Hyponatremia: Review and Update

Medical Grand Rounds
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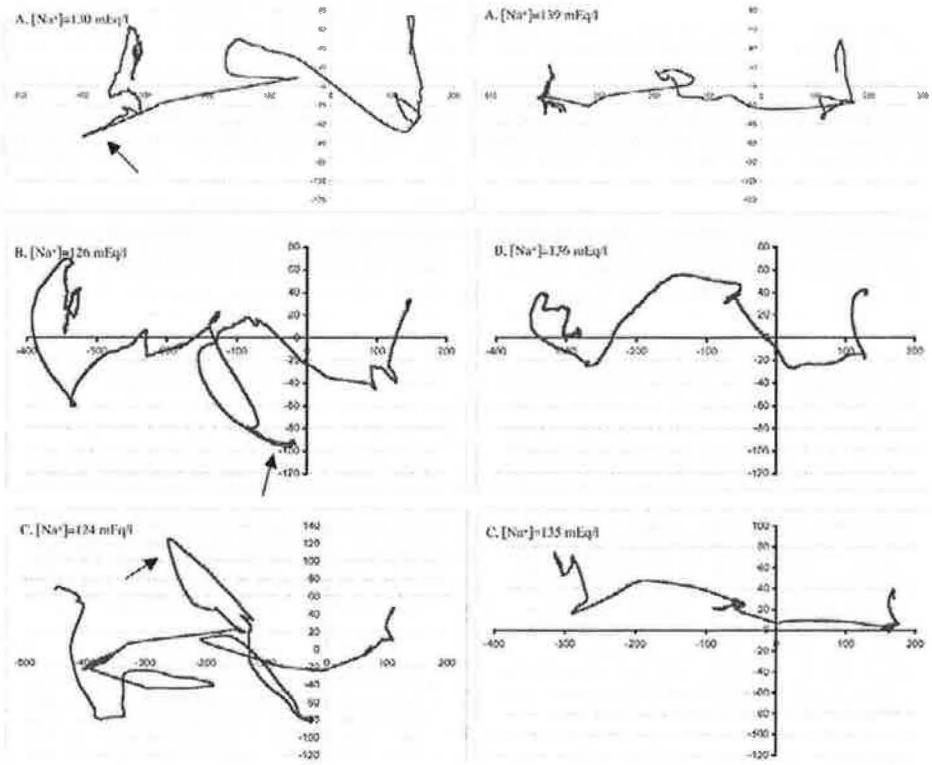
Gait in Chronic Hyponatremic Patients Before and After Correction



This is to acknowledge that Dr. Kuo has not disclosed any financial interests or other relationships with commercial entities related directly or indirectly to this program. Dr. Kuo will not discuss off-label use in this presentation.

Introduction

Hyponatremia is a common problem. However, the evaluation and treatment of this condition can be rather confusing (1, 2). This is because no formula or algorithm can completely replace the need for an understanding of the pathophysiology of hyponatremia. Such an understanding is very useful to clinicians to develop strategies in the differential diagnosis and management of hyponatremia.

The evaluation of hyponatremia starts with evaluation of the tonicity of plasma. A true hyponatremia is when the measured plasma tonicity is low and consistent with the low serum sodium concentration. A hyperosmolal hyponatremia is when the plasma tonicity is higher than normal, and the hyponatremia is the result of trapping of water in ECF by presence of osmoactive substances. A typical example is the hyponatremia associated with hyperglycemia. A normosmolal hyponatremia is a factitious hyponatremia due to the way we measure serum sodium in the lab. It occurs with certain methods used for measuring sodium concentration in solutions in which there is presence of space-occupying solid particles, such as excessive lipids or protein. This problem can be overcome by using direct ion selective electrode available in the blood gas machine for measurement of sodium concentration. It is critically important to properly differentiate the different types of hyponatremia as the therapies are very different. For hyperosmolal hyponatremia and factitious hyponatremia, we do not try to raise the serum sodium to an artificially normal level.

