www.nature.com/clinicalpractice/neph

Fatal hyponatremia in a young woman after ecstasy ingestion

Kamyar Kalantar-Zadeh*, Minhtri K Nguyen, Roger Chang and Ira Kurtz

SUMMARY

Background A 20-year old, otherwise healthy, female college student presented in an unresponsive state with respiratory distress after ingesting ecstasy (3,4-methylenedioxymethamphetamine). She had initial plasma sodium concentration of 117 mmol/l.

Investigations Physical examination, blood chemistry panel, urinary osmolality and electrolytes, arterial blood gas, chest X-ray, and CT scan of the brain.

Diagnosis Hyponatremia associated with noncardiogenic pulmonary edema and cerebral edema.

Management Administration of a total of 6.8 l of isotonic saline and 0.245 l of 3% hypertonic saline with sporadic administration of intravenous furosemide. The patient died approximately 12 h after admission.

KEYWORDS ecstasy, estrogen, hyponatremic encephalopathy, MDMA, noncardiogenic pulmonary edema

CME

K Kalantar-Zadeh is an Associate Professor of Medicine and Pediatrics and Director of the Dialysis Expansion Program and Epidemiology at Harbor-UCLA Division of Nephrology and Hypertension, MK Nguyen (co-primary author) is an Assistant Professor of Medicine and Director of Consultative Nephrology in the Division of Nephrology, and I Kurtz is Chief of Nephrology, Professor of Medicine, Factor Chair in Molecular Nephrology, and Director of the Molecular Physiology and Biophysics Transport Laboratory at UCLA, Torrance, CA. R Chang is a hospitalist at St Joseph's Hospital in Orange, CA, USA.

Correspondence
*Harbor-UCLA Medical Center, UCLA David Geffen School of Medicine, 1124 W Carson St, C-1 Annex, Box 406, Torrance, CA 90502-2064, USA
kamkal@ucla.edu

Received 1 July 2005 **Accepted** 20 February 2006
www.nature.com/clinicalpractice
doi:10.1038/ncpneph0167

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

In 2002, a 20-year-old, Asian American woman was brought to the emergency room at Harbor-UCLA Medical Center after having taken multiple tablets of ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) and large quantities of water while dancing and drinking excessively during a party the night before. She did not report any symptoms upon returning home after the party. In the morning, however, she was found unresponsive and foaming at the mouth although no seizures were reported. She had rapid and shallow breathing, a weak pulse and did not respond to painful stimuli. The patient was otherwise healthy, with no medical or surgical history or significant family history. She was not taking any medications and was a college student of good standing.

In the emergency room the patient was found to be in respiratory distress (respiratory rate 30–35 breaths per minute), hypothermic (temperature 34.7 °C), tachycardic (pulse 123 beats per minute), hypotensive (blood pressure 88/49 mmHg), hypoxemic (oxygen saturation 80% on a nonrebreather mask), and nonedematous. Her pupils were symmetrically dilated and minimally reactive to light. No jugular venous distention was noted. Chest auscultation revealed diffuse crackles bilaterally. The patient was intubated.

Table 1 shows results of initial plasma electrolyte measurements and arterial blood gas analyses and how these results changed over time with treatment. Initial laboratory examination also revealed a blood urea nitrogen (BUN) level of 6.4 mmol/l, a serum glucose level of 5.75 mmol/l, and a serum calcium level of 1.95 mmol/l. The patient had an initial serum osmolality of 245 mOsm/kg, urine specific gravity of 1.015, a white blood cell count of 18,300 cells/mm^3, a hemoglobin concentration of 133 g/l, and a platelet count of 310,000 cells/mm^3. The chest

Table 1 Chronologic course of events in the patient after ecstasy (3,4-methylenedioxymethamphetamine) ingestion.

