponatraemia; Atrial natriuretic peptide (ANP); Brain natriuretic peptide (BNP); Endogenous digitalis-like substance (EDLS); Antidiuretic hormone (ADH)

Introduction

Hyponatraemia is the most common electrolyte disturbance, occurring globally in 14% of hospitalized patients.[1] When caused by diseases of the central nervous system, it is clinically regarded as central hyponatraemia. The mortality rate of patients with severe hyponatraemia is 60 times higher than in patients with normal plasma sodium concentrations.[1] Since the cause of this disease varies, the treatment methods also vary.[2] In order to investigate how treatments might be improved for central hyponatraemia, we analysed blood sodium concentration in patients with acute craniocerebral injury (ACI) over the period of a year.

Patients and methods

PATIENT POPULATION

Patients' past and present clinical history, including any medications, were obtained by interviewing the patient or, if the patient was

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aphasic, unconscious or a child, from a family member. Hospital records were also reviewed. Patients were included in the study if they met the following inclusion criteria: (i) hospitalized within 24 h after craniocerebral injury without severe compound injuries or shock, and their diagnosis was confirmed by a computed tomography (CT) scan of the skull; (ii) no history of drinking alcohol prior to their injuries; no hypertension or any other heart disease; (iii) normal organ function (such as liver, kidney, thyroid and adrenal gland); and (iv) no treatment involving glucocorticoid hormone or mannite after their craniocerebral injury. Upon hospitalization, the patients were categorized according to the Glasgow Coma Scale (GCS)[3] as follows; GCS 12 – 15: slight injury; GCS 9 – 11: medium injury; GCS 6 – 8: grievous injury; and GCS 3 – 5: severely grievous injury.

The control group consisted of equal numbers of male and female healthy medical student volunteer blood donors. All had normal heart, liver, kidney and thyroid function and normal blood pressure.

The study was approved by Xinhua Hospital Medical Ethics Committee and verbal informed consent was obtained from each participant or, if the patient was aphasic, unconscious or a child, from a family member.

LABORATORY DATA COLLECTION

We measured the blood levels (pg/ml) of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endogenous digitalis-like substance (EDLS), and antidiuretic hormone (ADH) using a radioimmunoassay method as described previously.[4] The sodium concentrations (mmol/l) in blood and urine were measured by the dew-point test.[5] The osmotic pressure (mOsm/kgH_2O) of blood was measured by using the electrode method.[6]

HYPONATRAEMIA CATEGORIZATION

The ACI patients with hyponatraemia were categorized according to their clinical characteristics as either having inappropriate secretion of antidiuretic hormone syndrome (SIADH) or cerebral salt wasting syndrome (CSWS). The standard criteria for diagnosing SIADH included: (i) low blood sodium concentration (< 135 mmol/l); (ii) low plasma osmotic pressure (< 280 mOsm/l); (iii) high urine sodium concentration (> 20 mmol/l); (iv) urine osmotic pressure/plasma osmotic pressure ratio > 1; (v) normal renal and adrenal functions; and (vi) no dehydration or oedema in the ends of the extremities.[7] The criteria for diagnosing CSWS included: (i) hyponatraemia (< 135 mmol/l); (ii) increased urine sodium concentration (> 18 mmol/l); (iii) large urine volume (> 3000 ml/day); and (iv) low blood volume.[7]

HYPONATRAEMIA TREATMENT

Hyponatraemia required cautious administration of hypertonic saline solution (usually 3% NaCl administered through a central venous access).

SIADH demanded fluid restriction, whereas CSWS was treated with adequate fluid and sodium replacement therapy. All patients initially received crystalloids to expand the intravascular volume. Isotonic (0.9%) saline solution was usually appropriate in the early phases unless hyponatraemia was already present. Colloids (such as 5% albumin) were added for persistent signs of volume contraction. For more developed hyponatraemia, switching to hypertonic (1.5% or 3%) saline solutions was appropriate.

