Società Medico Chirurgica di Ferrara

dal 1846

LA GESTIONE CLINICA DEL PAZIENTE CON IPONATREMIA

Sabato, 17 ottobre 2015
Aula Magna Nuovo Arcispedale S.Anna
Cona, Ferrara

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

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Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

SIADH

Syndrome of inappropriate secretion of antidiuretic hormone

Described by Bartter & Schwartz in 1957

SIAD

Syndrome of inappropriate antidiuresis

1/3 of all cases of hyponatremia

the most common cause of euvolemic hyponatremia

Bartter FC, Schwartz WB. Am J Med 1967
Ellison et al, New Engl J Med 2007;356: 2064
Peri A JCEM, 2013;98:1321

Causes of the syndrome of inappropriate antidiuresis

Malignant diseases	Pulmonary disorders	Disorders of the nervous system	Drugs	Other causes
Carcinoma	Infections	Infection	Vasopressin release or action stimulants	Hereditary
Lung	Bacterial pneumonia	Encephalitis	Antidepressants	Gain-of-function mutation of the vasopressin V2 receptor
Oropharynx	Viral pneumonia	Meningitis	SSRIs	Idiopathic
Gastrointestinal tract	Pulmonary abscess	Brain abscess	Tricyclic	Transient
Stomach	Tuberculosis	Rocky Mountain spotted fever	MAOI	Exercise-associated hyponatraemia
Duodenum	Aspergillosis	AIDS	Venlafaxine	General anaesthesia
Pancreas	Asthma	Malaria	Anticonvulsants	Nausea
Genitourinary tract	Cystic fibrosis	Vascular and masses	Carbamazepine	Pain
Ureter	Respiratory failure associated with positive-pressure breeding	Subdural hematoma	Oxcarbazepine	Stress
Bladder		Subarachnoid haemorrhage	Sodium valproate	
Prostate		Stroke	Lamotrigine	
Endometrium		Brain tumours	Antipsychotics	
Endocrine thymoma		Head trauma	Phenothiazides	
Lymphomas		Other	Butyrophenones	
Sarcomas		Hydrocephalus	Anticancer drugs	
Ewing's sarcoma		Cavernous sinus thrombosis	Vinca alkaloids	
Olfactory neuroblastoma		Multiple sclerosis	Platinum compounds	
		Guillain–Barré syndrome	Ifosfamide	
		Shy–Drager syndrome	Melphalan	
		Delirium tremens	Cyclophosphamide	
		Acute intermittent porphyria	Methotrexate	
			Pentostatin	
			Antidiabetic drugs	
			Chlorpropamide	
			Tolbutamine	
			Miscellaneous	
			Opiates	
			MDMA (XTC)	
			Levamisole	
			Interferon	
			NSAIDs	
			Clofibrate	
			Nicotine	
			Amiodarone	
			Proton pump inhibitors	
			MABs	
			Vasopressin analogues	
			Desmopressin	
			Oxytocin	
			Terlipressin	
			Vasopressin	

AIDS, acquired immunodeficiency syndrome; MOAI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Spasovski G Eur Jour of Endocrinol. 2014; 170: G1

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Clinical practice guideline on diagnosis and treatment of hyponatraemia

Essential criteria

- Effective serum osmolality <275 mOsm/kg
- Urine osmolality >100 mOsm/kg at some level of decreased effective osmolality
- Clinical euvolaemia
- Urine sodium concentration >30 mmol/l with normal dietary salt and water intake
- Absence of adrenal, thyroid, pituitary or renal insufficiency
- No recent use of diuretic agents

Supplemental criteria

- Serum uric acid <0.24 mmol/l (<4 mg/dl)
- Serum urea <3.6 mmol/l (<21.6 mg/dl)
- Failure to correct hyponatraemia after 0.9% saline infusion
- Fractional sodium excretion >0.5%
- Fractional urea excretion >55%
- Fractional uric acid excretion >12%
- Correction of hyponatraemia through fluid restriction

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Clinical practice guideline on diagnosis and treatment of hyponatraemia

2.3 Which parameters to use for differentiating causes of hypotonic hyponatraemia? (

We recommend interpreting urine osmolality of a spot urine sample as a first step. (1D)

If urine osmolality ≤100 mOsm/kg, we recommend accepting relative excess water intake as a cause of the hypotonic hyponatraemia. (1D)

If urine osmolality >100 mOsm/kg, we recommend interpreting the urine sodium concentration on a spot urine sample taken simultaneously with a blood sample. (1D)

If urine sodium concentration ≤30 mmol/L, we suggest accepting low effective arterial volume as a cause of the hypotonic hyponatraemia. (2D)

If urine sodium concentration >30 mmol/L, we suggest assessing extracellular fluid status and use of diuretics to further differentiate likely causes of the hyponatraemia. (2D)

We suggest against measuring vasopressin for confirming the diagnosis of SIADH. (2D)

Spasovski G Eur Jour of Endocrinol. 2014; 170: G1

Strategy for correction of SIADH

DO individualize the nature of treatment and rapidity based on:

(1) Treatment of the underlying condition

(2) The presence of neurological symptoms (indicating likely acute onset)

(3) The speed of onset of the hyponatremia

DO discontinue any drugs known to be associated with SIADH at the initiation of therapy, if possible

DO ensure that all the appropriate diagnostic laboratory testing is undertaken in a patient suspected of SIADH

<u>However, therapy can be initiated before results are available</u>

Aylwin S et al. Cur Med Res & Opin. 2015; 31:1755

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Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Advantages and Problems of Conventional Treatments for Hypotonic Euvolemic or Hypervolemic Hyponatremia

Therapy	Advantages	Problems
Fluid restriction	Inexpensive	Modest efficacy, poor compliance
Hypertonic saline	Effective	Possible overly rapid correction
Loop diuretics	Effective in correcting volume overload	Electrolyte imbalance
Demeclocycline	Generally effective	Slow onset of action, nephrotoxicity
Lithium	Sometimes effective	Inconsistent efficacy, adverse effects
Urea	Generally effective	Unpleasant taste, limited experience

Peri A JCEM, 2013;98:1321

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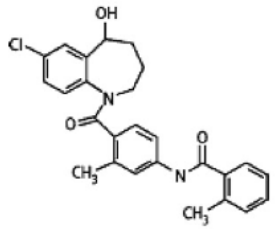
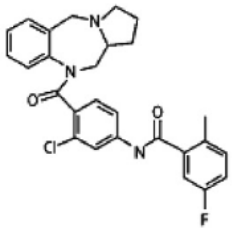
VAPTANS

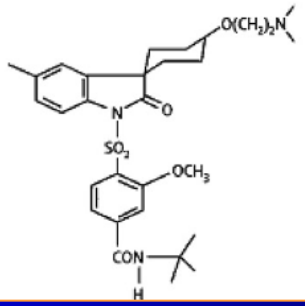
Tolvaptan



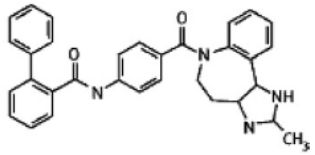
Lixivaptan



Satavaptan



Conivaptan



Pharmacological Properties of the Most Investigated Vaptans

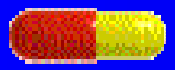
Pharmacological Properties	Tolvaptan	Lixivaptan	Satavaptan	Conivaptan
Receptor specificity	V_2	V_2	V_2	V_{1a}/V_2
Route of administration	Oral	Oral	Oral	Intravenous[a]
Elimination half-life, h	6–8	7–10	14–17	3–8
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic
Dosage, mg/d	15–60	10–400[b]	5–50[b]	20–40

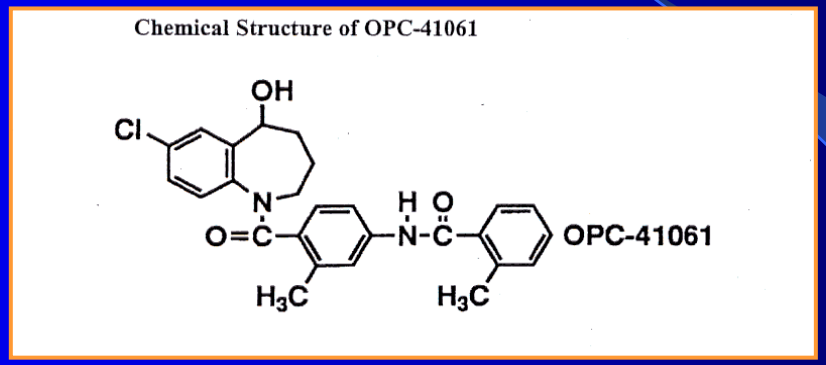
[a] An oral formulation has been evaluated in clinical studies but is not currently approved for use.