Time	Chemistry panel				Arterial blood gas			Events and intravenous fluids	Urine output
	Na (mmol/l; normal range: 135–145 mmol/l)	Cl (mmol/l; normal range: 95–105 mmol/l)	HCO_3 (mmol/l; normal range: 22–26 mmol/l)	Creatinine (μmol/l; normal range: 50–120 μmol/l)	pH (normal range: 7.35–7.45)	pCO_2 (mmHg; normal range: 38–42 mmHg)	pO_2 (mmHg; normal range: 80–100 mmHg)		
07:00	ND	ND	ND	ND	ND	ND	ND	Approximately 1 l normal saline in the ambulance	
07:20	117	87	15	88	7.14	37	99	Intubation, 3 l normal saline upon arrival in emergency room	2055 ml
10:00	ND	ND	ND	ND	ND	ND	ND	20 ml 3% hypertonic saline in intensive care unit	
10:30	121	94	15	62	7.29	40	51	2 l normal saline plus furosemide following nephrology consultation	270 ml
12:00	ND	ND	ND	ND	ND	ND	ND	225 ml 3% hypertonic saline with 60 g mannitol	250 ml
13:15	120	91	19	80	7.24	29	119	Central venous pressure increased to 23 cm, intravenous fluids discontinued	350 ml
15:30	ND	ND	ND	ND	7.29	27	75	500 ml normal saline	320 ml
18:00	129	104	17	115	ND	ND	ND	300 ml normal saline	350 ml
20:15	ND	ND	ND	ND	ND	ND	ND	Code blue: patient expired after 20 min	
Total								6.8 l isotonic saline 0.245 l 3% hypertonic saline	3595 ml

ND, not done.

GLOSSARY

NONCARDIOGENIC PULMONARY EDEMA
A status of pulmonary vascular congestion and/or edema that is not a result of congestive heart failure

X-ray showed severe pulmonary edema (Figure 1). A CT scan of the head showed evidence of cerebral edema.

The patient was given a total of 6.8 l of isotonic saline and 0.245 l of 3% hypertonic saline with intermittent administration of furosemide and 60 g of mannitol (Table 1). Plasma sodium concentration [Na^+] increased to 129 mmol/l after 10 h of hospitalization, but the patient's hemodynamic status remained unstable; 12 h after admission, she was found to have wide-complex tachycardia, which was followed by pulseless electrical activity. Resuscitation efforts were unsuccessful, and the patient expired.

DISCUSSION OF DIAGNOSIS

Hyponatremia can lead to increased intracranial pressure, which might trigger the development of neurogenic pulmonary capillary leak and result in NONCARDIOGENIC PULMONARY EDEMA. Cardiogenic pulmonary edema is highly unlikely in a young woman with no medical history of cardiovascular, pulmonary or renal disease. Encephalopathy is thought to result from brain edema caused by movement of water into the brain cells. Hyponatremic encephalopathy can also manifest as hypercapnic respiratory failure.[1] Even in chronic symptomatic hyponatremia, hypoxia can play a crucial role in morbidity and mortality.[2] The encephalopathic patient with hyponatremia usually presents with headache, nausea, vomiting, abdominal pain, confusion, and seizures, which can lead to permanent neurologic sequelae and imminent death due to brain edema and subsequent herniation.

Several factors that might contribute to MDMA-associated hyponatremia are noted in Box 1. Profuse sweating at a 'rave party' can lead to excessive water intake, which ultimately results in a decreased concentration of sodium in the blood.[3] Up to 2 l of perspiration can be lost per hour in a hot environment, especially during intense physical activity such as dancing.[4] If MDMA in some way also inhibits perspiration, hyponatremia is more likely to occur. A mood-altering drug such as MDMA might also stimulate thirst and cause primary polydipsia independent of perspiration or ambient temperature.[5] Moreover, partygoers are usually encouraged to drink large volumes of water to avoid dehydration.[4]

As in marathon runners, excess antidiuretic hormone (ADH, also known as vasopressin) release can result from rigorous physical activity such as dancing. MDMA can trigger inappropriate secretion of ADH independent of the degree of physical activity. In a study of eight healthy drug-free male volunteers Fallon *et al.* showed that concentrations of plasma arginine vasopressin increase significantly after administration of a low dose of MDMA.[6]

In MDMA users, gastrointestinal motility can decrease, resulting in a large static volume of electrolyte-free water in the lumen of the gastrointestinal tract.[4,7] An ileus with a 2-cm radius would lead to a 7-l water intake and its retention in the lumen of the stomach and small intestine.[4] This retained water might be absorbed abruptly through the gastrointestinal tract upon cessation of physical activity (e.g. at the end of a dance party) leading to acute hyponatremia.