STATISTICAL ANALYSIS

All measured data were presented as mean ± SD and they were statistically processed by analysis of variance, the χ^2 test and linear

correlation analysis. A *P*-value < 0.05 was considered to be statistically significant.

Results

A total of 68 patients (51 males; 17 females) with acute craniocerebral injury took part in this study. Mean age was 27.8 years (range 4 – 60 years). They were categorized into: GCS 12 – 15 (slight injury group), 17 cases; GCS 9 – 11 (medium injury group), 18 cases; GCS 6 – 8 (grievous injury group), 23 cases; and GCS 3 – 5 (severely grievous injury group), 10 cases. There were 24 control subjects (12 males; 12 females) of mean age 22.3 years (range 20 – 25 years).

The blood osmotic pressure for the ACI group of patients was significantly lower than that of the control group ($P < 0.05$) (Table 1); however, there was no statistically significant difference between the ACI patients grouped according to their GCS score (GCS > 8 versus GCS ≤ 8). The urine osmotic pressure for the ACI group was significantly higher than that of the control group ($P < 0.01$). There was, however, no statistically significant difference between the ACI patients grouped according to their GCS score. The blood sodium concentration of the ACI group was significantly lower than that of the control group ($P < 0.05$) and, within the ACI group, blood sodium concentration in patients with a GCS ≤ 8 was significantly lower than in patients with a GCS > 8 ($P < 0.05$). The urine sodium concentration of the ACI group was significantly higher than that of the control group ($P < 0.05$). Within the ACI group, patients with a GCS ≤ 8 had a significantly higher urine sodium concentration than patients with a GCS > 8 ($P < 0.01$).

A total of 27 hyponatraemic patients had a blood sodium concentration < 135 mmol/l, of which eight (80%) were in the severely grievous injury group (GCS ≤ 3), 17 (73.9%) were in the grievous injury group (GCS 4 – 8), and 2 (11.1%) were in the medium injury group (GCS 9 – 11) (Table 2). There were no hyponatraemic patients in the slight injury group (GCS 12 – 15). There was a significant difference in the incidence of hyponatraemia between those patients with a GCS ≤ 8 and those with a GCS > 8 ($P < 0.001$), with the former patients clearly experiencing a greater incidence of hyponatraemia (25/33; 75.8%).

TABLE 1:
Comparison of mean ± SD blood and urine sodium concentrations and osmotic pressures in patients with various levels of acute craniocerebral injury (*n* = 68) and healthy control subjects (*n* = 24)

		ACI group (*n* = 68)	
	Control group (*n* = 24)	GCS > 8 (*n* = 35)	GCS ≤ 8 (*n* = 33)
Osmotic pressure (mOsm/kgH_2O)			
Blood	326.05 ± 5.90[a]	289.28 ± 9.14	302.21 ± 4.91
Urine	554.12 ± 25.24[b]	715.19 ± 22.17	730.02 ± 20.11
Sodium concentration (mmol/l)			
Blood	142.18 ± 2.17[a]	143.02 ± 1.01	133.40 ± 0.54[c]
Urine	284.12 ± 6.77[a]	300.28 ± 7.44	370.65 ± 6.59[d]

ACI, acute craniocerebral injury; GCS, Glasgow coma scale.
[a]$P < 0.05$; [b]$P < 0.01$ for ACI group vs control group.
[c]$P < 0.05$; [d]$P < 0.01$ for GCS > 8 vs GCS ≤ 8.

The blood concentrations of ANP and BNP of ACI patients were significantly lower compared with those of the control subjects ($P < 0.05$) (Table 3). Within the ACI group, the ANP and BNP concentrations were not significantly different between patients with and without hyponatraemia. The blood EDLS and ADH concentrations of ACI patients were significantly higher than those of the control subjects ($P < 0.001$, $P < 0.01$, respectively) and, in ACI patients with hyponatraemia, were significantly higher compared with ACI patients without hyponatraemia ($P < 0.05$ for both). Correlation analysis showed that blood EDLS and ADH concentrations were significantly negatively correlated with blood sodium concentration ($r = -0.884$, $P < 0.01$; $r = -0.867$, $P < 0.01$, respectively), but there was a significant positive correlation between EDLS concentration and urine sodium concentration ($r = 0.918$, $P < 0.01$), and between EDLS concentration and urine osmotic pressure ($r = 0.873$, $P < 0.01$).