[b] Doses used in clinical trials.

Peri A JCEM, 2013;98:1321

TOLVAPTAN (OPC-41061)





antagonista non peptidico

del recettore V_2 (renale) dell'ADH

attivo per via orale

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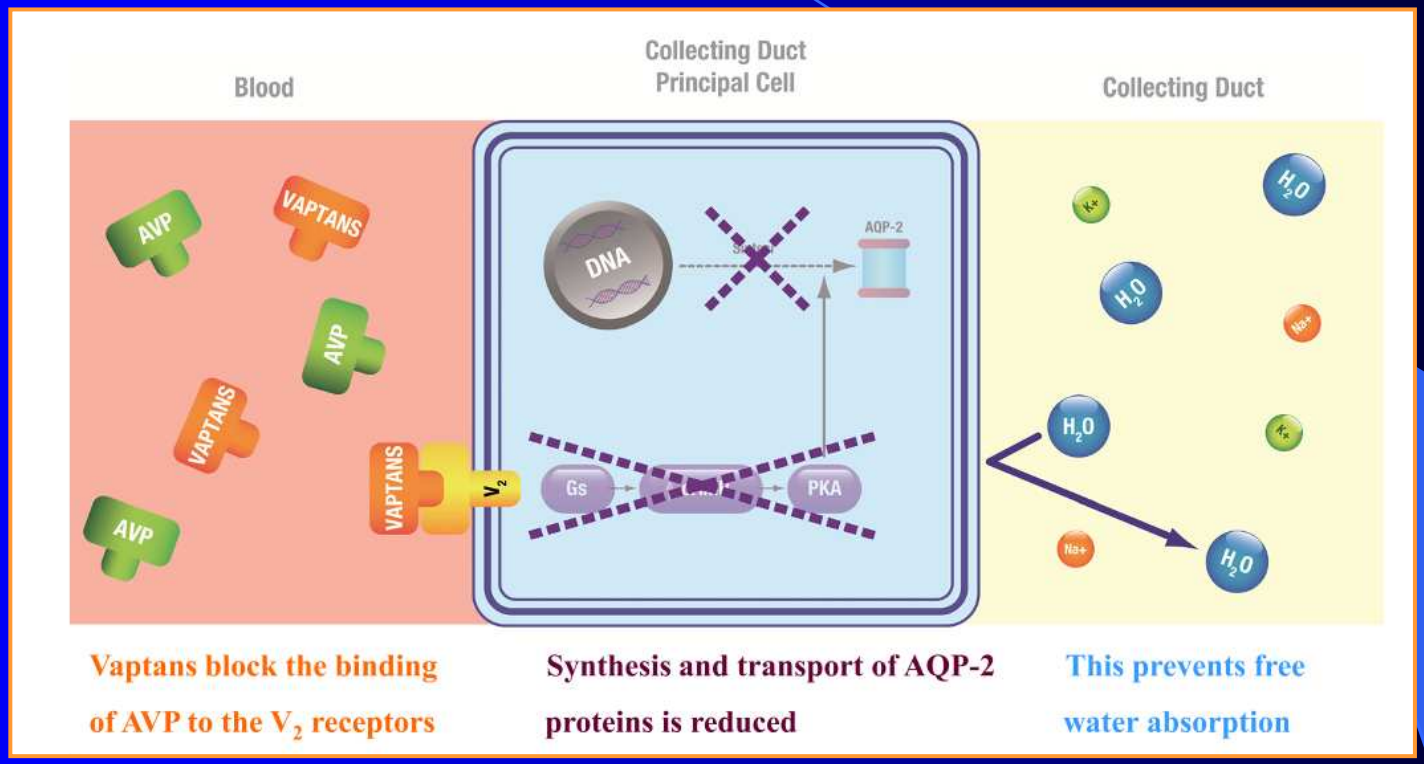
VAPTANI Meccanismo d'azione



Il legame al recettore V2 blocca l'azione dell'ADH sulla ritenzione di H2O

↓

effetto "acquaretico" (eliminazione di H2O pura e non elettoliti!)

Peri A JCEM, 2013;98:1321

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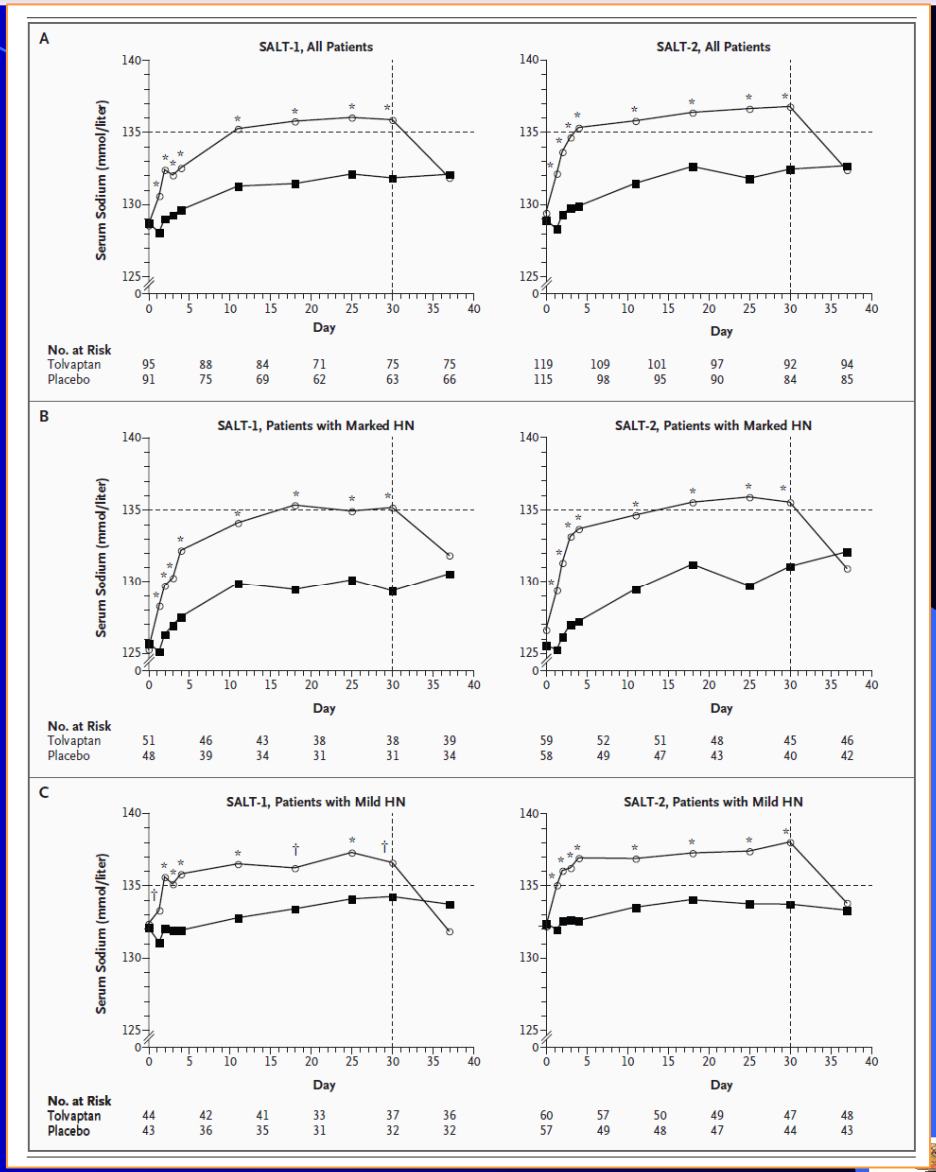
Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

