Hyponatremia in Advanced Liver Disease

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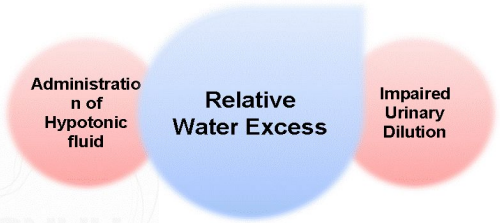
Hyponatremia



Hyponatremia

Hyponatremia

- **Dose not mean sodium depletion, Solute dilution by excessive water**
- Typical adults with normal renal function can excrete a massive free water load (upto 15 L per day) without diluting the serum.
- The factors necessary for the development of hyponatremia are free water intake (or administration of hypotonic fluids) in the setting of an underlying condition that impairs free water excretion

Hyponatremia

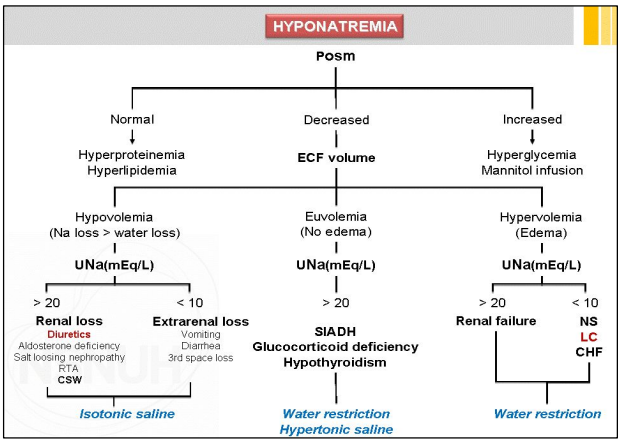
Hyponatremia

- Clinical manifestations of hyponatremia
  - Depend on its duration
  - Neurologic symptoms due to acute brain swelling or cerebral edema
    - ✓ headache, lethargy, seizures, and a progressively decreased level of consciousness eventuating in coma and death
  - Severity of symptoms depends more on the rate of hyponatremia than on the amount of hyponatremia

Hyponatremia

Diagnostic Evaluation of Hyponatremia

- **First step**: Measure serum osmolality
- **Second step**: Check urine osmolality
- **Third step**: Assess effective volume status
  - Weight changes, orthostatic variations in blood pressure
  - Heart rate, skin turgor (unreliable in elderly patients)
  - Jugular venous distension
  - Hct, BUN, bicarbonate, albumin, and uric acid: dehydration ↑
  - Hypovolemia with increased urinary Na
    - ✓ Salt wasting syndromes (such as CSW or adrenal insufficiency)
    - ✓ Metabolic alkalosis (urinary sodium excretion increases to neutralize the increased bicarbonate load)
    - ✓ Recent diuretic use
  - CVP, pulmonary capillary wedge pressures



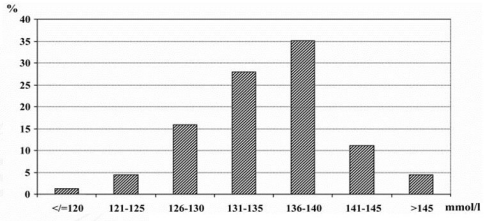
Hyponatremia in Cirrhosis

- Definition
  - sNa < 130 mmol/L
  - 130 – 135 mmol/L
    - ✓ not considered to have hyponatremia with the current definition
    - ✓ pathogenic and clinical features similar to those of patients with serum sodium below 130 mmol/L

Hepatology 1998;28:851

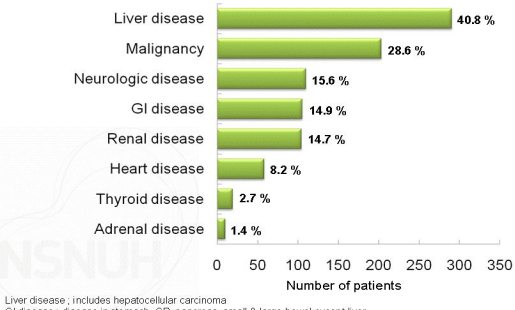
Hyponatremia in Cirrhosis

- Prevalence
  - sNa < 130 mmol/L : 21.6 % (50 % in patients with refratocry ascites or HRS)
  - sNa < 135 mmol/L : 49.4%