Several fatal cases of MDMA-associated hyponatremia have been reported;[8–12] most of

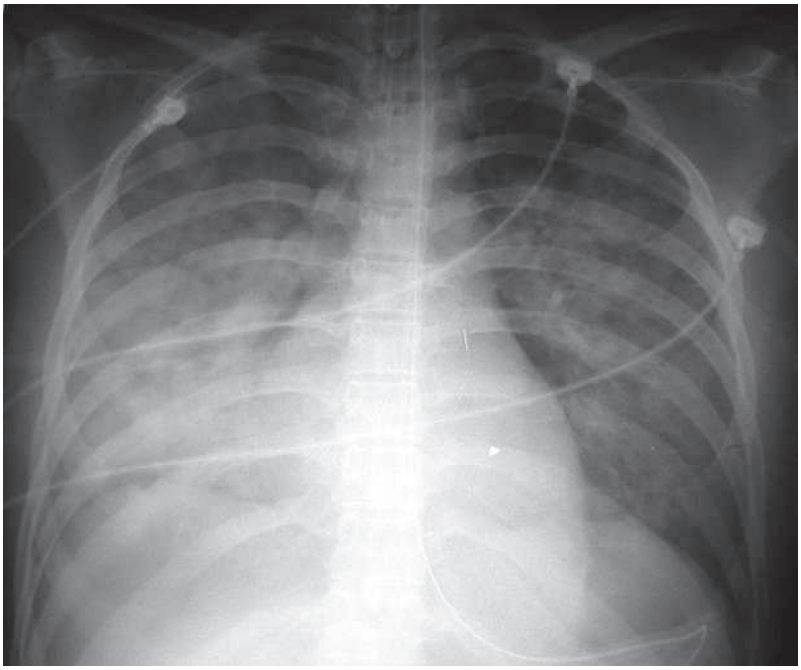

Figure 1 Chest X-ray of 20-year-old woman with a plasma sodium concentration of 117 mmol/l after ecstasy (3,4-methylenedioxymethamphetamine) ingestion. Note the cephalization of pulmonary vasculature consistent with pulmonary edema, which is noncardiogenic in this case.

Box 1 Factors that might contribute to fatal hyponatremia following ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) ingestion.

- Excessive fluid intake in response to central polydipsia (effect of MDMA on the central nervous system) or polydipsia as a result of perspiration during rigorous physical activity (e.g. dancing)
- Fluid third-spacing in the GI tract (ileus) with subsequent abrupt water reabsorption
- Reduction or inhibition of perspiration
- Overproduction and/or release of antidiuretic hormone either in response to, or independent of, rigorous physical activity
- Administration of hypotonic or isotonic intravenous fluids
- Low muscle mass (in thin women)
- Transient acute proximal tubular injury
- Estrogenic hormones (in menstruating women)
- Higher intracellular brain volume (relative to older women) or absence of age-related brain cell atrophy
- Neurotoxicity

Table 2 Comparison of clinical and laboratory findings, course of events, and management and outcome of three hyponatremic patients.