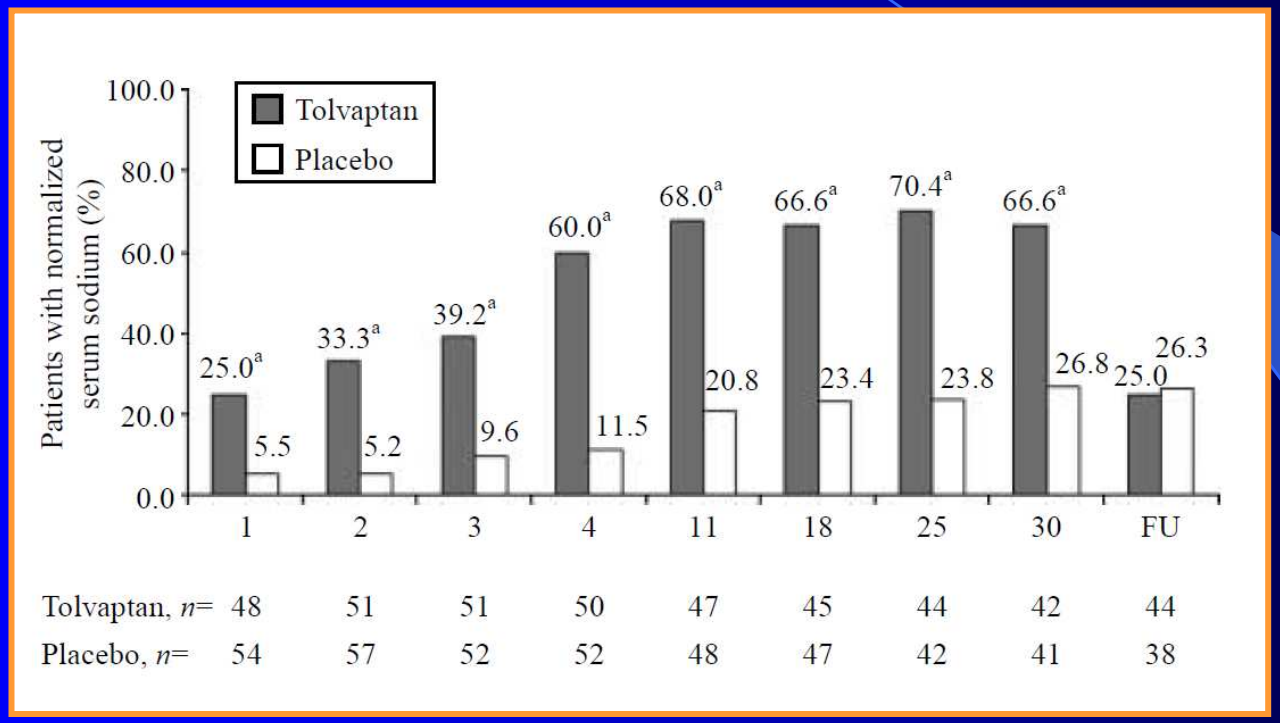
Tolvaptan, a Selective Oral Vasopressin V2-Receptor Antagonist, for Hyponatremia

In patients with euvolemic or hypervolemic, mild or marked hyponatremia, tolvaptan is effective in increasing serum sodium concentrations at day 4 and day 30



Schrier RW et al N Engl J Med 2006;355:2099

Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion



Serum NaC normalization rates in the combined SIADH subgroups of SALT-1 and SALT-2 compared with placebo at all days of measurement across the 30-day treatment period as well as 7 days after cessation of therapy (FU)
a P<0.05 compared with placebo group

Verbalis JG et al EurJour of Endocrinol.2011; 164: 725

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Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion

SF-12 General Health Survey summary scores in the combined SIADH subgroups in SALT-1 and SALT-2

	Tolvaptan mean ± S.D. (*n*)	Placebo mean ± S.D. (*n*)	*P* value
PCS score			
Baseline	34.82 ± 10.76 (49)	34.15 ± 10.06 (54)	–
Day 30	39.91 ± 10.68 (40)	34.54 ± 9.67 (41)	–
Change from baseline	3.64 ± 9.55 (39)	−0.16 ± 8.85 (41)	0.019
MCS score			
Baseline	44.90 ± 11.56 (49)	47.12 ± 10.91 (54)	–
Day 30	51.02 ± 11.81 (40)	48.47 ± 11.86 (41)	–
Change from baseline	5.47 ± 12.01 (39)	−0.45 ± 9.66 (41)	0.051

Positive changes from baseline indicate improvement

Tolvaptan therapy improved self-reported physical and mental symptoms

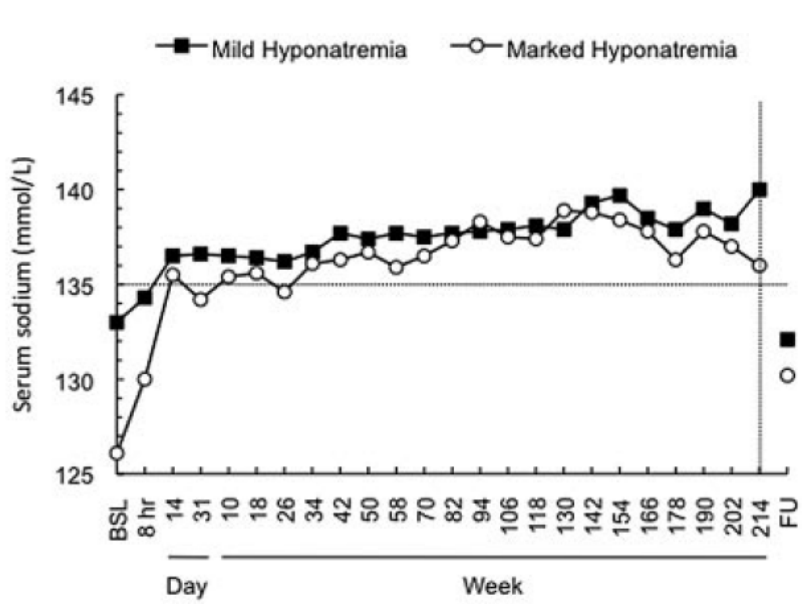
Verbalis JG et al EurJour of Endocrinol.2011; 164: 725