Angeli P et al. HEPATOLOGY 2006;44:1535

Underlying Diseases in Severe Hyponatremic Patients



Liver disease ; includes hepatocellular carcinoma
GI disease ; disease in stomach, GB, pancreas, small & large bowel except liver

김효상 등. 대한신장학회지 2008

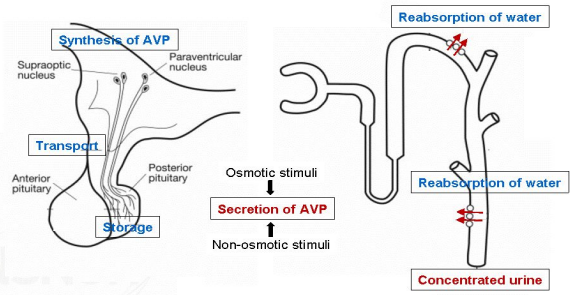
Types of Hyponatremia in Cirrhosis

- Hypovolemic hyponatremia
  - Causes
    - ✓ Due to important losses of extracellular fluid
      - – from the kidneys (because of overdiuresis due to treatment with excessive doses of diuretics)
      - – from the gastrointestinal tract
  - Less common
  - Characteristics
    - ✓ Contraction of plasma volume
    - ✓ lack of edema and ascites
    - ✓ signs of dehydration
    - ✓ prerenal renal failure and common hepatic encephalopathy

Types of Hyponatremia in Cirrhosis

- Hypervolemic hyponatremia
  - Causes
    - ✓ Marked impairment of renal solute–free water excretion
    - ✓ Spontaneously or as a consequence of excessive hypotonic fluids (i.e., 5% dextrose) or secondary to complications of cirrhosis, particularly bacterial infections
  - Frequent renal impairment
  - Characteristics
    - ✓ Increased plasma volume, but effective arterial hypovolemia (low plasma volume with respect to the marked vasodilation of the arterial circulation)
    - ✓ Increased total extracellular fluid volume with ascites and/or edema

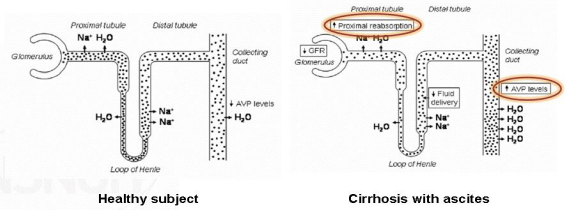
Role of AVP in the regulation of water balance



Bhardwaj A. Ann Neurol. 2006

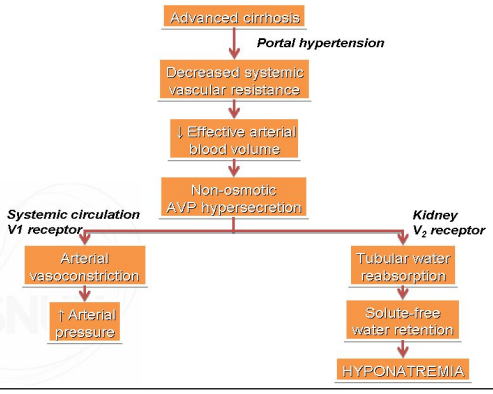
Pathogenesis

- Impairment in the renal capacity to eliminate solute-free water

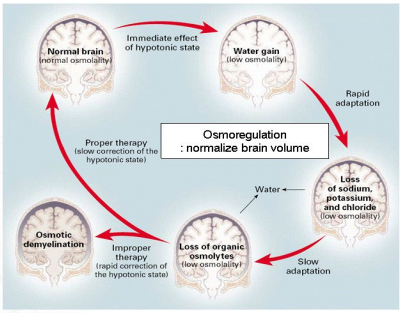


Healthy subject | Cirrhosis with ascites

Hepatology 48:1002, 2008



Effects of Hyponatremia on the Brain & Adaptive Mechanism



Adrogue HJ, et al. N Engl J Med. 2000

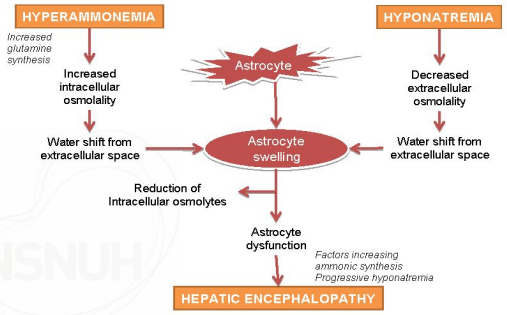
Clinical Significance of Hyponatremia

- Limited information on the clinical consequences
  - Hyponatremia almost always occurs in the setting of advanced liver failure
  - Consequences of hyponatremia versus those of other causes
  - Lack of an effective treatment of hyponatremia

