Hyponatremia: recent data

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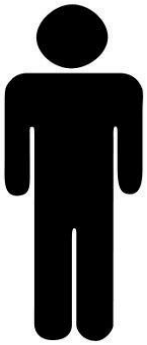
$$[\,Na\,] = \frac{Na^{+}_{e} + K^{+}_{e}}{TBW}$$



♂ 60 y BW 66 kg, TBW ± 33 L, SNa 140 mEq/L

Δ TBW 1 L → Δ SNa: 3% (or 4.2 mEq/L)

Retention or los of 33 mEq of Na^+ or K^+

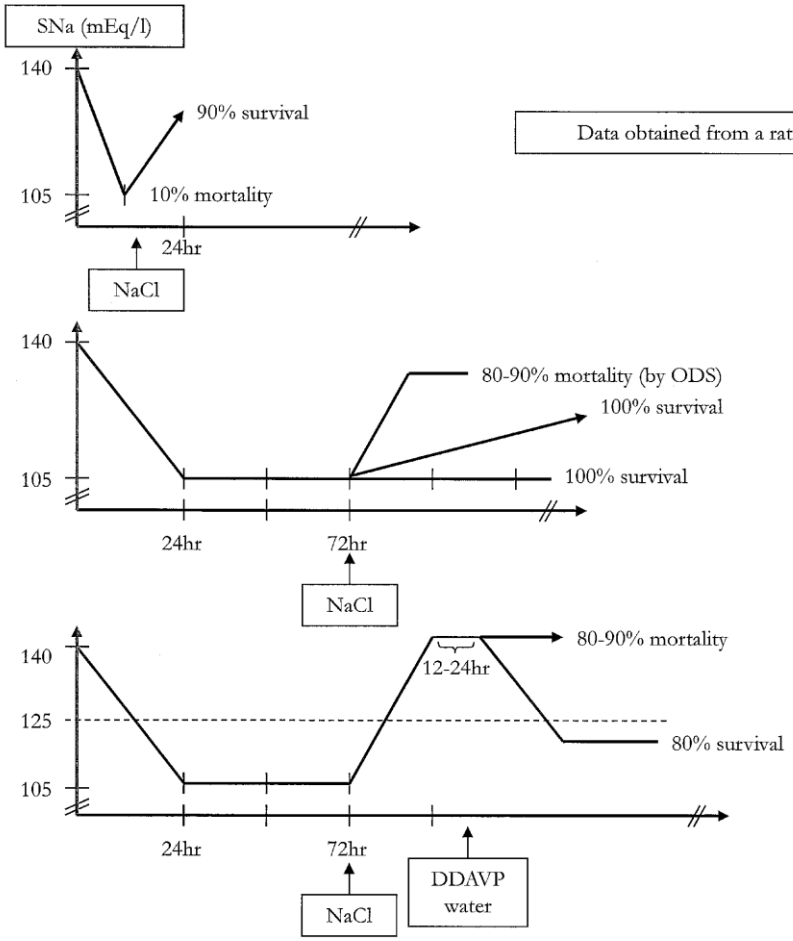
→ Δ SNa: 1 mEq/L

♀ 80 y BW 60 kg, TBW ± 25 L, SNa 140 mEq/L

Δ TBW 1 L → Δ SNa: 4% (or 5.6 mEq/L)

Retention or los of 25 mEq of Na^+ or K^+

→ Δ SNa: 1 mEq/L



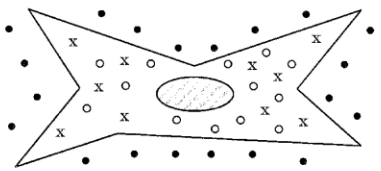
Data obtained from a rat model of SIADH

In rats increase of SNa by 15 mEq/l/d is well tolerated (even acutely)

Re-induction of hyponatremia after overcorrection reduces mortality particularly if rats are still asymptomatic

Soupart et al. Kidney Intern 1994; 45: 193-200

SNa 140 mEq/L

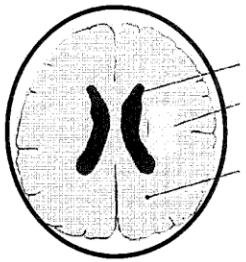


• Na

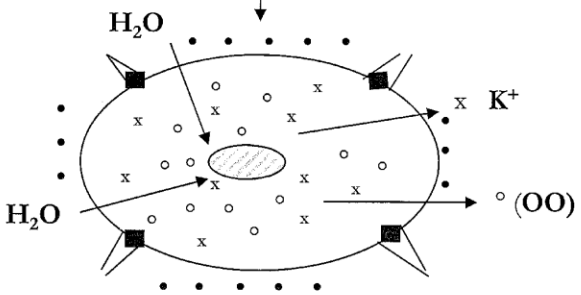
x K^+

° OO (organic osmolytes: *Myo*-inositol, taurine,…)

I

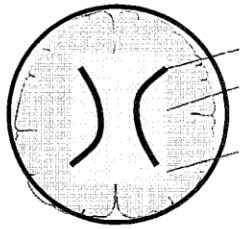


Acute 20% dilution



Brain volume expansion (skull tolerate 8-10%)
Nausea, emesis, headaches, coma, seizure
Risk of brain herniation, respiratory arrest and non cardiogenic pulmonary oedema (hypoxemia)

II

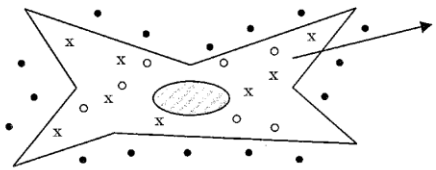


Ventricular collapse

SNa 118 mEq/L

48hr

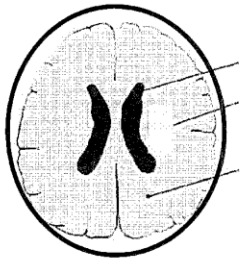
SNa 118 mEq/L



- Na
- x K^+
- ° OO (*Myo*-inositol, taurine,…)

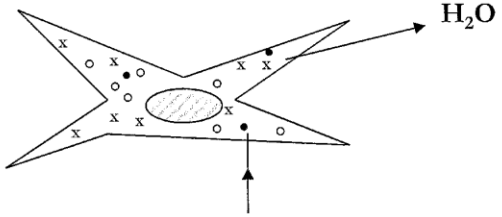
Brain adaptation (24-48hr) by intracellular solute depletion
Paucisymptomatic

I



Rapid correction of SNa

SNa 140 mEq/L



Intracellular hyperionisation and OO depletion (5-7 days to reaccumulate)
Apoptose of the astrocytes
→ ODS (or CPM)
(Urea protect the cell from apoptosis)

ACUTE (< 48 hr) (usually < 125 mEq/l)

Generally hospital acquired

- Post operative
- Excessive IV hypotonic fluids with inappropriate antidiuresis
- Post-TURP syndrome (Uterine surgery with glycine irrigant, …)
- Oxytocine
- Recent thiazides prescription
- Polydypsia (acquired generally outside the hospital) (beer potomania)
- Exercise induced (acquired outside the hospital)
- Ecstasy
- Colonoscopy preparation (PEG plus excessive water intake)
- Desmopressin therapy for nocturnal enuresis

↓

GENERALLY SYMPTOMATIC

Severe symptoms sometimes explosive in nature (coma, seizure)

↓

PROMPT CORRECTION MANDATORY

- Hypertonic saline (NaCl 3%) ± furosemide (20-40 mg)
  Rate of IV infusion: 1-2 ml/kg b.w./hr (increases the SNa by 1-2 mEq/l/hr and 2-4 mEq/l/hr if combined with furosemide)

OR

- Bolus infusion of 150 ml of 3% NaCl repeat 10 min later if no improvement
- TARGET: interrupt correction when symptoms disappear
  (rapid normalisation of the serum sodium usually safe but rarely necessary). Check SNa after 30 min, to be sure that SNa is increasing (then each 2-4hr)

CHRONIC (> 48hr), subacute or unknown duration

Acquired outside the hospital

- Edema states
- SIADH
- Diuretics
- Digestive losses, excessive sweating, third space
- Salt losing nephropathy
- Cerebral salt wasting syndrome
- Polydypsia (often acute surimposed upon chronic hyponatremia)
- Endocrine (hypocorticism and hypoaldosteronism, hypothyroidism)