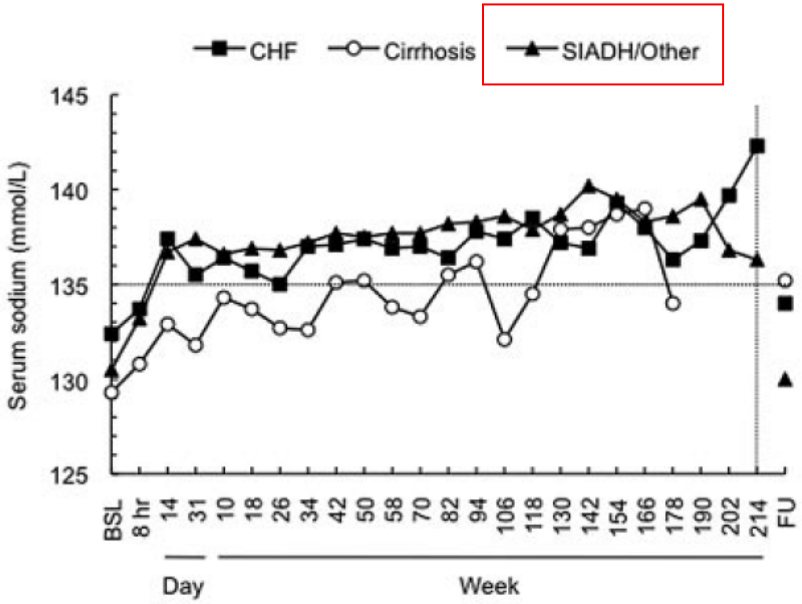
Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

SALTWATER

Oral Tolvaptan Is Safe and Effective in Chronic Hyponatremia

- 111 pts pNa<135
- Tolvaptan 15-60 mg/d
- mean FU 701 days





Berl T et al J Am Soc Nephrol 2010,21: 705

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Oral Tolvaptan Is Safe and Effective in Chronic Hyponatremia

Table 2. Investigator-assessed treatment-emergent adverse events

Parameter	Value[a]
Treated patients	111
Total exposure (patient-days)	77,369
Exposure per patient (days)	
mean	701
median	639
Total AEs (all causes; *n* [%])	105 (94.6)
Total AEs leading to discontinuation or death (all causes; *n* [%])	30 (27.0)
AEs leading to discontinuation	19 (17.1)
AEs leading to death before withdrawal	11 (9.9)
Drug-related AEs (*n* [%])	52 (46.8)
most common drug-related AEs[b]	
pollakiuria	11 (9.9)
thirst	10 (9.0)
fatigue	6 (5.4)
dry mouth	4 (3.6)
polydipsia	4 (3.6)
polyuria	4 (3.6)
hypotension	4 (3.6)
hypernatremia	4 (3.6)
dizziness	4 (3.6)
headache	4 (3.6)
peripheral edema	4 (3.6)
acute renal failure	4 (3.6)
Drug-related AEs leading to discontinuation	6 (5.4)
ventricular tachycardia	1 (0.9)
irritability	1 (0.9)
blood sodium increase	1 (0.9)
anorexia	1 (0.9)
blood creatinine increase	1 (0.9)
pruritus	1 (0.9)

Berl T et al J Am Soc Nephrol 2010,21: 705

Key points

TOLVAPTAN (SAMSCA)

is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone

Aylwin S et al. Cur Med Res & Opin. 2015; 31:1755

Key points

What is the dosing regimen for SAMSCA?

The starting dose for SAMSCA tablets is 15 mg administered once daily without regard to meals

After a minimum of 24 hours, the dose can be increased to 30 mg once daily to a maximum of 60 mg (two 30-mg tablets) once daily, as needed to achieve the desired level of serum sodium

During initiation and titration, frequent monitoring is advised for changes in serum electrolytes and volume

Concomitant use with hypertonic saline is not recommended

To avoid dehydration, patients must have water available at all times and continue ingestion of fluid in response to thirst

Key points

SAMSCA should be initiated and re-initiated only in a HOSPITAL where serum sodium can be monitored closely

Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.
In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable

Key points

SAMSCA

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Anuria
- Volume depletion
- Hypovolaemic hyponatraemia
- Hypernatraemia
- Patients who cannot perceive thirst
- Pregnancy
- Breastfeeding

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Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Key points

SAMSCA

Interaction between vaptans and other drugs

Vaptans are metabolized by cytochrome CYP3A4, and therefore caution should be exercised in case of coadministration of CYP3A4 inhibitors (eg, ketoconazole, macrolide antibiotics, diltiazem) or inducers (eg, rifampicin, barbiturates), which increase or reduce serum concentrations of vaptans, respectively

Grapefruit is a potent inhibitor of CYP3A4, and it has been demonstrated that grapefruit juice increases the bioavailability of tolvaptan (mean maximal concentration: 1.86-fold increase) Thus, patients taking these drugs should avoid ingesting grapefruit or grapefruit juice

Tolvaptan treatment did not have any effect on serum concentrations of other CYP3A4 substrates, such as warfarin or amiodarone

Serum digoxin concentrations have been found to be increased (mean maximal concentration: 1.27-fold increase) during coadministration of multiple (16 d) once daily 60-mg doses of tolvaptan Patients receiving digoxin should therefore be evaluated for excessive digoxin effects when treated with vaptans

Peri A JCEM, 2013;98:1321

Società Medico Chirurgica di Ferrara

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Key points

SAMSCA

The duration of treatment with tolvaptan,

which is currently the only V2 receptor antagonist available also for chronic use,

may vary based on several issues,

including

the etiology of hyponatremia
the chronicity of the underlying disease
the response to the drug
its tolerability
the coadministration of other drugs with lowering effects on serum Na

Etiology of SIADH	Likely duration of SIADH	Relative risk of chronic SIADH
Tumors producting vasopressin ectopically (small-cell lung carcinoma, head and neck carcinoma)	Indefinite	High
Drug-induced, with continuation of offending agent (carbamazepine, SSRI)	Duration of drug therapy	
Brain tumors	Indefinite	
Idiopathic (senile)	Indefinite	
Subarachnoid hemorrhage	1-4 weeks	
Stroke	1-2 weeks	
Inflammatory brain lesions	Dependent on response to therapy	Medium
Respiratory failure (chronic obstructive lung disease)	Dependent on response to therapy	
HIV infection	Dependent on response to therapy	
Traumatic brain injury	2-7 days to indefinite	
Drug-induced, with cessation of offending agent	Duration of drug therapy	
Pneumonia	2-5 days	
Nausea, pain, prolonged exercise	Variable depending on cause	
Post operative hyponatremia	2-3 days postoperatively	Low

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone secretion; HIV, human immunodeficiency virus.

Peri A JCEM, 2013;98:1321

Samsca (tolvaptan): Drug Warning - Potential Risk of Liver Injury

Posted 01/25/2013

FDA

Safety Announcement

[04-30-2013] FDA has determined that the drug Samsca (tolvaptan) should not be used for longer than 30 days and should not be used in patients with underlying liver disease because it can cause liver injury, potentially requiring liver transplant or death.

EMA

Patients who are refractory to or unable to tolerate or obtain other therapies for hyponatremia, and in whom the benefit of tolvaptan treatment out weighs the risks, remain candidates for longterm therapy with tolvaptan;
but in such cases, liver function tests should be monitored carefully and serially (ie, every 3 months), and the drug discontinued in the event of significant changes in liver function tests (ie, 2 ULN of ALT).

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Approved pharmacological agents for the treatment of hyponatremia.

	Canada	Europe	Japan	US
Demeclocycline	No licence	No EMA authorization Approved in UK (SIADH secondary to malignancy, if fluid restriction ineffective and no cirrhosis) Approved in France (SIADH particularly secondary to malignancy, if fluid restriction ineffective)	No licence	No licence
Lithium	No licence	No licence	No licence	No licence
Loop diuretics	No licence	No licence	No licence	No licence
Urea	No licence	No licence	No licence	No licence
Vaptans	Tolvaptan (clinically significant non-hypovolemic hyponatremia)	Tolvaptan (hyponatremia secondary to SIADH)	Mozavaptan (SIADH secondary to malignancy)	Tolvaptan (clinically significant hypervolemic and euvolemic hyponatremia, incl. heart failure and SIADH) Conivaptan (euvolemic and hypervolemic hyponatremia)

EMA, European Medicines Agency; SIADH, syndrome of inappropriate anti-diuretic hormone secretion.