Clinical Significance of Hyponatremia

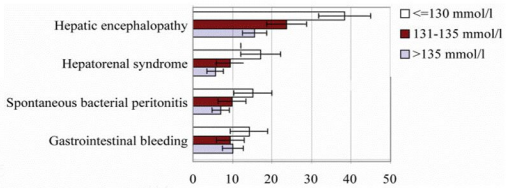
- Neurological function
  - Uncommon significant neurological symptoms
    - ✓ Chronic hyponatremia rather than acute hyponatremia
  - Low grade cerebral edema in the pathogenesis of hepatic encephalopathy
    - ✓ Ammonia and other neurotoxins
      - → Increased intracellular content of glutamine
      - → Swelling of astrocytes
      - → Alterations of neurological function
      - → Facilitation of development of hepatic encephalopathy
    - ✓ Hyponatremia
      - → Second osmotic hit to astrocytes
      - → Further depletion of osmotic counteractive systems

Clinical Significance of Hyponatremia



Clinical Significance of Hyponatremia

- Complications of cirrhosis



Percentage of patients (95% CI) with complications of cirrhosis within a 4-week period

Angeli P et al. HEPATOLOGY 2006;44:1535

Clinical Significance of Hyponatremia

- Complications of cirrhosis
  - Frequent finding in patients with cirrhosis and SBP
    Follo A et al. HEPATOLOGY 1994;20:1495
  - Occurs in close association with renal failure and correlates with poor prognosis
  - High risk of developing hepatorenal syndrome
    Gine's A et al. Gastroenterology 1993;105:229
    - ✓ Common finding in patients with hepatorenal syndrome
      - Increased AVP
      - Markedly reduced GFR
      - Increased proximal Na reabsorption
  - Independent predictive factor of impaired health-related quality of life
    Gine's P et al. HEPATOLOGY 2007;46:567A.

Clinical Significance of Hyponatremia

- Liver Transplantation
  - Increased risk of CPM after TPL
  - Increased risk of neurological complications after TPL
    Abbasoglu O et al. Clin Transplant 1998;12:263
  - Increased risk of
    - ✓ Renal failure
    - ✓ Infectious complications
    - ✓ Longer duration of hospital stay
    - ✓ Increased short-term mortality
      London'o MC et al. Gastroenterology 2006;130: 1135
      Dawwas MF et al. Liver Transpl 2007;13:1115

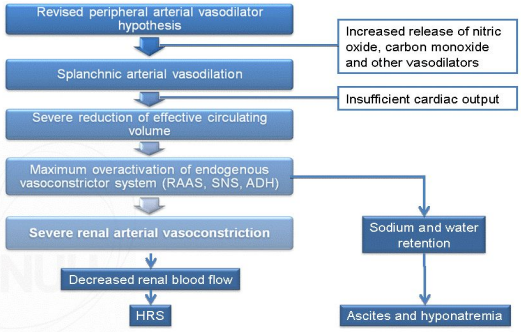
Diagnostic Criteria of Hepatorenal Syndrome

- Cirrhosis with ascites
- Serum creatinine >133 μmol/l (1.5 mg/dl)
- No sustained improvement of serum creatinine (decrease to a level of 133 μmol/l or less) after at least 2 days of diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg/day to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs (aminoglycosides, nitrates, prazosin, RAS inhibitors etc.)
- Absence of parenchymal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high-power field) and/or abnormal renal ultrasonography