SYMPTOMATIC | **ASYMPTOMATIC**

SYMPTOMATIC	ASYMPTOMATIC
INITIAL RAPID BUT LIMITEDCORRECTION	**NO NEED FOR RAPID CORRECTION**
- Obviously, electrolyte-free water intake must be withheld - NaCl 3% by controlled IV infusion Rate of infusion 1-2 ml/kg b.w./hr during 4-5hr OR - 1 L NaCl 0.9%/12hr with urea (IV or by gastric tube) 0.5 to 1 g/kg b.w. in one or two doses during the first 24hr (except if volume depletion) - TARGET: interrupt correction if symptoms improvement and/or - ΔSNa > 10 mEq/1/24hr	- Conservative measures: . Withdrawal of causative factors(drugs, ...) . Water restriction (SIADH, Edema states) . Oral urea 0.5 gr/kg/24hr in one or two doses (SIADH) . Furosemide with salt supplements (SIADH) . Isotonic saline if salt depletion . Captopril + Furosemide (heart failure) . Dialysis (renal failure, cirrhosis) . Hormonal substitution . Fluorohydrocortisone (cerebral salt wasting syndrome) . V2 antagonist (Conivaptan; Tolvaptan)

Case 1

♂ 74 y.o.

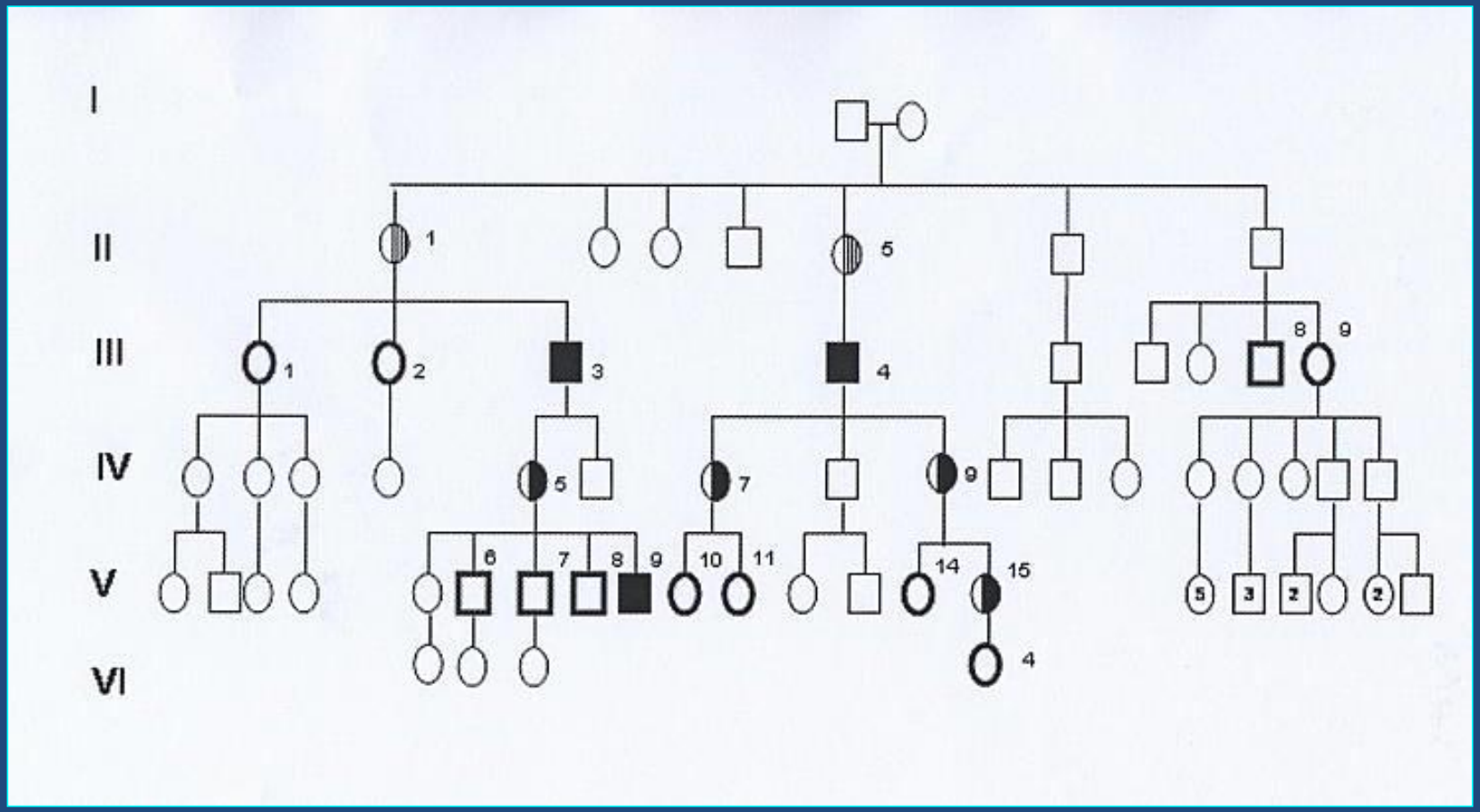
- Chronic SIADH at least since 1991

  Treatment by urea since 5 year (30 g/d)

- Treatment by Tolvaptan and later by Satavaptan without success

  ⇒ Diagnosis? (his grand-son presents also chronic hyponatremia)

- **Mutation analysis revealed changing arginine to cysteine at codon 137 (R137C) in the AVPR2 gene in 7 members of his family**
- **This mutation converts constitutive activity to the receptor** ***(N. Engl. J. Med 2005; 352: 1884-1890)*** **(the opposite: nephrogenic diabetes insipidus)**
- **X-linked (« dominant » in man and woman are expected to be asymtomatic)**


I
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Type of SIADH

S38 The American Journal of Medicine, Vol 119 (7A), July 2006

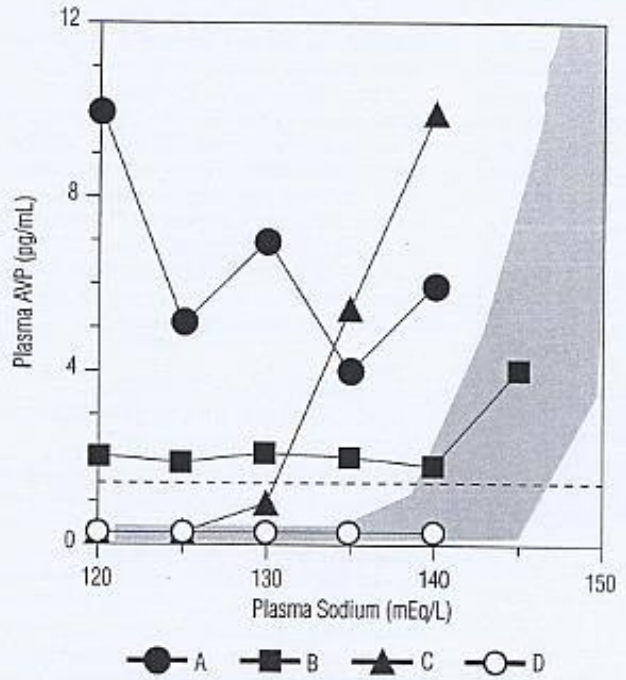


Figure 1 Osmoregulation of plasma arginine vasopressin (AVP) in patients with the syndrome of inappropriate antidiuresis is depicted for types A, B, C, and D. 1 mEq/L = 1 mmol/L.