Verbalis JG.Cur Med Res & Opin 2014, 1–7

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

AGENZIA ITALIANA DEL FARMACO
DETERMINA 17 luglio 2014

Riclassificazione del medicinale per uso umano «Samsca (tolvaptan)», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 753/2014). (14A05990) (GU Serie Generale n.175 del 30-7-2014)

Classe di rimborsabilita' H

Ai fini delle prescrizioni a carico del SSN, i centri utilizzatori specificatamente individuati dalle Regioni, dovranno compilare la scheda raccolta dati informatizzata di arruolamento che indica i pazienti eleggibili e la scheda di follow-up, applicando le condizioni negoziali secondo le indicazioni pubblicate sul sito dell'Agenzia, piattaforma web - all'indirizzo https://www.agenziafarmaco.gov.it/registri/ che costituiscono parte integrante della presente determinazione.

Nelle more della piena attuazione del registro di monitoraggio web-based, onde garantire la disponibilita' del trattamento ai pazienti le prescrizioni dovranno essere effettuate in accordo ai criteri di eleggibilita' e appropriatezza prescrittiva riportati nella documentazione consultabile sul portale istituzionale dell'Agenzia: http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottop osti-monitoraggio

I dati inerenti ai trattamenti effettuati a partire dalla data di entrata in vigore della presente determinazione, tramite la modalita' temporanea suindicata, dovranno essere successivamente riportati nella piattaforma web, secondo le modalita' che saranno indicate nel sito: http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottopos ti-monitoraggio

International and national treatment recommendations for SIADH

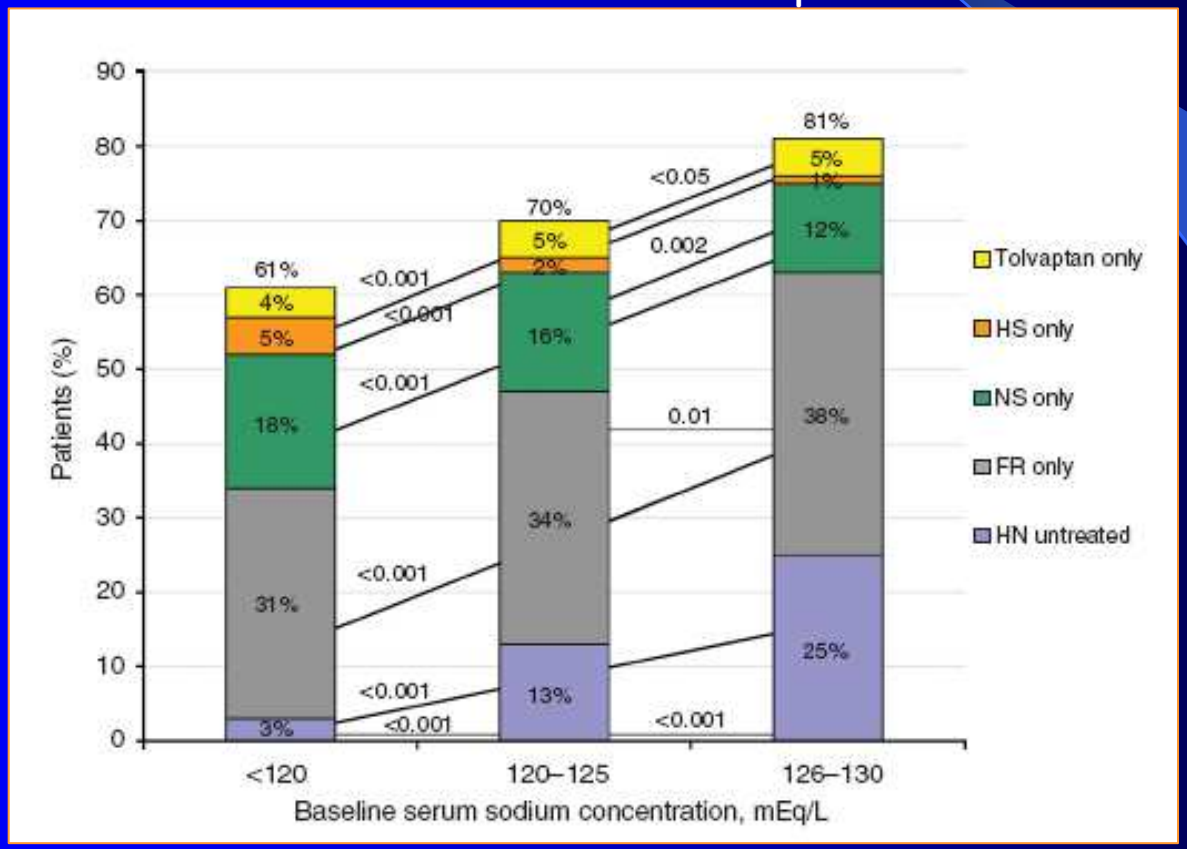
	Fluid restriction	Vaptans (tolvaptan)	Urea	Loop diuretics	Demeclocycline	Lithium
International						
European Clinical Practice Guideline	First-line treatment in moderate or profound hyponatremia	Not recommended in moderate hyponatremia; Recommended against in profound hyponatremia	Equal second-line treatment	Equal second-line treatment (combined with oral NaCl)	Recommended against in moderate or profound hyponatremia	Recommended against in moderate or profound hyponatremia
Expert Panel Recommendations	Generally first-line treatment; Consider alternative treatments in the presence of predictors of failure of fluid restriction	Recommended: 'Have the potential to replace water restriction as first-line treatment'	Recommended as an alternative oral treatment	*	Recommended as an alternative oral treatment	*
National						
Spain	First-line treatment	Recommended in patients not suitable for fluid restriction or furosemide	Recommended as an option; Could be therapy of choice in children with SIADH	Recommended as short-term treatment when urinary osmolality is sufficiently high; NaCl supplements recommended	*	*
Sweden	First-line treatment; Calculate electrolyte-free water clearance prior to initiation	First-line treatment in patients not suitable for fluid restriction	*	*	*	*
UK	First-line treatment; Calculate electrolyte-free water clearance prior to initiation	Consider if fluid restriction is not advised, or has a poor response	*	*	Consider if fluid restriction is not advised, or has a poor response	*

*Treatment option was not mentioned by the recommendation/guideline.
SIADH, syndrome of inappropriate anti-diuretic hormone secretion

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Current treatment practice and outcomes. Report of the hyponatremia registry

Choice of initial therapy according to baseline serum sodium concentration: all patients