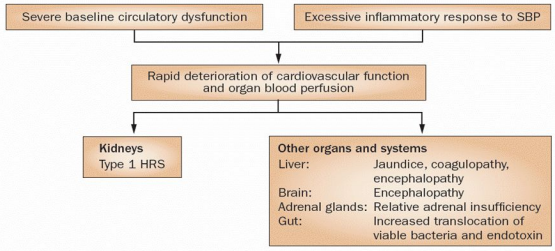
Types of Hepatorenal Syndrome

- Type 1
  - Rapid progression of renal failure (initial sCr doubles in less than 2 weeks to a final value >2.5 mg/dL)
  - Acute renal failure
  - Median survival : about 2 weeks
  - Precipitating factors
    - ✓ Spontaneous bacterial peritonitis (1/3), urinary tract infections and infections of the biliary or intestinal tract
      - Risk factors of renal failure d/t bacterial infection
        - » the severity of infection
        - » the MELD score at the diagnosis of infection
        - » the lack of resolution of infection
- Type 2
  - More stable degree of impairment from renal failure
  - Refractory ascites
  - Median survival : 4 – 6 months

Pathophysiology of HRS



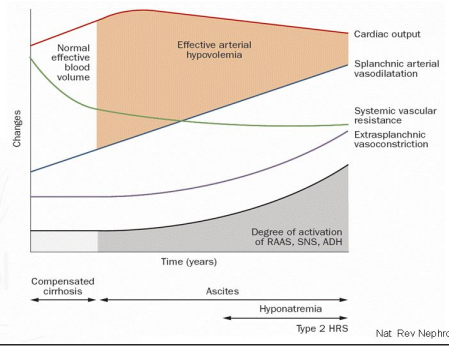
Type 1 HRS (Acute-On-Chronic Liver Failure)



Mechanisms leading to type 1 HRS and MOF in patients with SBP

Nat Rev Nephrol 2011; 7: 517-526

Type 2 HRS (Extreme Expression of the Systemic Circulatory Dysfunction)



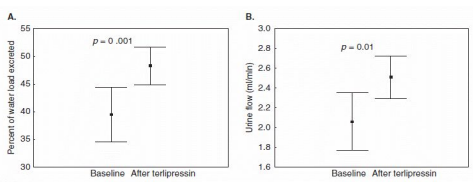
Nat Rev Nephrol 2011; 7: 517-526

Specific Therapies for HRS

- Vasoconstrictor drug
  - Terlipressin
  - Norepinephrine
  - Midodrine with octreotide
- Albumin
- Others
  - TIPS
  - Renal replacement therapy

Pere Gines et al, N Engl J Med 2009;361:1279-90.

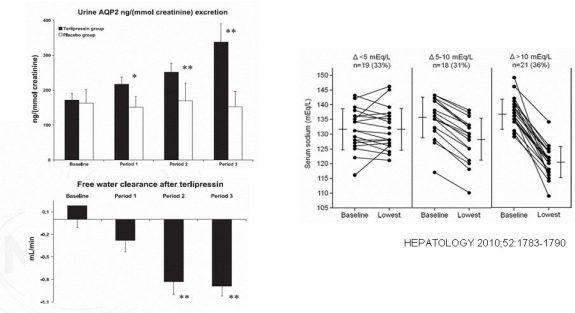
Terlipressin and Hyponatremia : No



Percentage of oral water load excreted (A) and diuresis (B)

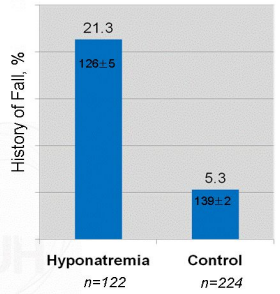
Scandinavian Journal of Gastroenterology, 2010; 45: 1509

Terlipressin and Hyponatremia : Yes



HEPATOLOGY 2010;52:1783-1790

Case Control Study of the Association of "Mild, Asymptomatic"Hyponatremia with Falls

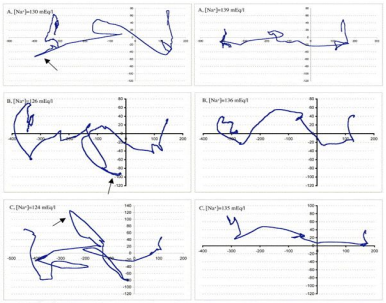


OR: 9.45 (2.64–34.09)
AOR: 67.43 (7.48–607.42)