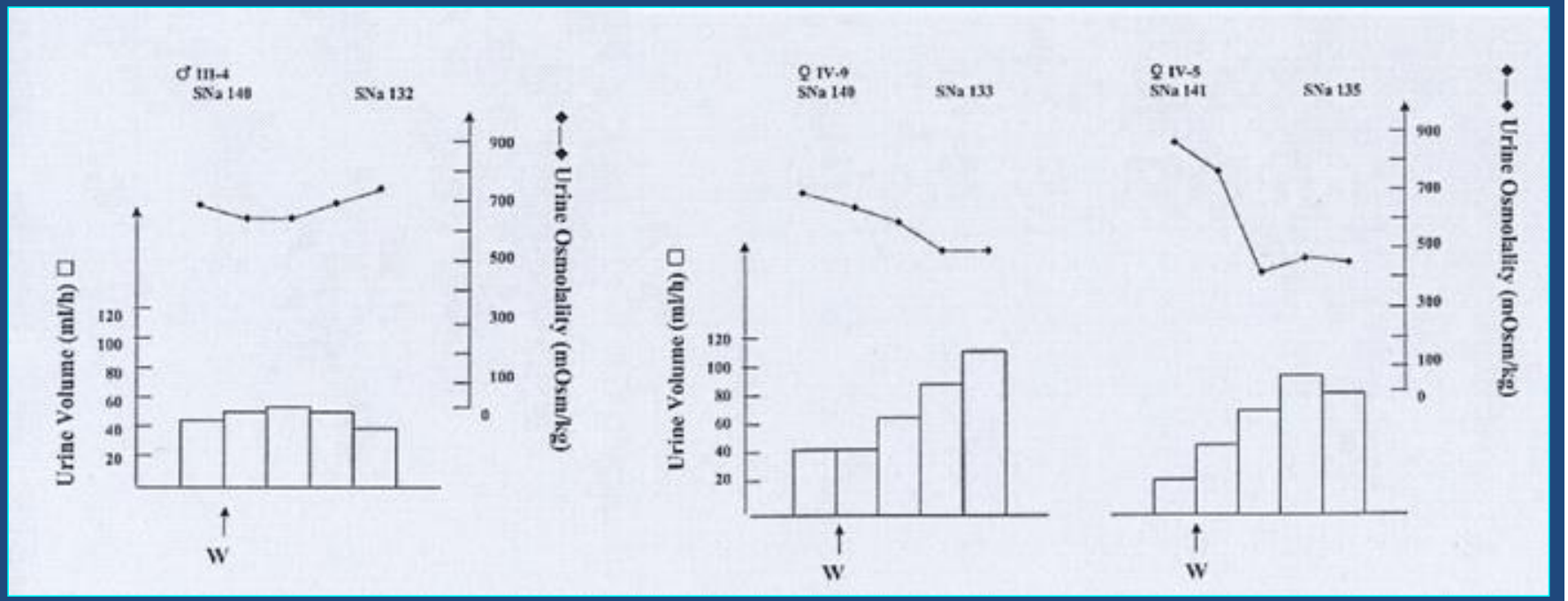
- **NSIAD are best treated by urea if water restriction ineffective**

Table: Effect of urea in hypothetical case of inappropriate secretion of antidiuretic hormone compared with normal person receiving same intake of food and fluid (Food intake shown as amount of solute of excretion in urine)

	Daily intake	Urinary composition	Urine volume (L/day)	Water balance (L/day)
Normal	500 mmol solute; 2 L Water*	250 mmol/L	2	0
Inappropriate secretion of hormone	500 mmol solute; 2 L Water*	500 mmol/L	1	+ 1
Inappropriate secretion of hormone treated with 30 g urea daily	500 mmol solute; 500 mmol urea; 2 L Water	500 mmol/L	2	0

*Intake minus insensible loss. Conversion: SI to traditional units – Intake and urinary composition: 1 mmol = 1 mOsmol

Decaux G. et al. Br Med J 1981;283:1081-3



Decaux et al. JASN, 2007

Case 2 (*Neurology 2001*)

Hôpital Erasme | ULB

M 76 yr

- For days:
. General malaise
. Lethargic
. Desorientation

- On admission:
. SNa^+ 106 mEq/l K^+ 3.6 mEq/l
. Brain CT Scan
Large mass (pituitary tumor)
Corticotrop insufficiency?

*** Treatment**

- Hormone replacement
  - Hydrocortisone 20 mg/day
  - Thyroxin 50 mg/day
- Correction of hyponatremia
  - IV Saline 0.9L/ (aim Δ 12 mEq/l/24hr)

*** Evolution**

	Serum Na			Symptoms
SNa+	(0)	106 mEq/l		
	(12hr)	111 mEq/l		
	(24hr)	118 mEq/l	Δ 12 mEq/l/24hr	Improvement Consciousness
	(48hr)	129 mEq/l	Δ 11 mEq/l/24hr	Full oriented

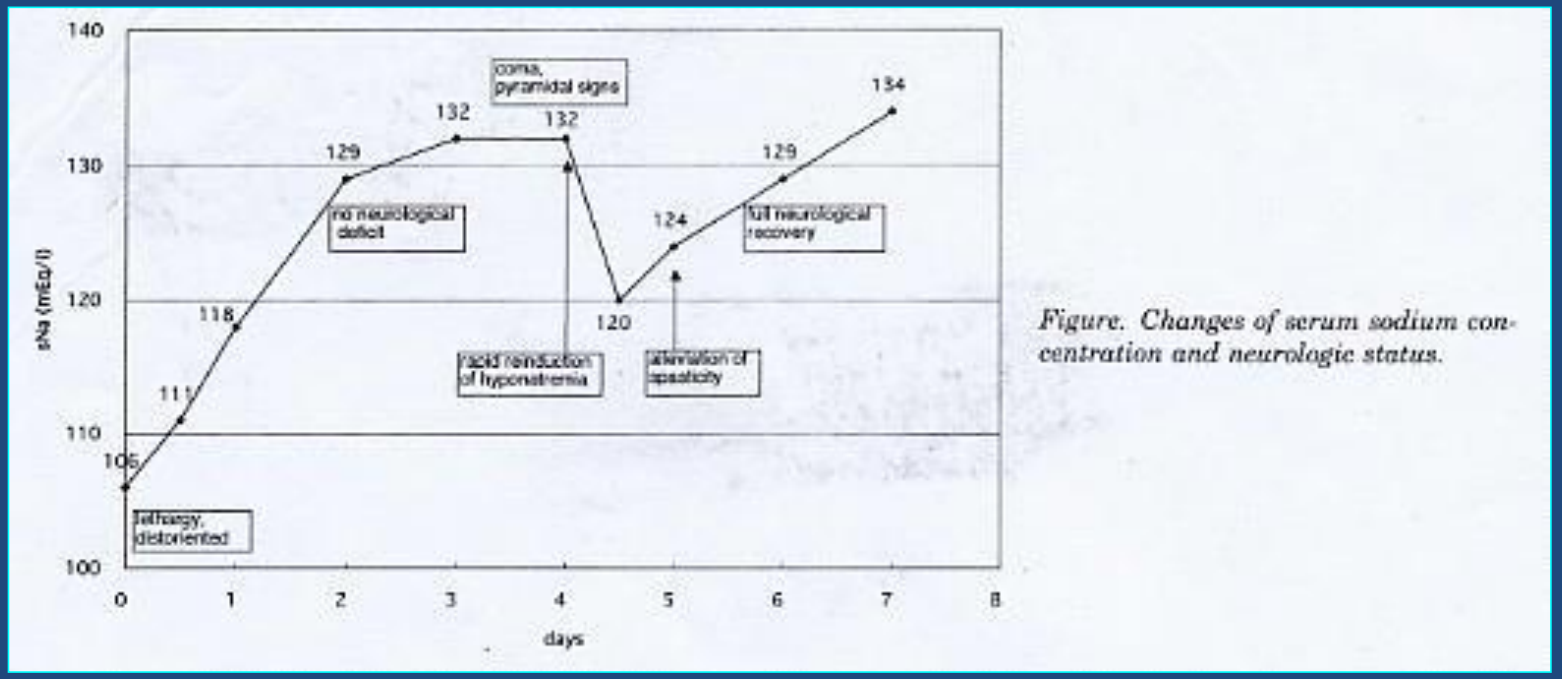


Figure. Changes of serum sodium concentration and neurologic status.