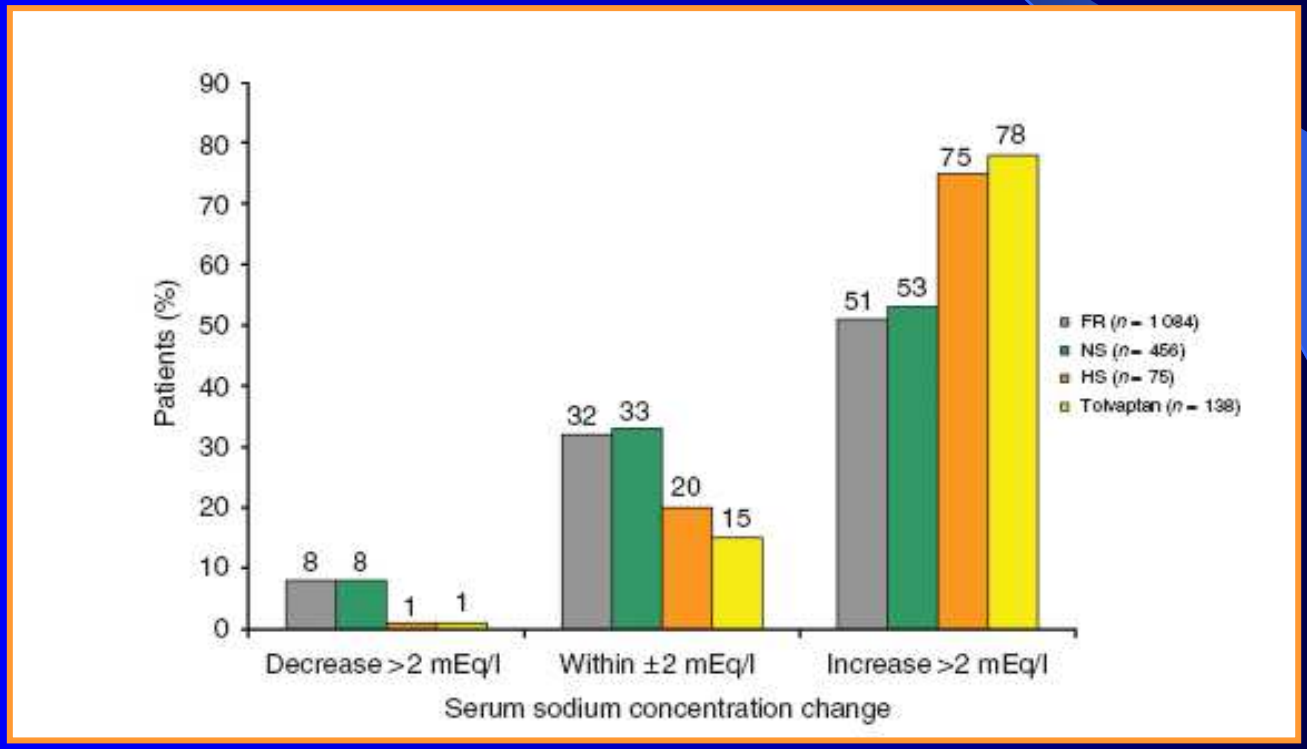


Greenberg A et al Kidney International.2015:88, 167

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Current treatment practice and outcomes. Report of the hyponatremia registry

Change in serum sodium concentration from baseline by initial monotherapy



FR, fluid restriction; HN, hyponatremia; NS, isotonic saline

Greenberg A et al Kidney International.2015:88, 167

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Current treatment practice and outcomes. Report of the hyponatremia registry

Table 5 | Rate of overly rapid correction of [Na^+] during any 24- or 48-hour period of therapy

	Initial Rx, *n/N* (%)[a]	Any monotherapy, *n/N* (%)[b]	Any use, *n/N* (%)[c]
All	58/2033 (2.9)	119/2399 (5.0)	203/2578 (7.9)
By Rx			
No Rx	7/509 (1.4)	NA	NA
Fluid restriction	15/1084 (1.4)	43/1614 (2.7)	106/1960 (5.4)
Isotonic saline	13/456 (2.9)	19/564 (3.4)	57/1150 (5.0)
Hypertonic saline	12/75 (16.0)	20/117 (17.1)	57/353 (16.1)
Tolvaptan	16/138 (11.6)	34/314 (10.8)	68/582 (11.7)

Overly rapid correction is defined as [Nap] 412meq/l in any 12 h period or 418mEq/l in any 48 h period.
a Initial therapy refers to first treatment modality selected for hyponatremia. Only episodes during which a patient received only a single modality (or no treatment) during that initial interval are included.
b Monotherapy includes any interval, initial or subsequent, during which only the single listed treatment was received.
c Any use includes any therapy period during which specified treatment was received irrespective of whether another treatment was also received.

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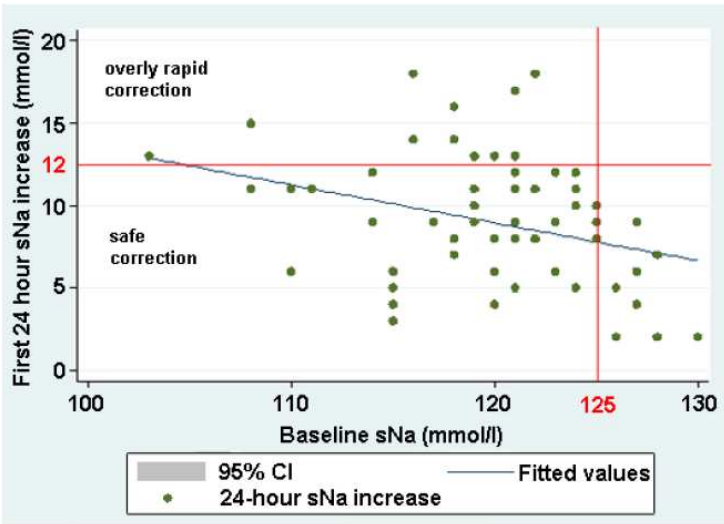
Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

Real-life experience of tolvaptan use in the treatment of severe hyponatraemia due to syndrome of inappropriate antidiuretic hormone secretion

Contingency table for rate of sNa correction with tolvaptan

		Number of patients (N) (%) as per rate of sNa correction	
Baseline sNa (mmol/l)	Total N	N (%) (within safe limits)	N (%) (overly rapid)
<125	49	35 (71.4%)	14 (28.6%)
≥125	12	12 (100%)	0 (0)

Linear regression between baseline sNa (x axis) and sNa correction in first 24 hours after initiation of tolvaptan (y axis)



Red vertical line indicates baseline sNa of 125 mmol/l
Red horizontal line indicates sNa increase of 12 mmol/l in first 24 hours
Correlation coefficient: - 0.23 (p value 0.012)

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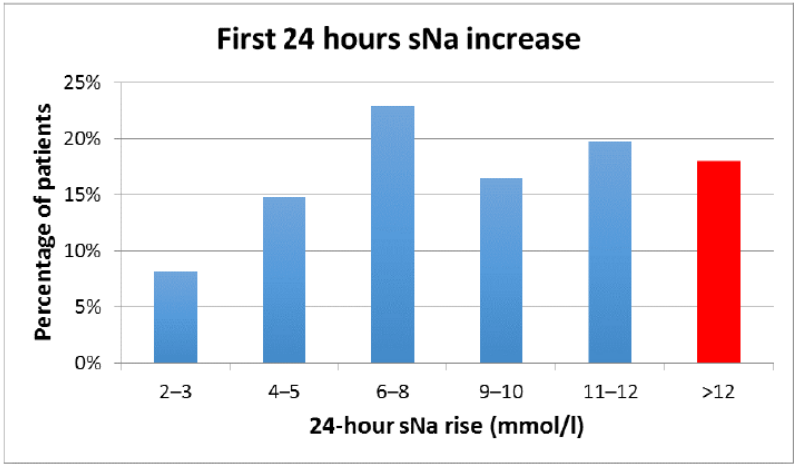
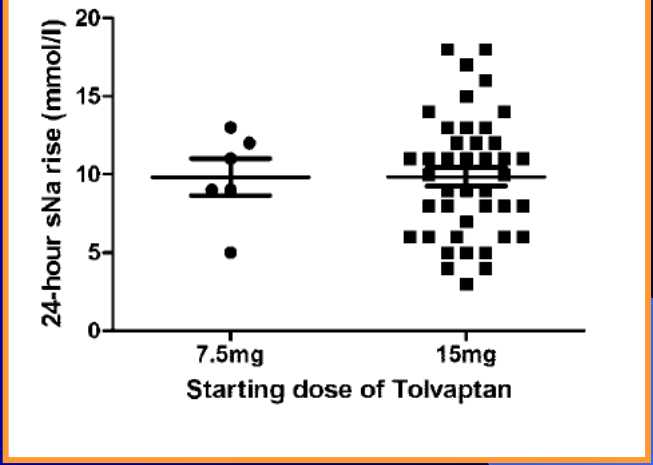
Relative frequency distribution of sNa change in first 24 hours after tolvaptan therapy