122 ≤ [Na] ≤ 132

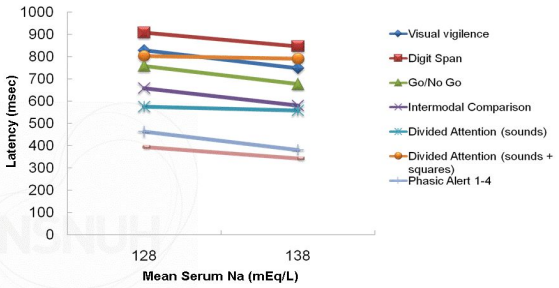
Renneboog B. Am J Med. 2006;119:71e1

"Mild, Asymptomatic"Hyponatremia Association with Gait Abnormalities



B.Renneboog, Am J Med. 2006;119:e71

Hyponatremia Impairs Attention



Renneboog B et al. Am J Med 119;e71-78, 2006

Mild Chronic Hyponatremia

- Patients with moderate chronic hyponatremia fall dramatically more frequently than patients with normal serum [Na^+] levels.
- These falls could be due to gait and attention impairments, as measured in comparable patients.
- The number of hospitalizations could probably be avoided if these patients were treated.

Management of Hyponatremia in Cirrhosis

- Hyponatremia defined as < 130 mmol/l should in cirrhosis be considered for treatment.
- Hypovolemic hyponatremia
  - often induced by drugs and should be treated by cessation of the drug
  - infusion of isotonic NaCl with an aimed increase in serum sodium < 0.5 mmoles/hr.
- If serum sodium decreases to < 120 mmol/l
  - diuretics should be discontinued.
  - If cerebral symptoms develop, fluid restriction (< 1 l/day) may be tried.

Dan Med J 2012;59(1):C4372

Management of Hyponatremia in Cirrhosis

- Goal of management (Hypervolemic hyponatremia)
  - **Increasing renal solute-free water excretion**
  - **Induce a negative water balance**

  - normalizing the increased total body water

  - improvement of serum sodium concentration

Management of Hyponatremia in Cirrhosis

Treatment	Term of Use	Comment
Fluid Restriction	Short or Long	Cheap. Not well tolerated or observed. Not effective unless U_{Osm} low.
Hypertonic Saline	Short	Reliable, cheap. Not suitable for patients with volume overload. Requires care to avoid too rapid correction.
Isotonic Saline	Short	Cheap. Effective only when volume depletion is cause of hyponatremia.
Demeclocycline	Long	Variable efficacy, nephrotoxic, not FDA approved.
Urea	Long	No USP formulation, not FDA approved, not well tolerated and acceptance poor.
Vaptans	Short or Long	Elegant. Conivaptan IV only; short term use. Tolvaptan short or long term.

Management of Hyponatremia in Cirrhosis

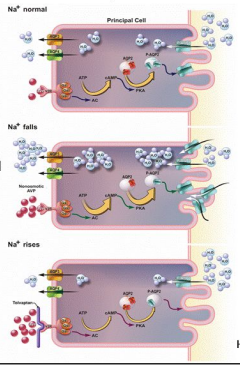
- Fluid restriction
  - Standard of care but is seldom effective
  - helpful in preventing a further decrease in serum sodium levels
  - total daily fluid intake cannot be restricted to less than 1 L/day
- Hypertonic saline
  - used commonly in severe hypervolemic hyponatremia
  - Efficacy is partial,
    - ✓ usually short-lived
    - ✓ increases the amount of ascites and edema.
- The administration of albumin
  - appears to improve serum sodium concentration
  - Low number of enrolled patients, short follow-up
    - ✓ More data is needed

Mechanism of Action: Vasopressin and V_2RA

Normal

Patient with cirrhosis and increased nonosmotic release of AVP

Effect of tolvaptan



Hepatology 2010;51:699

Vasopressin Receptors

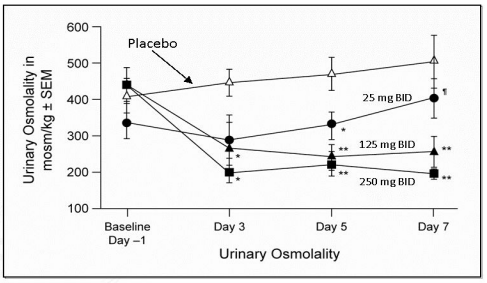
Receptor	Localization	Function
V1a (V1)	Vascular smooth muscle Platelets Hepatocytes Myometrium	Vasoconstriction, myocardial hypertrophy Platelet aggregation Glycogenolysis Uterine contraction
V1b (V3)	Anterior pituitary	ACTH release
V2 (V2)	Basolateral membrane, collecting tubule Vascular endothelium Vascular smooth muscle	Insertion of AQP2 water channels into apical membrane Induction of AQP2 synthesis vWF and factor 8 release Vasodilatation