Oya et al. Neurology 2001

TABLE: RISK FACTORS FOR MYELINOLYSIS

- **Major risk factors: daily magnitude of the SNa increase (ΔSNa/24hr < 10-15 mEq/l)**
- **Hypokaliemia (ΔSNa/24hr < 10 mEq/l/24hr)**
- **Alcoholism, malnutrition, cirrhosis… (ΔSNa < 10 mEq/l)**
- **(most cases of myelinolysis: initial SNa < 115 mEq/l and ΔSNa > 12 mEq/l/24hr)**
- **Isolated cases occurred after ΔSNa of only 9 to 10 mEq/l**

Case 3

Hôpital Erasme

ULB

R.J. 28 y.o. woman (1998)

- Symptoms: headaches, nausea since a few days
- No medications, no smoking
- Biology blood: SNa 116 mEq/l, SK 4.2 mEq/l, SCl 85 mEq/l, SCO_2T 25 mmol/l, Glucose 105 mg/dl, Urea 20 mg/dl, uric acid 3 mg/dl, creatinin 0.9 mg/dl, Cortisol N, Thyroid N
- Urine: UOsmololaty 720 mOsm/kg H_2O, UNA 80 mEq/l

Case 3

Hôpital Erasme

ULB

R.J. 28 y.o. woman (1998)

- Brain RMN: normal
- Chest CT: normal
- Abdominal echography: normal

Diagnostic?

Idiopathic SIADH (?)

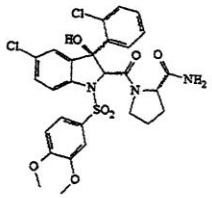
Inefficacity of water restriction

Treated 4 years with urea (30 g/day after the meal) and a water intake of about 1.5-2 l/day (body weight monitoring)

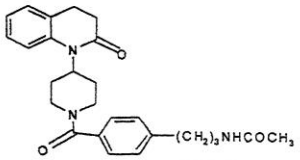
<u>Pregnancy in 2002</u>: SNa high normal value without urea! (urea was stopped after the first trimester
Relapse of hyponatremia after delivery

Treated with Tolvaptan (NO NSIAD) during one year

V1a-receptor antagonists

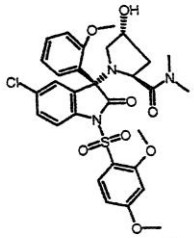


Relcovaptan (SR49059)

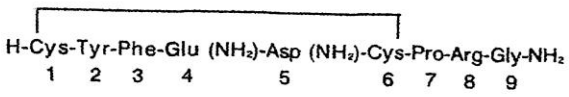


OPC 21268

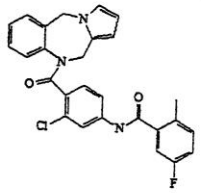
V1b receptor antagonists



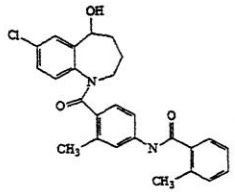
SSR149415



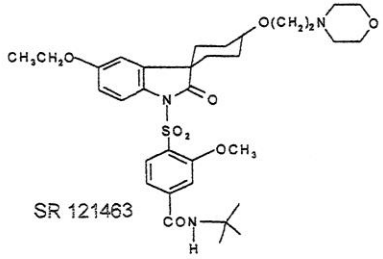
V2-receptor antagonists



Lixivaptan (VPA-985)

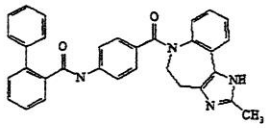


Tolvaptan (OPC-41061)

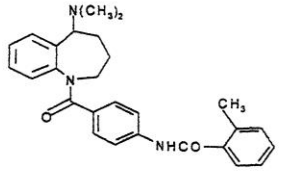


SR 121463

Non-selective V1/V2-receptor antagonists



Conivaptan (YM087)



OPC 31260

G. Decaux, A. Soupart, G. Vassart. Lancet 2008, in press

Sinusitis

Sinus CT:

Figure 1: CT scan of the sinus showing a para-ethmoidal mass (arrow)

Olfactory neuroblastoma

- **Surgery/radiotherapy**
- **Normal water load test (Fig.)**
- **Free water intake without therapy**

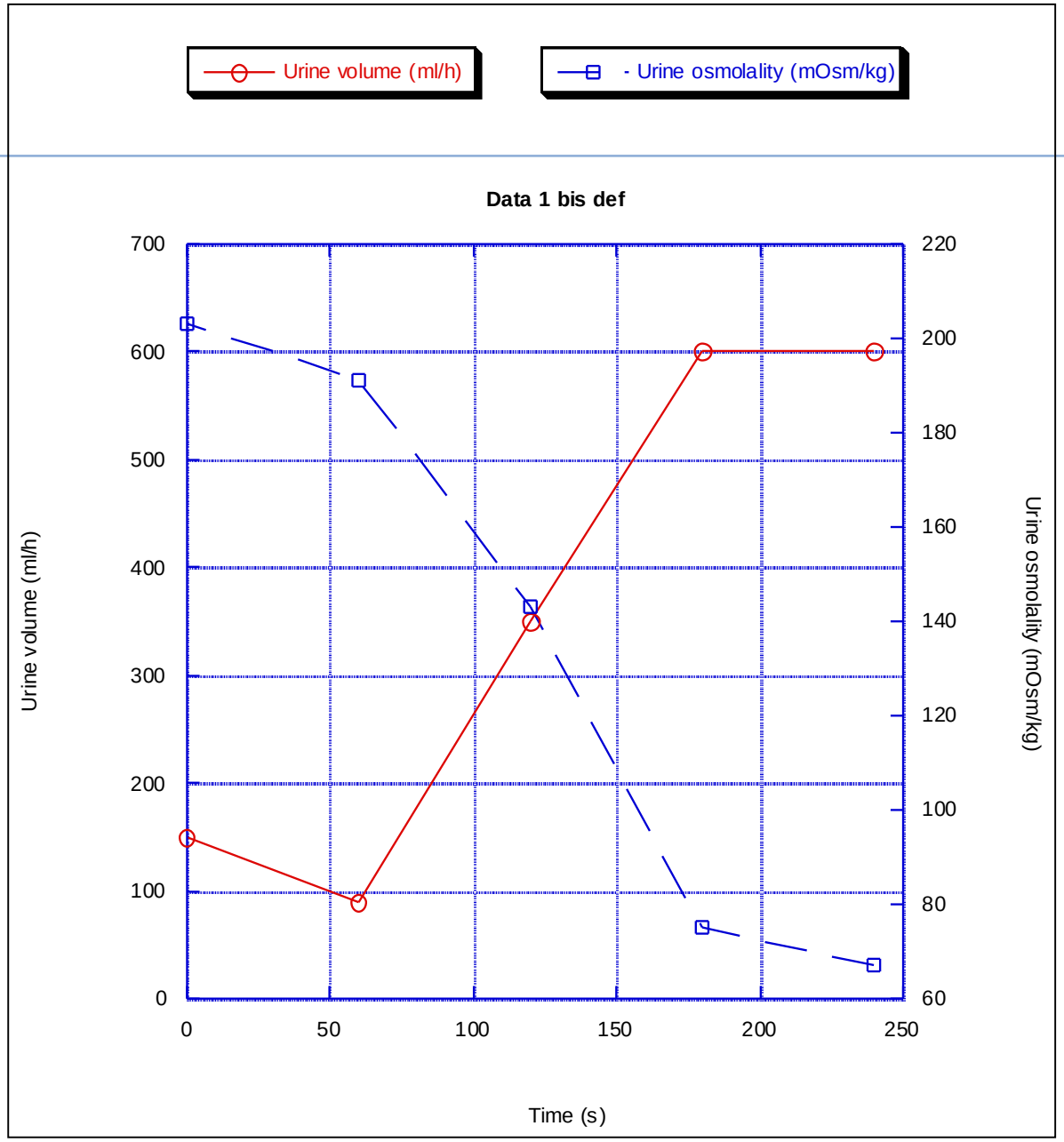


Figure: Normal acute water load test in our patient one month after the resection of her olfactory neuroblastoma. Serum Sodium during all the test remained strictly normal (between 137 and 144 mEq/L.)