Scatter plot of magnitude of sNa rise for different initiation doses (7.5 mg vs 15 mg)



Horizontal lines indicate the mean 24-hour sNa rise for each group

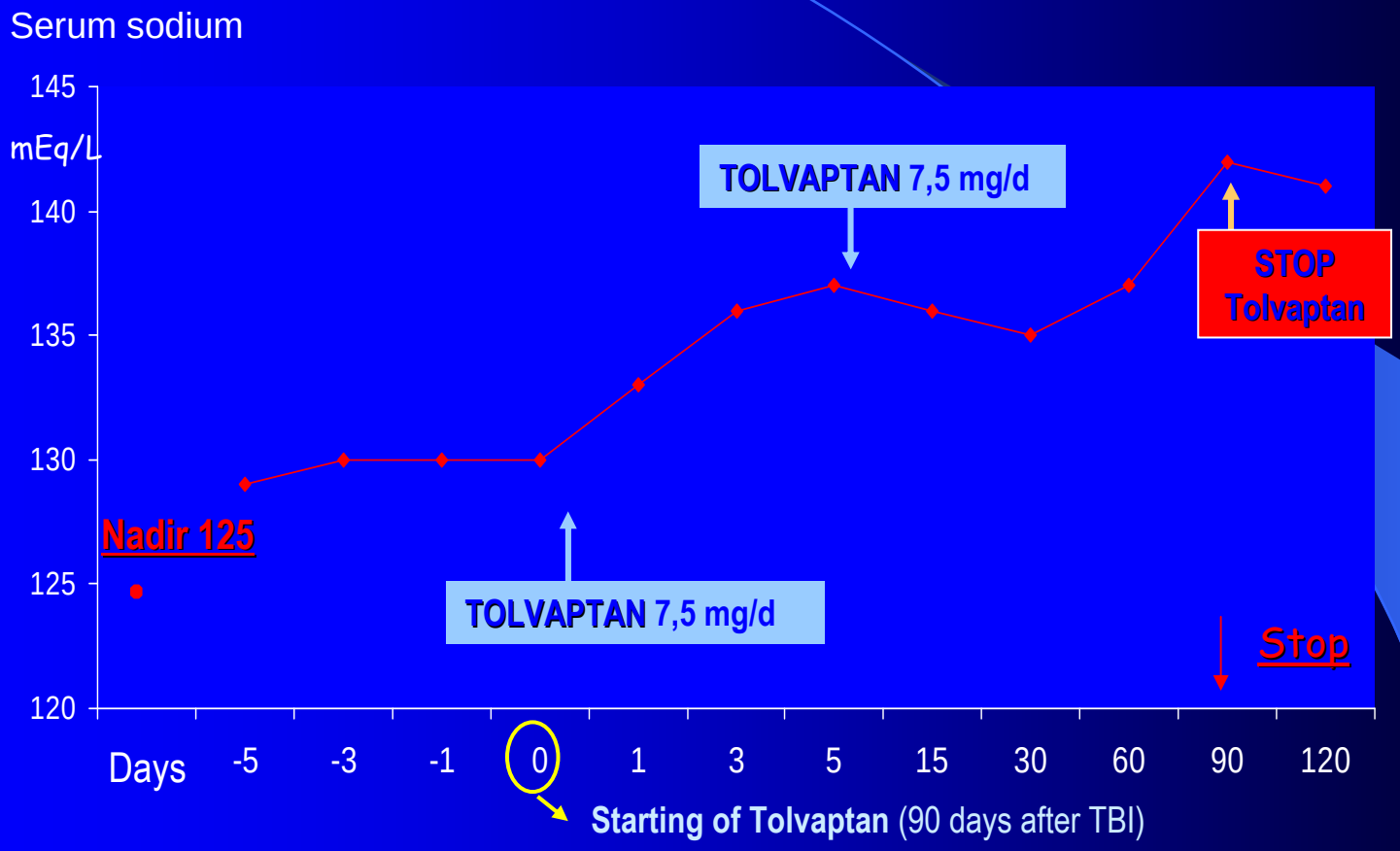
In conclusion,
this study confirmed the effectiveness of tolvaptan in correcting hyponatraemia in SIADH, but it also showed a significant risk of overly rapid sodium correction in real-life clinical practice when rigorous electrolyte monitoring was not in place. Our real-world data highlight the need for prospective studies examining the safety of tolvaptan use under appropriate monitoring in patients with sNa < 125 mmol/l and also for studies evaluating the efficacy and safety of lower tolvaptan doses such as 7.5 and 3.75 mg.

Tzoulis P et al.2015

Tolvaptan therapy in the post-acute phase of TBI

M, 28 yr, severe TBI (GCS=3), post-traumatic seizure treated with levetiracetam
Extremely severe disability at admission and moderate disability at discharge from the IRU

Intensive Rehabilitation Unit (IRU)



Low dose Tolvaptan therapy for 3 months

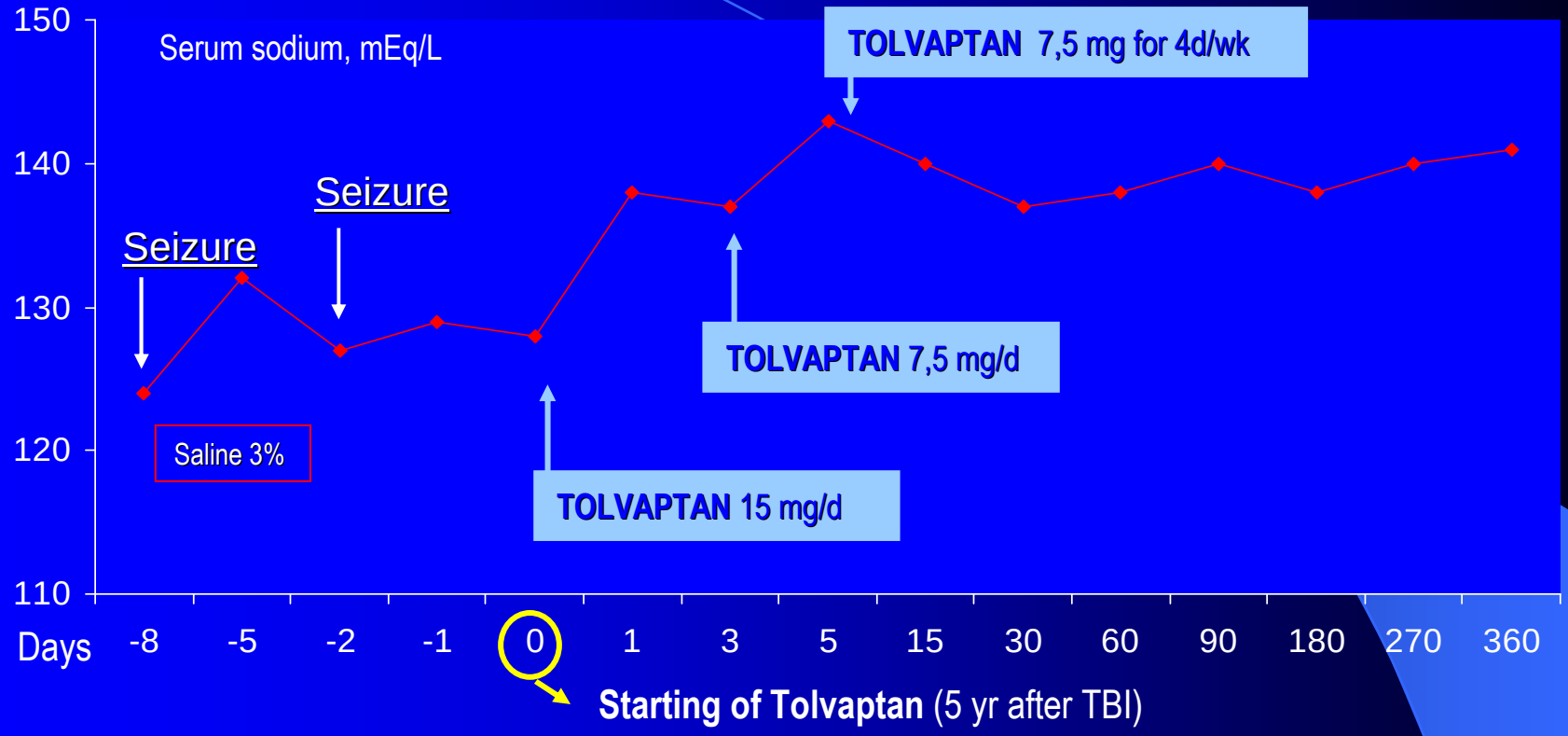
- Normalization of serum sodium
- Good response to the rehabilitation treatment