The 27 ACI patients with hyponatraemia when categorized according to their clinical characteristics indicated that seven were SIADH and 20 were CSWS. Table 4 presents the treatment observations for hyponatraemic ACI patients with SIADH or CSWS.

Discussion

Hyponatraemia is the most common and important electrolyte disorder encountered by patients with severe craniocerebral injuries. Once hyponatraemia occurs, the

TABLE 2:
Relationship between hyponatraemia and the level of craniocerebral injury in patients with craniocerebral injuries ($n = 68$)

	GCS ≤ 3 ($n = 10$)	GCS 4 – 8 ($n = 23$)	GCS 9 – 11 ($n = 18$)	GCS 12 – 15 ($n = 17$)
Number of patients with hyponatraemia	8	17	2	0
Incidence of hyponatraemia	80.0%	73.9%	11.1%	0%

GCS, Glasgow coma scale.
$P < 0.001$ for GCS > 8 vs GCS ≤ 8.

TABLE 3:
Comparisons of mean ± SD blood atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endogenous digitalis-like substance (EDLS), and antidiuretic hormone (ADH) concentrations among acute craniocerebral injury (ACI) patients with and without hyponatraemia and healthy control subjects

		ACI group ($n = 68$)	
	Control group ($n = 24$)	With hyponatraemia ($n = 27$)	Without hyponatraemia ($n = 41$)
ANP (pg/ml)	335.05 ± 19.79[a]	293.18 ± 20.40	290.11 ± 15.41
BNP (pg/ml)	24.64 ± 1.93[a]	20.41 ± 1.80	18.91 ± 1.35
EDLS (pg/ml)	268.67 ± 10.52[b]	513.63 ± 19.75[d]	389.16 ± 24.46
ADH (pg/ml)	66.25 ± 3.33[c]	130.87 ± 4.32[d]	82.66 ± 7.41

[a]$P < 0.05$; [b]$P < 0.001$; [c]$P < 0.01$ for ACI group vs control group.
[d]$P < 0.05$ for with vs without hyponatraemia.

fatality rate increases by 14.3%.[8] Following a drop in the blood sodium level, patients with severe hyponatraemia rapidly become somnolent; they can also show signs of mental confusion, become comatose, and they might even experience an epileptic fit. If these symptoms are not monitored, identified and treated in a timely manner, they will almost certainly result in a serious setback in the patient's recovery.

In ACI patients, hyponatraemia is more common in those with grievous or severely grievous craniocerebral injuries. Its pathological basis, in terms of neuroendocrinology, may be damage to the normal regulatory relationship between the two vital endocrine systems that maintain water–salt balance.[9] These two systems are: (i) the ADH system involving renin–angiotensin–aldosterone; and (ii) the natriuretic peptides, such as ANP, BNP and EDLS. These two systems, which act in a coordinated, antagonistic way with each other, jointly maintain the body's water–salt balance. ANP, BNP, EDLS and ADH are stored, released or regulated under the control of the hypothalamus in the central nervous system (CNS). Patients with ACI, especially those with severe brain trauma, usually have their hypothalamus–pituitary functions damaged, directly or indirectly, and this has a big impact on their ability to control their levels of ADH and natriuretic peptides.[10]