Comments

- **Caution with a diagnosis of idiopathic SIADH in young people…**
- **Normal pregnancy is associated with reduced plasma Na concentration (Δ 5mEq/l) ("reset" of the thresholds for vasopressin release and thirst)**

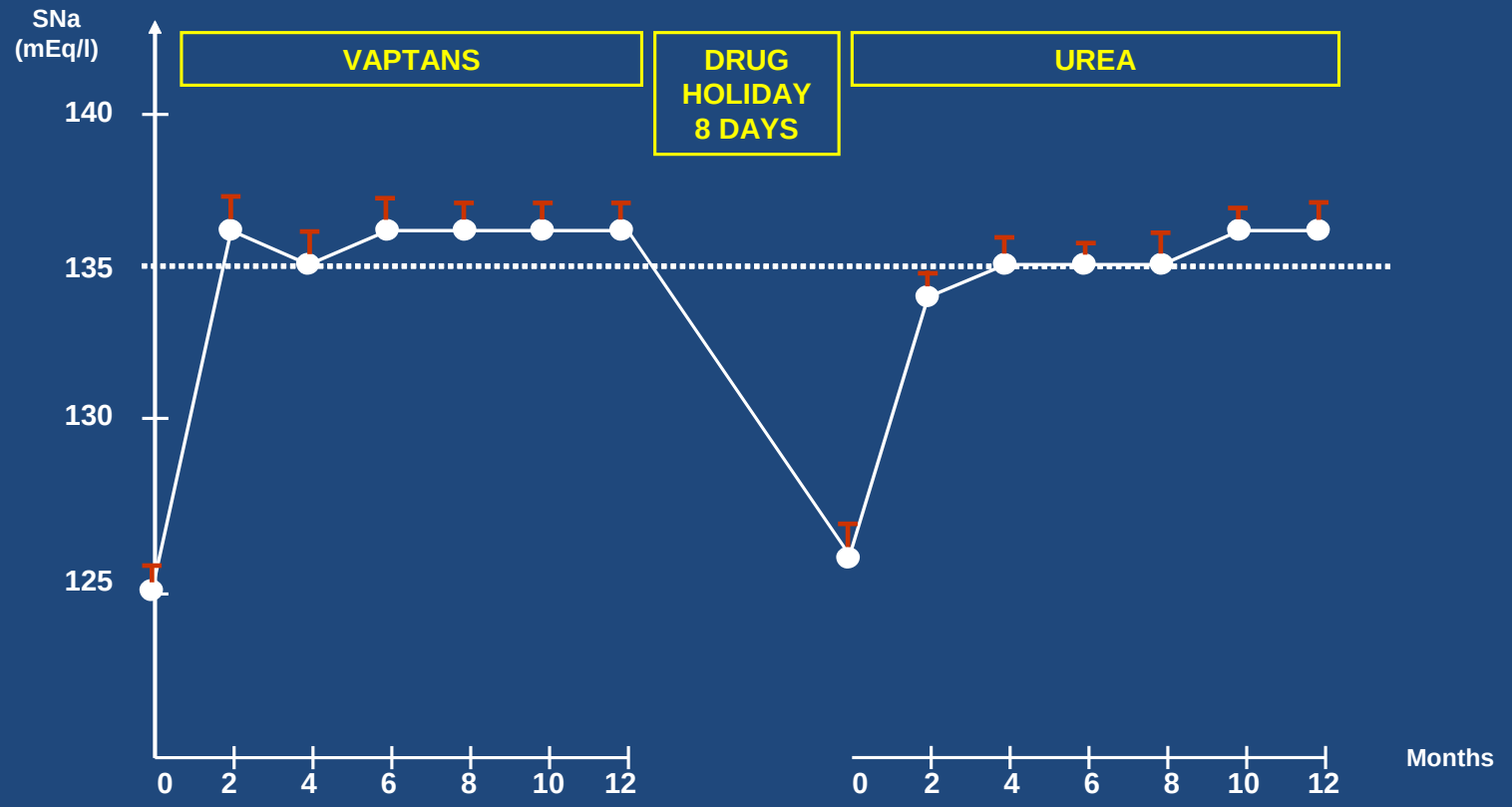


Figure 1

N = 12

Soupart A., Decaux G. CJASN, 2012 (in press)

Case 4

Hôpital Erasme ULB

A 70-year-old female patient is hospitalized because she fall on the street without obvious reasons. She lose her husband one year ago and was treated by citalopram (20 mg/day) for chronic depression.

Physical examination was normal.

Laboratory data showed the following results

SNa^+ 128 mEq/l	K^+ 4.2 mEq/l	Cl^- 98 mEq/l
TCO_2 24 mmol/l	Urea 28 mg/dl	Uric acid 4.5 mg/dl
Creatinine 0.9 mg/dl		

The patient received isotonic saline (2 l/24 hr), twenty four hours later SNa was 134 mEq/l.

Case 4

- **Was fall in this patient due to hyponatremia?**
- **The fact that SNa increased with isotonic saline reflected salt depletion and not citalopram related SIADH?**

Table 1. Traditional routine biochemical data generally allowing differentiation between appropriate and inappropriate ADH secretion

	Appropriate [hypovolemic (low ECV; low EABV)] [hypervolemic (high ECV; low EABV)]	Inappropriate [euvolemic (high ECV; high EABV)]
Plasma		
Na	Low	Low
Urea	NL-high	NL-low
Uric acid	NL-high	Low (mostly <4 mg/dL)
Anion gap	NL-high	Low
Urine		
Osmolality	High	High
Na (mEq/L)	<30*	>30***
Clearance ratios		
FENa (%)	<0.5*	>0.5***
FE urea (%)	Low-NL (<55)	NL-high
FE uric acid (%)	Low-NL (<12)**	>12-(16)****
Test infusion	Plasma Na increases usually	Plasma Na decreases only if Uosm >530 mosm/kg
2 L NaCl 0.9%/24 h	Salt retention (DFENa t24-t0 <0.5%) Water diuresis	Rapid salt excretion (DFENa t24-t0 >0.5%)

* unless salt depletion is of renal origin

** urate clearance can be increased in hyponatremia related to cerebral salt wasting or liver cirrhosis

*** if salt intake is normal

**** normal value for FE uric acid in the elderly until 16%

ECV = extracellular volume; EABV = effective arterial blood volume

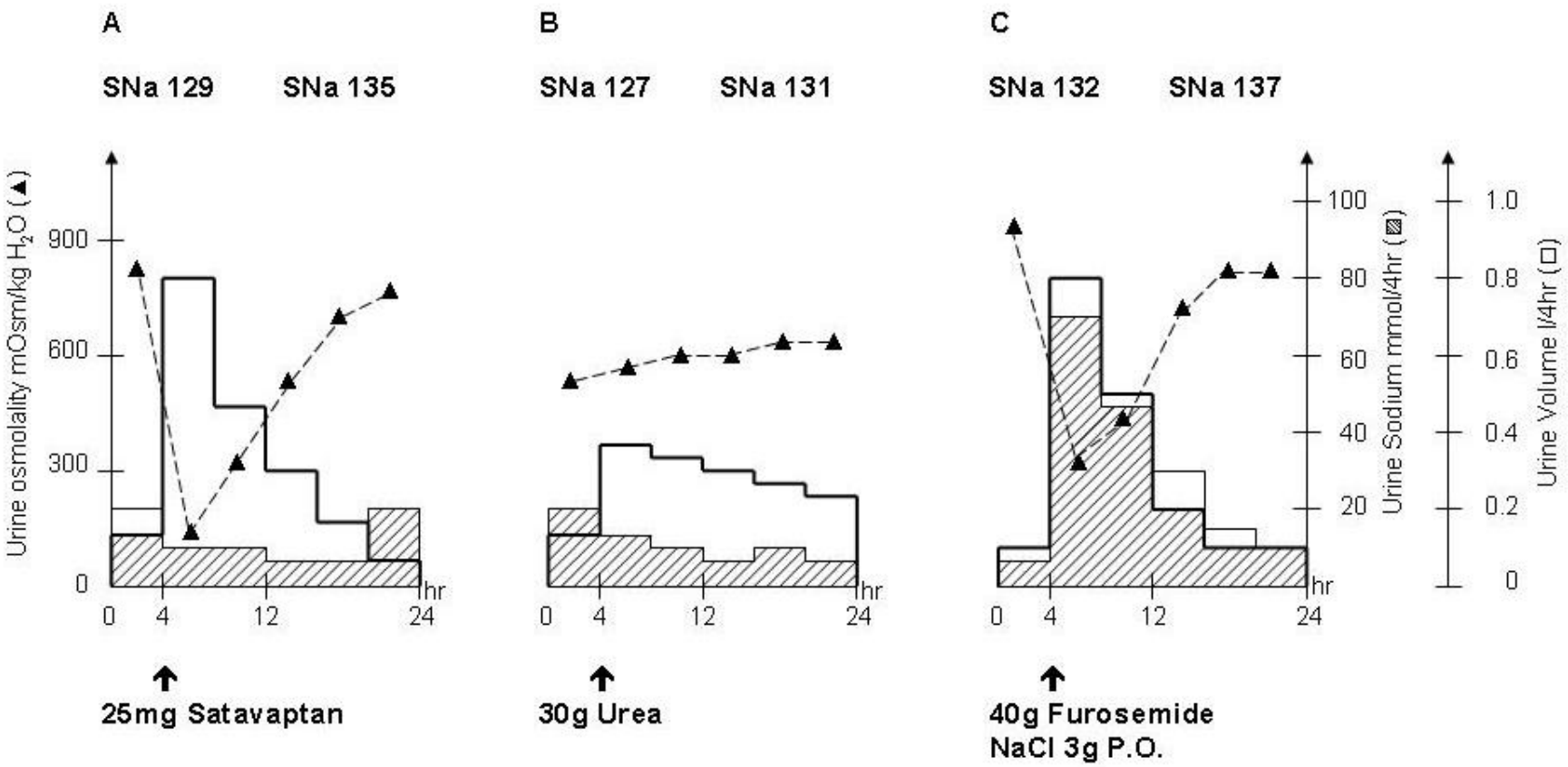
Decaux G. et al. Act Clin Bel 2000;55:68-78