Non-Peptide Vasopressin Antagonists

Compound	Receptor(s)	Route	Where Approved	Manufacturer
		Approved		
Conivaptan	V1a & V2	IV	USA, 2005	Astellas
Tolvaptan	V2	PO	2009-2011*	Otsuka
Mozavaptan	V2	PO	Japan, 2006	Otsuka
		Under Development		
Lixivaptan	V2	Oral		CardioKine
		Development Suspended		
Satavaptan	V2	Oral		Sanofi-Aventis

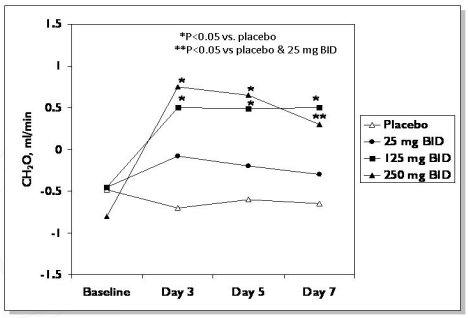
*2009: USA & EMA (UK, Germany, Spain, Italy, Scandinavia)
2010: Hong Kong, Japan, Taiwan
2011: South Korea, China, Canada

U_{Osm} during Lixivaptan -- SIADH, CHF, or Cirrhosis



Wong F. Hepatology 2003;37:182

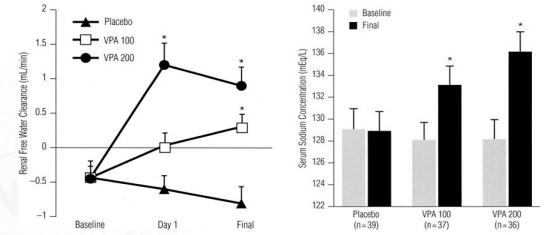
Free Water Clearance during Lixivaptan - SIADH, CHF, or Cirrhosis



Wong F. Hepatology 2003;37:182

Therapy of Hyponatremia in Cirrhosis with Lixivaptan

- 60 patients with cirrhosis and dilutional hyponatremia to 100 or 200 mg/day of VPA-985 or placebo in a double-blind study
- Concomitant restriction of fluid intake to 1000 mL/d



Gerbes AL et al. Gastroenterology 124:933, 2003

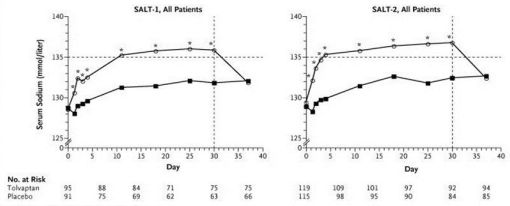
Tolvaptan - SALT I & II

- Study of Ascending Levels of Tolvaptan in Hyponatremia
- RCT 223 placebo, 225 tolvaptan
- 42% SIADH, 31% CHF, 27% Cirrhosis
- ↓ [Na] Mild (130 - 134, 51%), Marked (< 130, 49%)
  ; excluded if [Na] < 120 mmol/L & neuro sx
- Fluid restriction omitted day 1
- Dosage titrated up or down in 15-60 mg range depending on rate of rise of [Na]

Schreier et al. New Engl J Med 355;2099-2112, 2006

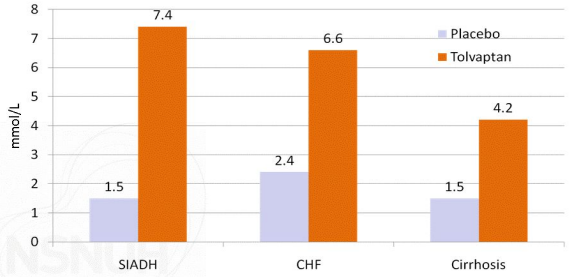
SALT I and II Trial

- Tolvaptan improved hyponatremia



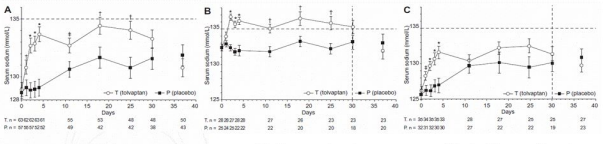
Schreier et al. New Engl J Med 355;2099-2112, 2006