	MDMA user	Marathon runner	Post-surgical patient
Patient characteristics	20-year-old Asian-American female	38-year-old Caucasian female	24-year-old Caucasian female
Preceding events	MDMA ingestion, dancing, excessive water intake	64.4-km marathon, ingestion of 25 250 ml bottles of water	5% dextrose infusion preoperatively and postoperatively to avoid hypoglycemia
Initial symptoms	Found unresponsive morning after MDMA ingestion	Confusion, headache, abdominal pain, nausea, vomiting, diarrhea, shortness of breath	Post-appendectomy headache and shortness of breath
Serum [Na^+] at presentation (mmol/l)	117	121	119
Serum osmolality (mOsm/kg)	245	253	249
Urine osmolality (mOsm/kg) and/or specific gravity	SG 1.015	UOsm 245 SG 1.020	UOsm 210
Symptoms upon presentation	Coma	Tachycardia (pulse 120 beats per minute), tachypnea and respiratory distress	Respiratory distress and moderate obtundation
Respiratory distress	Severe, patient intubated	Moderate (respiratory rate 30–40) with hypoxemia	Mild to moderate, rales on both lungs
Oxygen saturation (%)	80 on nonrebreather mask	82–88 on 4–6 l O_2 via nasal cannula	88–92 on ambient air
Other notable observations	None	Weight 4 kg greater than normal, no jugular venous distention, bilateral basilar crackles on chest auscultation	None
Chest X-ray finding	Pulmonary edema	Pulmonary venous congestion and edema	Pulmonary vascular congestion and edema
CT scan of head	Cerebral edema	No immediate CT; CT was normal the following day	Not done
Initial intravenous fluid/ medications	Essentially, 4 l normal saline	Hypertonic saline, normal saline, 40 mg intravenous furosemide	Intravenous fluids discontinued, 40 mg intravenous furosemide administered
Nephrology consultant aware of recent literature	Yes	Yes	No
Hypertonic saline recommendation questioned by other physicians	Emergency room, medical and nephrology teams expressed concern about hypertonic saline recommendation	Nephrologist convinced concerned emergency room physicians to use hypertonic saline after presentation of recent literature[5]	Neither nephrology team nor other physicians recommended hypertonic saline
Repeat/final serum [Na^+] (mmol/l)	129 after 10 h	125 after 2.5 h,141 after 48 h	136 after 24 h
Outcome	Death	Improved with no sequelae, discharged after 2 days	Improved (2.5 l urine produced in 6 h) with no sequelae, discharged after 1 day

MDMA, 3,4-methylenedioxymethamphetamine; [Na^+], sodium concentration; SG, urine specific gravity; UOsm, urine osmolality.

these cases were premenopausal women.[8–12] This finding is consistent with the findings of 'Ayus–Arieff syndrome', in which women of this age develop noncardiogenic pulmonary edema, hypoxemia and brain edema.[13,14] The relative risk of death or permanent neurological damage from hyponatremic encephalopathy is reported to be 30 times greater for women than for men, and 25 times greater for menstruant females than for postmenopausal females.[13] The higher morbidity and mortality rates among menstruating women have been attributed to the effects of estrogenic hormones, via two possible mechanisms: (1) inhibition of

cerebral Na^+/K^+-ATPase activity, which impairs the ability of brain cells to extrude sodium in the initial defense of cell volume; and (2) increased vasoconstriction of cerebral blood vessels by vasopressin, which leads to decreased brain perfusion.[15,16]

The gender discrepancy could also be due to the fact that women have less muscle mass than men. As half of total body water is located in skeletal muscle cells, an individual with low muscle mass is at high risk for development of severe hyponatremia when a given volume of electrolyte-free water is retained.[4] Individuals with muscle atrophy resulting from illness or a nutritional problem (e.g. anorexia nervosa) are also at risk. In addition, differences in brain adaptation could account for part of the gender discrepancy—women are less able to adapt to cerebral edema than men.[15]

Age might also have a bearing on hyponatremia-associated morbidity. Young patients seem to be affected to a greater degree than older patients, possibly because of the absence of age-related brain cell atrophy and the resulting higher intracellular brain volume. If acute hyponatremia develops, a larger intracellular brain volume could result in a greater increase in cell volume within the confined space of the skull.

DISCUSSION OF TREATMENT OPTIONS

In edematous patients with otherwise asymptomatic hyponatremia, combined water restriction and loop diuretics or vasopressin-receptor antagonists are appropriate treatment options. In patients with acute or symptomatic hyponatremia, however, the administration of a loop diuretic plus intravenous saline is often necessary to achieve a higher rate of correction of the plasma $[Na^+]$ (Figure 2).

Table 2 outlines two nonfatal cases of hyponatremia in premenopausal women who had signs and symptoms similar to those of our patient but had favorable outcomes. These patients were treated primarily with hypertonic saline or with the diuretic furosemide, and their symptoms resolved within 48 h. The decision to administer hypertonic saline (plus furosemide therapy) to patients with pulmonary and cerebral edema is counterintuitive and might be questioned by many physicians. Indeed, in the case presented here, the recommendation of hypertonic fluid made by the consulting nephrologist was questioned by the emergency room physicians and by the intensivist. Agreement to proceed with hypertonic fluid treatment was reached after the team reviewed relevant literature.[10] In the setting of noncardiogenic pulmonary edema and cerebral edema, treatment of the hyponatremia should be aimed at both correcting dysnatremia and achieving negative water balance.