Table 2 Effect of 2 l isotonic saline administration in a theoretical SIADH patient with 30 l total body water, an initial PNa of 128 mEq/l and variable levels of antidiuresis, indirectly presented as the maximal UNa+K values for the corresponding urine osmolalities

UNa+K (mEq/l)	Water excreted for 2 l isotonic saline (l)	New TBW (l)	New PNa (mEq/l)	DPNa (mEq/l)
75	2 × 154/75 = 4.11	27.89	137.7	9.7
100	2 × 154/100 = 3.08	28.92	132.8	4.8
150	2 × 154/150 = 2.05	29.95	128.2	0.2
200	2 × 154/200 = 1.54	30.46	126.1	−1.9
250	2 × 154/250 = 1.23	30.77	124.8	−3.2
300	2 × 154/300 = 1.03	30.97	124	−4

Total Body Osmoles (TBO) = Total Body Water (TBW) x 2PNa (plasma sodium). After isotonic saline, TBO remain unchanged since the administered NaCl will be excreted. New TBW = initial TBW + 21-water excreted for 2 l isotonic saline. New PNa = TBO/2 New TBW.

Musch W. et al. Q J Med 1998;91(11):749-53


A
SNa 129
SNa 135
B
SNa 127
SNa 131
C
SNa 132
SNa 137
Urine osmolality mOsm/kg H_2O (▲)
900
600
300
0
0
4
12
24
hr
100
80
60
40
20
Urine Sodium mmol/4hr (▨)
1.0
0.8
0.6
0.4
0.2
0
Urine Volume l/4hr (□)
25mg Satavaptan
30g Urea
40g Furosemide
NaCl 3g P.O.

Falls and hypoNa in the emergency department

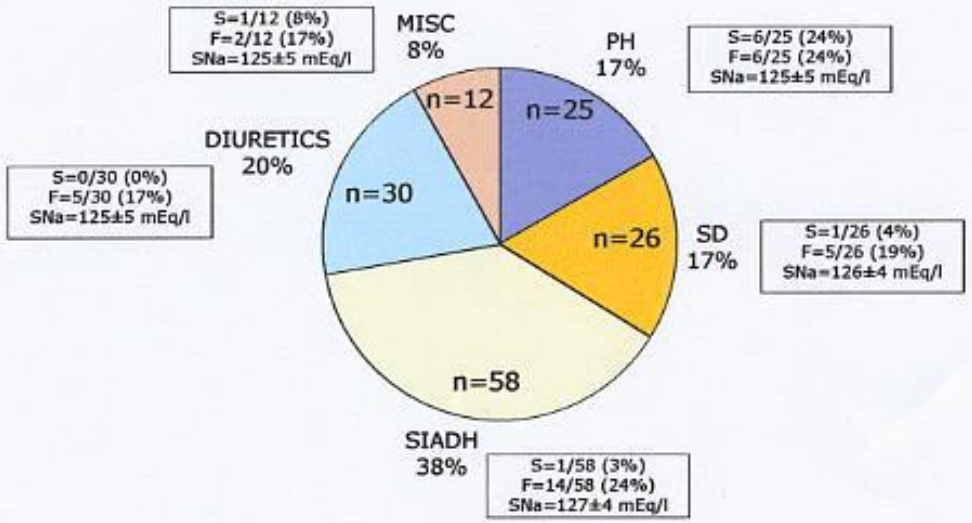
Hôpital Erasme | ULB

- **122** consecutive patients admitted with hypoNa at the emergency room of hopital Bracops (Na 126 +/- 5)
  - *21%* admitted for fall
- **244** consecutive patients matched for sex and age with normal Na (control group)
  - *5%* admitted for fall

Incidence of falls significatively higher among patients in hypoNa (OR 67 / p<0.001)

Renneboog & al. Am J Med 2006, 71

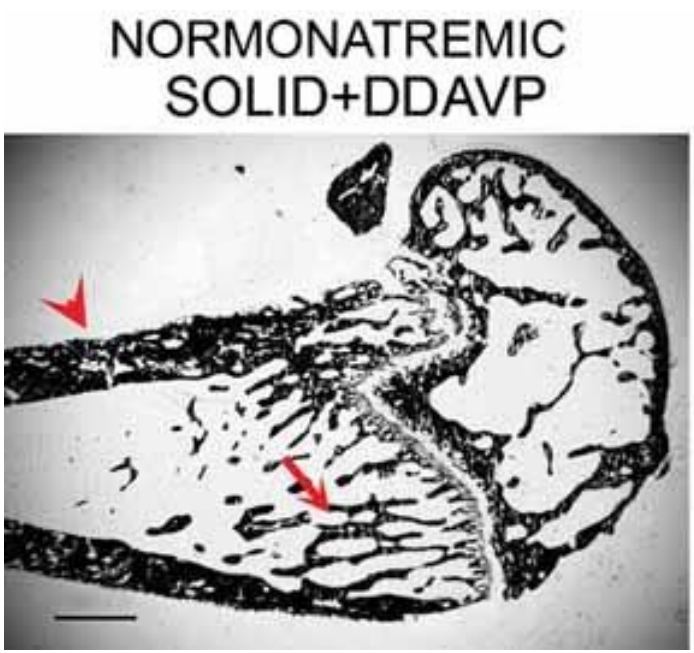
Figure 1: Causes of hyponatremia, number of falls and seizures in151 consecutive patients without edema or ascites hospitalized via the emergency room.



n refers to the number of patients; PH refers to polydypsia induced hyponatremia;
SD refers to salt depletion; SIADH refers to the syndrome of inappropriate secretion of the antidiuretic hormone;
MISC refers to miscellaneous causes of hyponatremia.
S refers to seizure; F refers to fall; SNa refers to mean serum sodium of the subgroup on admission.