Mean [Na] Change from Baseline by Etiology 30 days, SALT I & II



EMEA Filing, Tolvaptan, EMEA/502935/2009

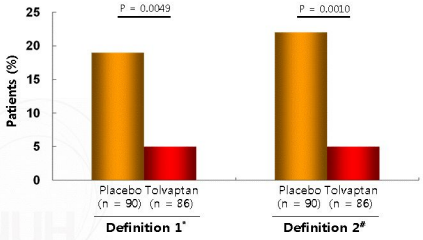
Use of Tolvaptan in Cirrhosis



J Hepatol 2012 56 ; 571

SALT I and II Trial

- Percentage of patients requiring fluid restriction



* Patients with no fluid restriction at baseline but imposed during treatment period
#Definition 1 plus patients requiring continuous fluid restriction from baseline throuh end of treatment period

Schreier et al. New Engl J Med 355;2099-2112, 2006

Potential Side Effects of Vaptans

- Thirst
  - Upto 29 %
- Hypernatremia
  - Uncommon in short term studies (2 – 4 %)
  - Increased risk in patients with
    - ✓ an altered mental state (encephalopathy)
    - ✓ or status that are not able to drink fluid in an amount sufficient to compensate for urine losses
- Rapid increase in serum sodium concentration
  - CPM : not reported thus far
- Renal failure
  - No significant renal function impairment in short-term studies

Potential Beneficial Effects of Treating Hyponatremia

- Allow patients to drink fluids normally and avoid fluid restriction.
- Treatment with vaptans may prevent the reduction in serum sodium levels commonly seen in patients under diuretic therapy.
  - Allowing diuretics to be continued in the management of ascites
- May reduce risk of hepatic encephalopathy
- Theoretically improve quality of life
- May help reduce the frequency and severity of neurological complications after transplantation
- Some promise as an agent in the management of ascites

Front Gastrointest Res 2011, 28: 91
J Hepatol 2009;50:S42

Vaptans in the Treatment of Hyponatremia
: EASL clinical practice guidelines

- Treatment with vaptans may be considered in patients with severe hypervolemic hyponatremia (< 125 mmol/L).
- Treatment with tolvaptan should be started in the hospital and the dose titrated to achieve a slow increase in serum sodium.
- Serum sodium should be monitored closely particularly during the first days of treatment and whenever the dose of the drug is increased.
- Rapid increases in serum sodium concentration (> 8 - 10 mmol/day) should be avoided.
- Neither fluid restriction nor administration of saline should be used in combination with vaptans to avoid a too rapid increase in serum sodium concentration.
- Concomitant treatment with drugs that are either potent inhibitors or inducers of the CYP3A should be avoided.
- The duration of treatment with vaptans is not known. Safety has only been established for short-term treatment (1 month)

J Hepatol 2009;50:S42

Limitation of Vaptans in Cirrhosis

- Tolvaptan
  - Only limited long-term safety data
  - Long-term, placebo-controlled studies in patients with cirrhosis treated with tolvaptan are clearly needed.
- Conivaptan
  - No prospective evaluation on the efficacy and safety in patients with cirrhosis and hyponatremia.
- Satavaptan
  - phase-3 randomized double-blind placebo-controlled study comparing the efficacy of long-term treatment with satavaptan in combination with diuretics : *preventing ascites recurrence in patients with cirrhosis following LVP*
  - increased frequency of complications and reduced survival

J Hepatol 2009;50:S42

Limitation of Vaptans in Cirrhosis

- Lack of information on how vaptan works when given in concert with diuretics
- Lack of safety and efficacy data when the drug is used for patients with Child-Pugh scores of greater than 10
- Concerns about excessive correction and renal impairment
- No randomized controlled trials documenting the value of adjusting serum sodium in hyponatremia

Front Gastrointest Res 2011, 28: 91
J Hepatol 2009;50:S42