In the fatal case presented here, the patient's weight was 55 kg and her plasma $[Na^+]$ increased from 117 mmol/l to 129 mmol/l after administration of intravenous fluids. The relative contributions of isotonic saline and

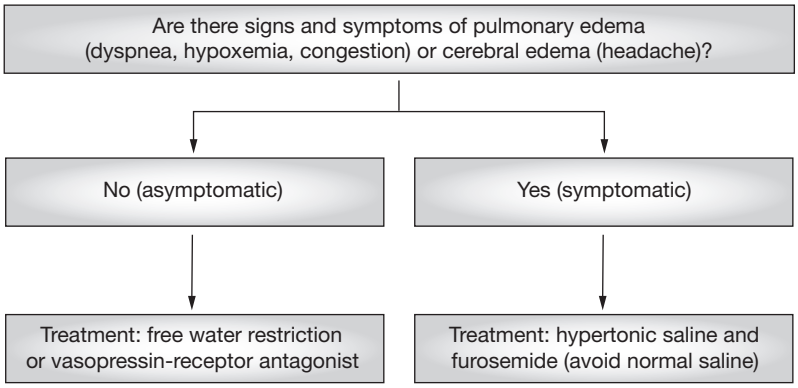

Figure 2 Algorithm for treatment of premenopausal women with hyponatremia.

Box 2 The Nguyen-Kurtz equation can predict post-intervention plasma sodium concentration based on pre-intervention plasma sodium concentration, total body water and other factors including the type and amount of administered fluid, urine output and urinary electrolytes.[17,18]

$$[Na^+]_{2\ plasma} = \frac{([Na^+]_{1\ plasma} + y_1)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - y_2$$

where

$[E] = [Na^+ + K^+]$

$E_{MB} = (Na^+ + K^+)_{input-output}$ = mass balance of $Na^+ + K^+$ in a chosen duration of time.

$= [E]_{IVF} \times V_{IVF} + [E]_{oral} \times V_{oral} + [E]_{tube\ feed} \times V_{tube\ feed} + [E]_{TPN} \times V_{TPN} - [E]_{urine} \times V_{urine} - [E]_{GI} \times V_{GI} - [E]_{sweat} \times V_{sweat}$

$V_{MB} = V_{input} - V_{output}$ = mass balance of H_2O in a chosen duration of time.

$= V_{IVF} + V_{oral} + V_{tube\ feed} + V_{TPN} + V_{oxidation} - V_{urine} - V_{GI} - V_{sweat} - V_{insensible}$

$y = 23.8 + (1.6/100)([G] - 120)$ where $[G]$ = plasma glucose concentration.

In patients with euglycemia, $y_1 = y_2 = 23.8$ for the sake of simplification.

E_{TPN}, $[Na^+ + K^+]$ in the administered total parenteral nutrition; $[Na^+]_{1\ plasma}$, pre-intervention plasma sodium concentration; $[Na^+]_{2\ plasma}$, post-intervention plasma sodium concentration; TBW, total body water; $V_{insensible}$, amount of insensible water losses; $V_{oxidation}$, volume of water produced as a result of oxidation; V_{TPN}, administered volume of TPN.

GLOSSARY

NGUYEN-KURTZ EQUATION
An equation for predicting changes in plasma sodium concentration resulting from a given mass balance of Na^+, K^+, and H_2O

Acknowledgments
K Kalantar-Zadeh is supported by the NIH grant DK61162 and I Kurtz is supported by the NIH grants DK63125, DK58563, DK07789, the Max Factor Family Foundation, the Richard and Hinda Rosenthal Foundation, and the Fredrika Taubitz Fund.