Renneboog B., Musch W. et al. Am J Med 2006

- HYPONATREMIA-INDUCED OSTEOPOROSIS
  - *Verbalis et al. J Bone Miner Res 2010 (rats SNa 110, 3 months - 30%)*
  - *Hoorn EJ et al. J Bone Miner Res 2011 (Rotterdam study, 5208)*



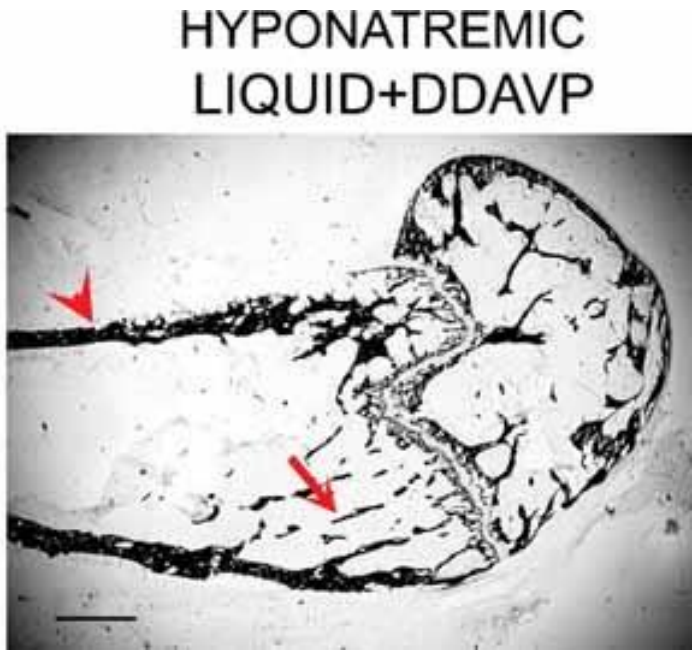
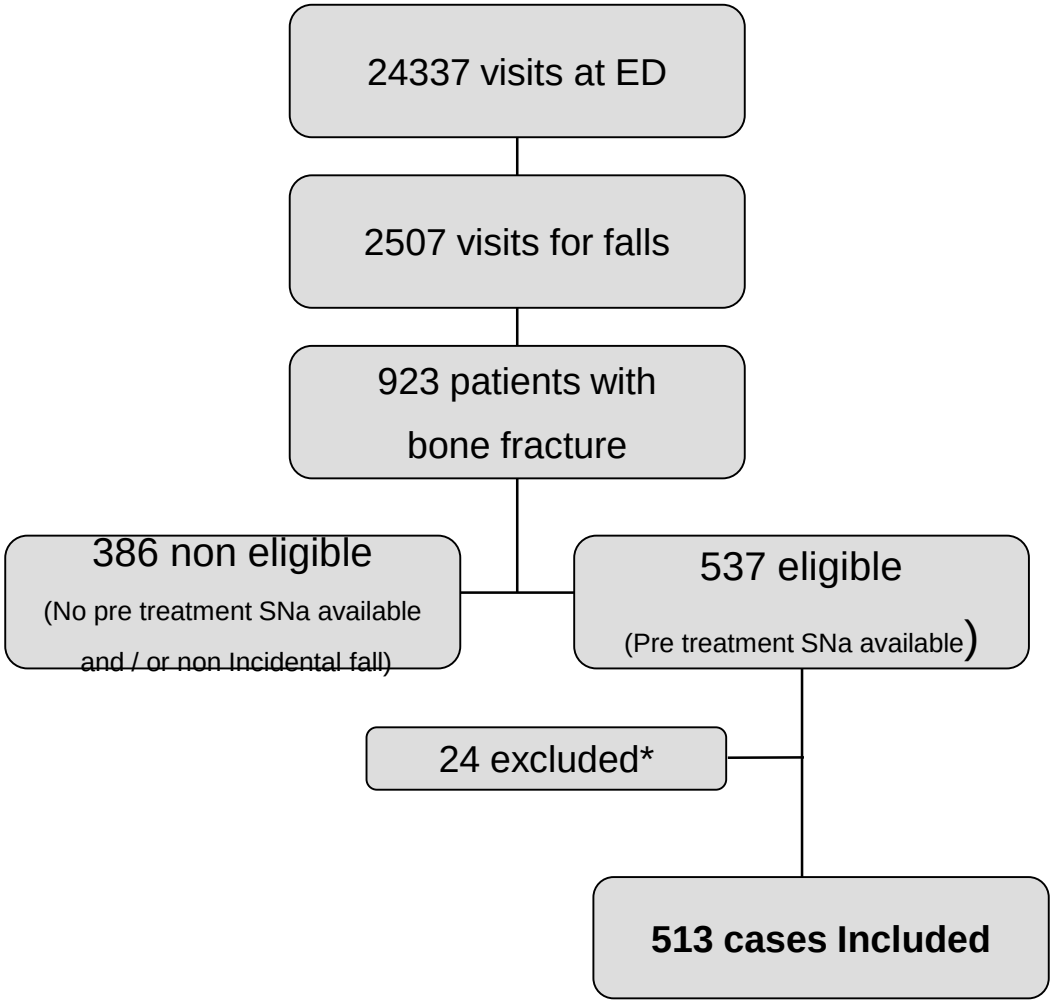


Fig 1: Selection of patients included in the study (all patients are 65 yo or older)



Gankam Kengne F. et al. Q J Med. 2008; 101 (7): 583-588

Table 3: Prevalence of hyponatremia in patients and controls (matched for age and sex) and odds ratios for bone fracture associated with hyponatremia

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	Patients (%) n = 513	Controls (%) n = 522	Unadjusted OR (CI)	Adjusted OR (CI)
Hyponatremia Mean Na = 131	67 (13.06)	20 (3.90)	3.47 (2.09 – 5.79)*	4.16 (2.24 - 7.71)*