ADH is synthesized by the supra-optic and paraventricular nuclei of the hypothalamus and is released into the blood through the lobus posterior hypophyseos. In contrast to the function of ANP, BNP and EDLS, the function of ADH is to stimulate the distal convoluted tubules and the collecting tubes of the kidney to re-absorb water.[11] As a result, ADH is essential for maintaining the body's water–osmotic pressure balance. Patients with ACI and hyponatraemia usually have increased blood ADH concentrations.[12] This might be because of damage to the hypothalamus resulting in a decreased sensory threshold for osmotic pressure.[13] If the ADH secretory system in the hypothalamus is damaged, ADH could directly enter into the bloodstream resulting in trauma stress reactions and a decrease in ANP and BNP concentrations, reducing their inhibitory effect on ADH secretion. Increased angiotension II concentrations in the CNS can also stimulate ADH secretion.[14]

An increase in the blood ADH concentration can lead to a series of pathophysiological changes, such as increased water reabsorption by the renal

TABLE 4:
Observations of the effects of various treatments on patients with acute craniocerebral injury and hyponatraemia due to the inappropriate secretion of antidiuretic hormone syndrome (SIADH) (n = 7) or cerebral salt wasting syndrome (CSWS) (n = 20)

	Water restriction[a]	Supplementing blood volume[b]	Supplementing sodium salt[c]
CSWS (increase in EDLS)	Patient's condition worsened	Effective	Effective
SIADH (increase in ADH)	Effective	Patient's condition worsened	Effective

EDLS, endogenous digitalis-like substance; ADH, antidiuretic hormone.
[a]Fluid intake was restricted to 800 – 1000 ml/day for 2 – 3 days to create a negative water balance.
[b]Blood volume is increased by water supplementation.
[c]Sodium supplementing volume: (142 mmol/l – practically measured serum sodium) × 0.2 × body weight (kg).

tubules, decreased urine volume, water retention, and an increase in extracellular fluids.[15] If adrenocorticotropic hormone (ACTH) is also secreted relatively insufficiently, resulting in decreased plasma ACTH levels and lowered aldosterone secretion, the ability of the renal tubules to excrete potassium and retain sodium is reduced, resulting in increased urine sodium excretion. The consequences of an increase in extracellular fluids and loss of urine sodium is inevitably a decrease in plasma osmotic pressure and lowered blood sodium, which is clinically manifested as SIADH.[9] A water loading test can be used as a diagnostic test for SIADH whereby if, after rapidly drinking 1500 ml water (20 ml/kg), their micturition volume has not reached 65% of the water taken in within 4 h, or 80% within 5 h, they are diagnosed as having SIADH, except for cases of adrenal or renal insufficiency.[16]

The main principle in treating SIADH is to restrict water intake to 800 – 1000 ml/day in order to create a negative water balance. By doing this, ACI patients with slight injuries will improve and their blood sodium level will rise after 2 – 3 days. For patients with severely low sodium and low serum osmolality (blood sodium < 125 mmol/l), we treat as follows. (i) Diuresis and salt supplementation, using the diuretics furosemide, etacrynic acid and mannite to excrete water whilst providing sodium supplementation with isotonic or hypertonic saline, determined according to the formula: sodium supplementing volume = (142 mmol/l – measured serum sodium) × 0.2 × body weight (kg). The rate of blood sodium increase over 24 h is controlled at 8 – 10 mmol/l to avoid a too rapid increase causing central pontine myelinolysis. (ii) Supplementation of ACTH by intramuscular injection (25 U) twice daily, in order to correct the imbalance between ADH and ACTH. (iii) Antagonism of thyrotropin-releasing hormone against ADH, a new area for the treatment of SIADH.[17]

The regulatory effect of the natriuretic peptides ANP, BNP and EDLS in the CNS on water–salt balance is mainly through two mechanisms: (i) acting directly on the CNS; and (ii) acting as neurotransmitters.[18] When the natriuretic peptides act as neurotransmitters, their functions include: (i) promoting release of the peripheral natriuretic peptides, leading to an increased volume of blood flow in the kidney, a rise in the glomerular filtration rate and filtration fractions, and inhibition of reabsorption of sodium and water by the proximal convoluted tubules; (ii) inhibiting the renin–angiotensin–aldosterone system; (iii) inhibiting activity of the sympathetic nerves and release of peripheral catecholamine; and (iv) inhibiting salt intake and ADH release.[19]