Competing interests
The authors declared they have no competing interests.

hypertonic saline to correction of this patient's hyponatremia can be determined quantitatively by applying the NGUYEN-KURTZ EQUATION (Box 2).[15] Administration of 6.8 l of isotonic saline is predicted to have raised plasma $[Na^+]$ by 3.6 mmol/l, whereas infusion of 0.245 l hypertonic saline is predicted to have increased plasma $[Na^+]$ by 3.4 mmol/l. For a given urinary output, the volume of isotonic saline required to raise the plasma $[Na^+]$ to a target value will be significantly greater than that of hypertonic saline. In the setting of hyponatremia associated with cerebral and pulmonary edema, this additional fluid will worsen volume overload, as was the case with this patient. Administration of hypertonic saline and furosemide is therefore preferable to infusion of isotonic saline and furosemide, as the former approach facilitates attainment of negative water balance by limiting the amount of infusate needed to increase the plasma $[Na^+]$ to a target value.

CONCLUSIONS

Nephrologists are often consulted on the management of patients with MDMA-associated hyponatremia. At the dawn of the 21st century, however, many nephrologists, as well as emergency room physicians, cardiologists and intensivists, might still be unaware of the potentially fatal outcome and might not feel comfortable recommending administration of hypertonic saline in the presence of noncardiogenic pulmonary edema. This counterintuitive measure could, however, save lives, as recently indicated.[13] Early symptoms of hyponatremic encephalopathy (e.g. nausea, abdominal pain, headache and mild obtundation) and signs and symptoms of noncardiogenic pulmonary edema (e.g. dyspnea, hypoxemia and pulmonary congestion or edema) in a young woman with mild to moderate hyponatremia, should prompt immediate hospitalization (preferably in the intensive care unit) and administration of hypertonic, rather than isotonic, saline in conjunction with furosemide therapy.

References

1 Ayus JC and Arieff AI (1995) Pulmonary complications of hyponatremic encephalopathy: noncardiogenic pulmonary edema and hypercapnic respiratory failure. *Chest* **107:** 517–521
2 Ayus JC and Arieff AI (1999) Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. *JAMA* **281:** 2299–2304
3 Gowing LR *et al.* (2002) The health effects of ecstasy: a literature review. *Drug Alcohol Rev* **21:** 53–63
4 Cherney DZ et al. (2002) Acute hyponatraemia and 'ecstasy': insights from a quantitative and integrative analysis. *QJM* **95:** 475–483
5 Brvar M *et al.* (2004) Polydipsia as another mechanism of hyponatremia after 'ecstasy' (3,4 methyldioxymethamphetamine) ingestion. *Eur J Emerg Med* **11:** 302–304
6 Fallon JK *et al.* (2002) Action of MDMA (ecstasy) and its metabolites on arginine vasopressin release. *Ann NY Acad Sci* **965:** 399–409
7 Haldane JS and Priestley JG (1916) The regulation of excretion of water by the kidneys. *J Physiol London* **50:** 296–303
8 Budisavljevic MN *et al.* (2003) Hyponatremia associated with 3,4-methylenedioxymethyl amphetamine ("Ecstasy") abuse. *Am J Med Sci* **326:** 89–93
9 Hartung TK *et al.* (2002) Hyponatraemic states following 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') ingestion. *QJM* **95:** 431–437
10 Balmelli C *et al.* (2001) Fatal brain edema after ingestion of ecstasy and benzylpiperazine. *Dtsch Med Wochenschr* **126:** 809–811
11 Parr MJ *et al.* (1997) Hyponatraemia and death after "ecstasy" ingestion. *Med J Aust* **166:** 136–137
12 O'Connor A *et al.* (1999) Death from hyponatraemia-induced cerebral oedema associated with MDMA ("Ecstasy") use. *NZ Med J* **112:** 255–256
13 Ayus JC *et al.* (2000) Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. *Ann Intern Med* **132:** 711–714
14 Arieff AI and Ayus JC (1993) Endometrial ablation complicated by fatal hyponatremic encephalopathy. *JAMA* **270:** 1230–1232
15 Arieff AI *et al.* (1995) Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. *Am J Physiol* **268:** R1143–R1152
16 Ayus JC *et al.* (1992) Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* **117:** 891–897
17 Kurtz I and Nguyen MK (2003) A simple quantitative approach to analyzing the generation of the dysnatremias. *Clin Exp Nephrol* **7:** 138–143
18 Nguyen MK and Kurtz I (2004) New insights into the pathophysiology of the dysnatremias: a quantitative analysis. *Am J Physiol Renal Physiol* **287:** F172–F180