OR: Odds ratio. CI: 95% confidence interval; * P < 0.001

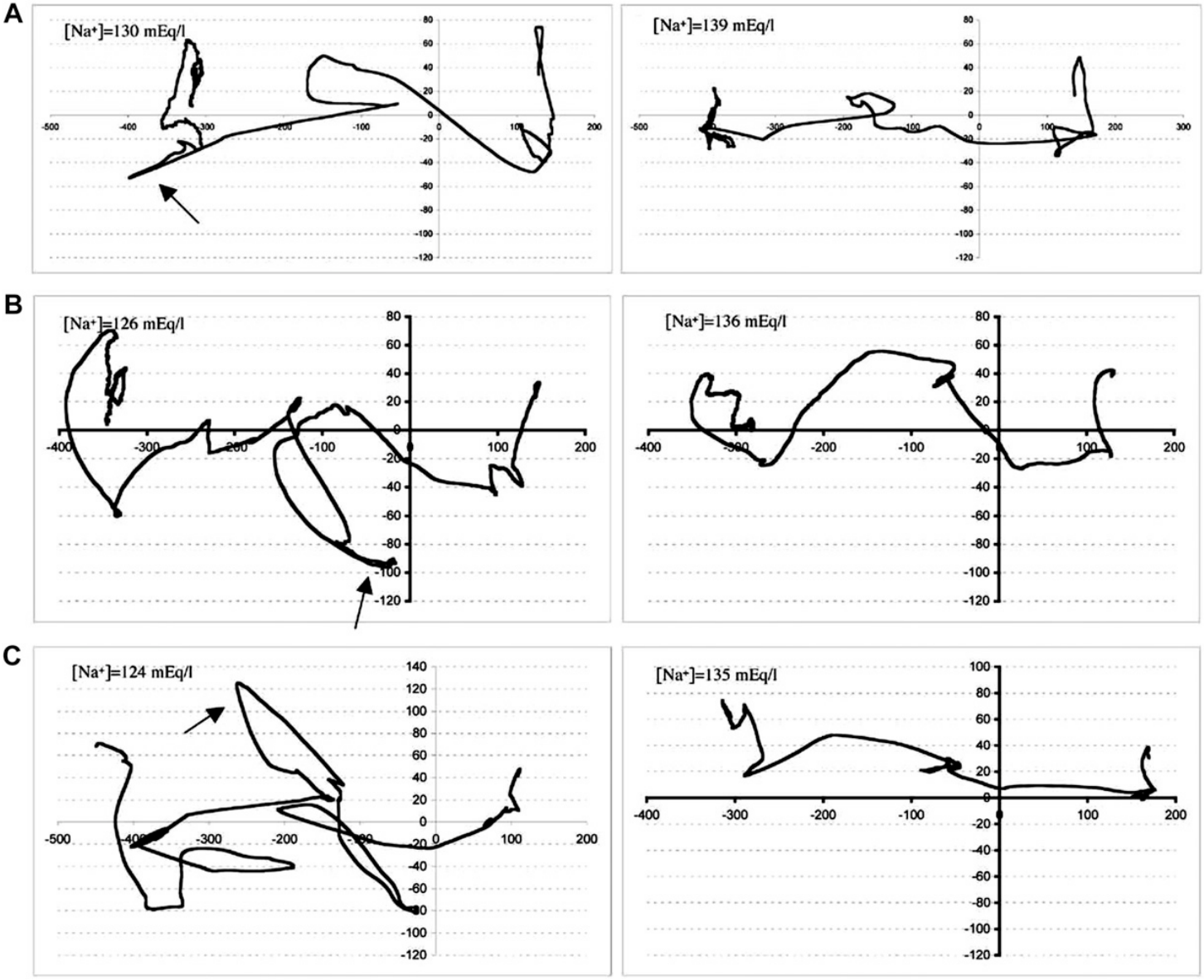

Figure 1. | Mild chronic hyponatremia is associated with gait disturbances. The recorded projection of the center of gravity over a pressure- sensitive calibrated platform or total traveled way (TTW) in three patients (A–C) after a 10-second tandem walk from right to left with eyes opened is shown. The left panel shows the TTW during mild chronic hyponatremia, and the right panel shows the TTW after correction of hyponatremia. Irregular paths of the center of pressure were observed in the hyponatremia condition (arrows). Reprinted from reference 18, with permission.

Table 2. Evolution of electrophysiological variables before and after correction of profound hyponatremia

		N	Normal values mean ± SD (LN)	Before correction mean ± SD	After correction mean ± SD	Variation in percentage	p-value
Motor NCV (m/sec)	Right peroneal	7	48.3 ± 3.9 (40)	35.9 ± 6.7	38.5 ± 6.6	+7.2 %	0.005
	Left peroneal	5		35.0 ± 2.5	40.0 ± 1.2	+14.3 %	0.028
	Right tibial	7	48.5 ± 3.6 (41)	36.5 ± 5.9	40.3 ± 4.5	+10.4 %	0.033
	Left tibial	5		33.2 ± 2.8	37.7 ± 3.8	+13.5 %	0.002
	Right median	4	57.7 ± 4.9 (48)	48.5 ± 3.1	53.2 ± 2.4	+ 9.7 %	0.046
	Left Median	6		47.6 ± 4.1	47.3 ± 2.6	-0.6 %	0.887
Sensory NCV (m/sec)	Left radial	6	58 ± 6 (48)	40.4 ± 3.9	44.8 ± 2.9	+10.9 %	0.013
F-wave latencies (ms)	Right peroneal	6	48.4 ± 4 (56)	56.0 ± 10.1	51.1 ± 9.1	- 8.8 %	0.008
	Left peroneal	4		63.3 ± 5.8	49.6 ± 16.4	-21.6 %	0.006
	Right tibial	6	47.7 ± 5 (58)	57.9 ± 7.4	54.0 ± 9.8	-7.2 %	0.09
	Left tibial	5		64.2 ± 7.1	59.1 ± 6.9	-8.0 %	0.018
	Left median	7	26.6 ± 2.2 (31)	31.2 ± 5.1	27.9 ± 3.8	- 10.6 %	0.041

Legend LN : limit of normal corresponding for NCV to lower LN and for F-wave latency to upper LNLN normal values see reference (13)

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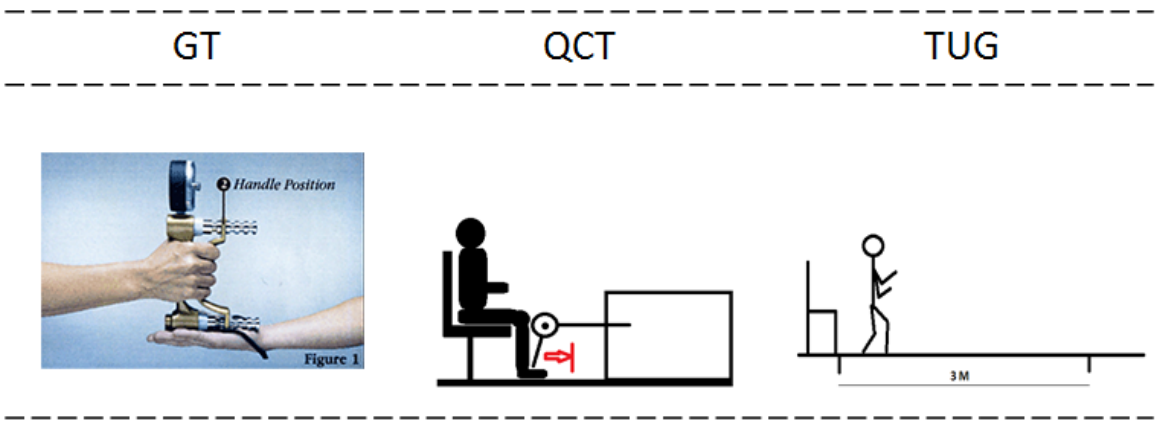
Figure 1. Representation of tests evaluating muscular strength



GT: Grip test; QCT: Quadriceps contraction test; TUG: Timed Up and Go test

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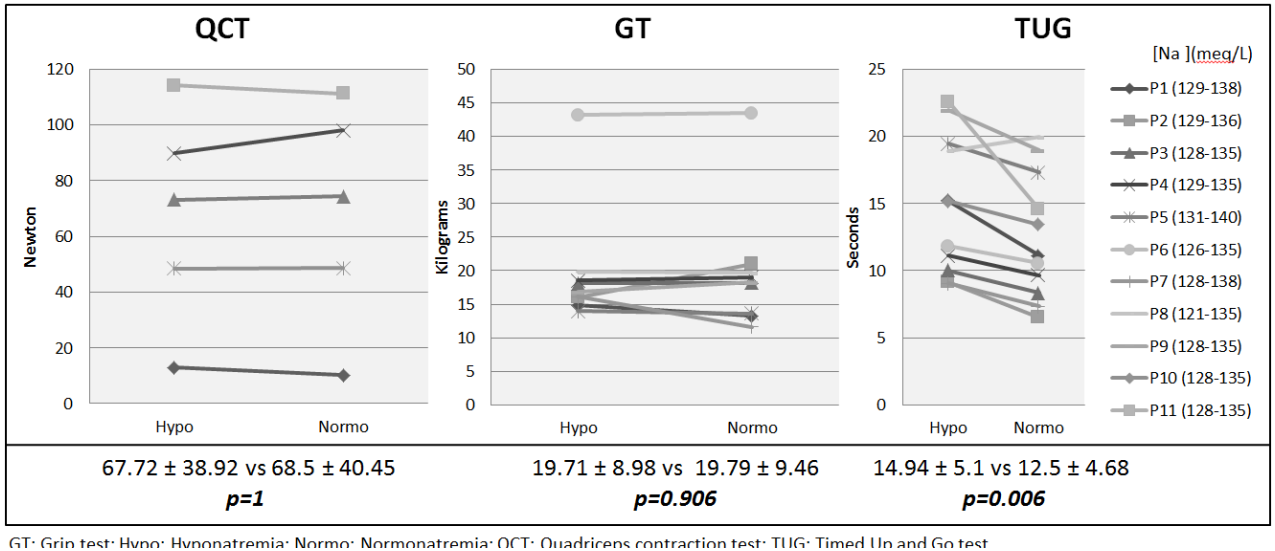
Figure 2. Evolution of quadriceps contraction test, grip test, timed up-and go test



GT: Grip test; Hypo: Hyponatremia; Normo: Normonatremia; QCT: Quadriceps contraction test; TUG: Timed Up and Go test

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Chronic **Hyponatremia** Causes Neurologic and Psychologic Impairments

Fujisawa H, Sugimura Y, Takagi H, Mizoguchi H, Takeuchi H, Izumida H, Nakashima K, Ochiai H, Takeuchi S, Kiyota A, Fukumoto K, Iwama S, Takagishi Y, Hayashi Y, Arima H, Komatsu Y, Murata Y, Oiso Y.

J Am Soc Nephrol. 2015 Sep 16. pii: ASN.2014121196