It is known that atrial natriuretic peptide and BNP are the bioactive peptides with the greatest diuretic and natriuretic functions.[20] The blood–brain barrier means that the activity of ANP and BNP as CNS mediators is independent of their activity as peripheral circulating hormones.[7] Although the concentrations of ANP and BNP in the CNS are extremely low, they have a large effect on the regulation of peripheral blood ANP and BNP concentrations, and this regulation originates in the heart.[21] The decreased blood ANP and BNP concentrations that we observed in ACI patients may be due to damage to the hypothalamus–pituitary ANP and BNP systems, preventing ANP and BNP from entering the blood and acting on the heart. Increased angiotensin II concentrations in the CNS and peripheral blood might inhibit the release of ANP and BNP.[19] According to our observations, the decrease in blood ANP and BNP concentrations did not have any direct effect on the blood

sodium concentration in ACI patients.

EDLS is synthesized and released by the hypothalamus and has powerful peripheral diuretic and natriuretic effects, inhibiting renal tubular sodium reabsorption.[22] The present study demonstrated that the blood concentration of EDLS in ACI patients with hyponatraemia was significantly increased compared with control subjects and those ACI patients without hyponatraemia. This might be because the EDLS that is located within the secretory cells could directly enter into the blood because of injury to the hypothalamus, resulting in the occurrence of trauma stress reactions, increased ADH secretion, increased extracellular fluids and increased EDLS antagonism.[19] The increase in blood EDLS concentration causes increased urine sodium levels and high urine osmotic pressure, leading to sodium-losing hyponatraemia, which is clinically recognized as CSWS.[9,16]

The cause of CSWS is excessive excretion of sodium and water by the kidneys arising from CNS diseases, and its clinical manifestation is a series of clinical syndromes, such as low blood sodium, low blood volume and high urine sodium.[23] It is currently thought that CSWS is much more common than SIADH when hyponatraemia is complicated due to pathological changes in the CNS.[24] In addition to sodium supplementation, the main method for treating CSWS is to focus on water supplementation in order to correct the low levels of blood sodium and blood volume.[25]

The main features differentiating CSWS from SIADH are the decrease in extracellular fluids and the negative sodium balance.[15] The resulting differences in, for example, pulmonary wedge pressures, central venous pressures, and packed cell volumes contributes to differentiation between the two conditions. The critical treatment difference between SIADH and CSWS is whether water or sodium is supplemented. Traditionally, before these two conditions had been characterized and differentiated, it was usual to use 3 – 5% sodium chloride solution to supplement the salt, and the decision to supplement water was based mainly on measurements of blood pressure, heart rate and/or central venous pressure.[26]

In summary, hyponatraemia that is complicated in patients with severe craniocerebral injury is the result of pathological mechanisms that are common to both SIADH and CSWS, as follows: increased EDLS secretion leads to increased urine sodium levels, leading to increased urine volume, leading to hyponatraemia, raised ADH secretion, reduced renal excretion, hence raised extracellular fluid levels, aldosterone secretion, hyponatraemia, water retention (dilutional hyponatraemia) and reabsorption of sodium by the renal tubules. In the clinical treatment of traumatic cerebral oedema, a large dose of dehydrating agent is usually used, which might induce further serious salt loss. Having a clear idea, therefore, of the cause of central hyponatraemia and correctly treating it are of vital clinical value. The focal point in treating SIADH should be to restrict fluid intake, whereas the treatment of CSWS should involve supplementing blood volume and lost sodium. When supplementing sodium, use of a mineralocorticoid can help recovery of the blood sodium concentration.[15,27] The volume of salts and water to be supplemented should be based on comprehensive analysis of each patient's physiological status, such as their blood and urine sodium concentrations, and their blood volume.[28,29]

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this paper.

• Received for publication 6 January 2008 • Accepted subject to revision 28 January 2008
• Revised accepted 19 May 2008

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