After drug withdrawal serum sodium remained stable

EFE 2015

Tolvaptan therapy in a patient with previous severe TBI

M 35 yr, previous severe TBI (GCS=3) with residual moderate disability and post-traumatic epilepsy treated with levetiracetam



Diagnosis of SIADH

↳ **Low dose Tolvaptan therapy for 12 months**

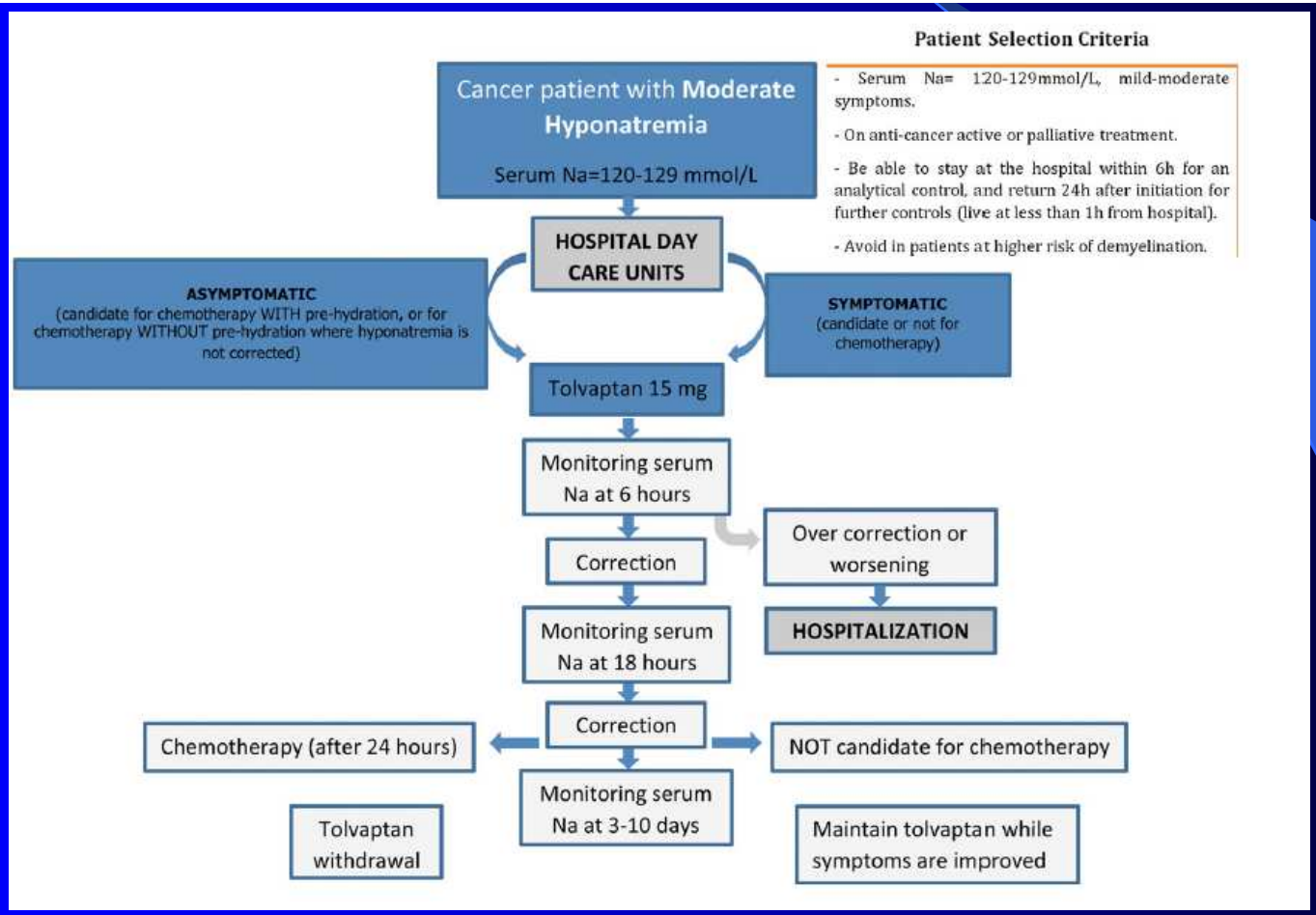
- normalization of serum sodium
- disappearance of seizures
- amelioration of neurological picture

The patient is undergoing therapy with low dose Tolvaptan since 15 months without side effects

Uso degli antagonisti del recettore della vasopressina nella pratica clinica: Tolvaptan nella SIADH

SIADH-related hyponatremia in hospital day care units: clinical experience and management with tolvaptan

Recommendations for treating hyponatremia in cancer patients in hospital day care units



De las Peñas R et al Support Care Cancer 2015

SIADH-related hyponatremia in hospital day care units: clinical experience and management with tolvaptan

Patients, n (%)	35		
Days to restore the natremia, n° of patients (%)			
- 1–4 days	18 (51)		
- More than 4 days	13 (37)		
- Partial response	3 (9)		
- No response	1 (3)		
Adverse events reported, n° of patients	Mild	Moderate	Severe
- Thirst	9	3	0
- Polyuria	6	4	0
- Dry mouth	4	0	0
- Hepatic enzymes elevation	2	0	0
- Others	0	0	0

De las Peñas R et al Support Care Cancer 2015

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'Dos and don'ts' in the use of tolvaptan in SIADH

- ➔ DO consider tolvaptan therapy for patients with hyponatremia due to SIADH without severe symptoms, in accordance with its license in the EU
- ➔ DO NOT commence tolvaptan as an outpatient
- ➔ DO NOT initiate tolvaptan immediately after use of hypertonic saline
- ➔ DO monitor patients from the time of initiation of tolvaptan to avoid overly rapid correction
- ➔ DO use caution in treating patients with tolvaptan if their serum [Na^+] is <120 mmol/L, owing to the higher risk of overly rapid correction
- ➔ DO encourage oral fluid intake when using tolvaptan
- ➔ DO consider interrupting therapy for 1–2 days once [Na+] reaches 125 mmol/L if the initial [Na+] was <120 mmol/L to allow slower equilibration
- ➔ DO consider the likely need for continued tolvaptan therapy in relation to the underlying cause of SIADH
- ➔ DO check liver function tests if there are symptoms suggesting liver toxicity

Aylwin S et al. Cur Med Res & Opin. 2015; 31:1755

Research agenda

Future studies are needed to assess

- the exact indications for vaptans
- the impact of treatment with vaptans on length of stay and mortality
- the optimal regimen of care
- the cost/effectiveness analysis

Tanks for the attention

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