Once it has been determined that the patient has a true hypoosmolal hyponatremia, the next step is to determine the cause of this problem. The kidneys are normally able to excrete over 10 liters of electrolyte-free water (EFW) per day, as long as the osmole intake is in the normal range. Impairment in this EFW excretion suggests the effect of ADH which causes the kidneys to produce concentrated urine. To further evaluate this inappropriate release of ADH in the setting of hyponatremia, one is reminded that ADH release can be stimulated by hyperosmolality as well as hypovolemia. It is therefore helpful to determine the volume status of the patient to further classify the hypoosmolal hyponatremia into three categories. There are those associated with overt edema, such as in CHF and cirrhosis, and there are those with obvious volume contraction, as seen in severe diarrhea and diuretic use. The mechanism of hyponatremia in both types is felt to be due to decreased effective blood volume which stimulates the release of ADH, known as the non-osmotic stimulation of ADH by the volume-sensitive baroreceptors. The treatment for such patients is to address the underlying hemodynamic abnormality that causes the ADH release. The third category is clinically euvolemic hyponatremia. This can be from binge water drinking exceeding the water excreting capacity of kidneys, or from inappropriate ADH release. The former is characterized by maximally dilute urine, the latter by less than maximally dilute urine and is known as SIADH.

SIADH is a diagnosis that should only be applied to when patients have been determined not to have adrenal insufficiency, hypothyroidism, or renal failure, as in these three conditions, inappropriate release of ADH is not the primary dysfunction, and the treatment also is different.

Add to the above familiar understanding is the concept of tonicity balance, a topic that I will emphasize in this talk.

Pathophysiology of Hyponatremia Based on Tonicity Balance

Case #1:

Case 1

53 year-old male with CHF from ischemic heart disease admitted to PMH for CHF exacerbation.

PE: Acutely ill-appearance with SOB. BP 105/55 mmHg; PR 115, regular; RR 32; crackles ¼ way up bilaterally; 2/6 systolic m at LLSB, RR; 2+ edema LE.

Medications: Lisinorpil 20 mg qd; Isordial 40 mg tid; Lasix 20 mg bid, Lipitor 20 mg qd (has not taken his med for the past 2 weeks)

Lab:

126	91	42
4.3	27	1.6

Urine: Na 15; K 75; Cl 26; Cr 63.5; Sp Gr 1.020
FeNa 0.3%

What is the mechanism of hyponatremia?

Figure 1

A look at his urine potassium shows a large amount of potassium (Figure1). This is consistent with the diagnosis of secondary aldosteronism in the setting of decreased cardiac output. But how does high urinary potassium lead to hyponatremia?

Potassium is the major cation in ICF, and sodium is the major cation in ECF (Figure 2). The source of urinary potassium is ultimately from the ICF. Because the cellular membrane is not readily permeable to these ions, they are kept in their respective compartments in spite of the concentration gradients. On the other hand, water permeates freely across the membrane, and moves along the osmolal gradient in the direction to maintain an identical tonicity between the two compartments. Therefore, when the ICF loses potassium and therefore lowers its osmolality, water will shift from ICF to ECF in order to establish new tonicity equilibrium. This translocation of water will then dilute the serum sodium in ECF. An alternative explanation for the observed effect

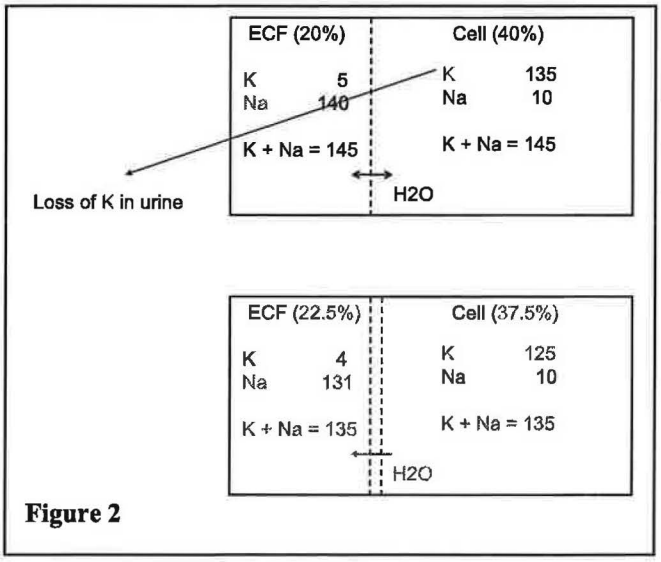


Figure 2

of potassium in the pathogenesis of hyponatremia is that sodium cation from ECF enters the cells to replace the potassium wasted in urine. This will also result in hyponatremia in ECF, but is less likely due to the membrane impermeability to sodium.

It is important, thus, to include potassium in the management of hyponatremia because the gain and loss of potassium can have an effect on sodium concentration in the body.

Case #2:

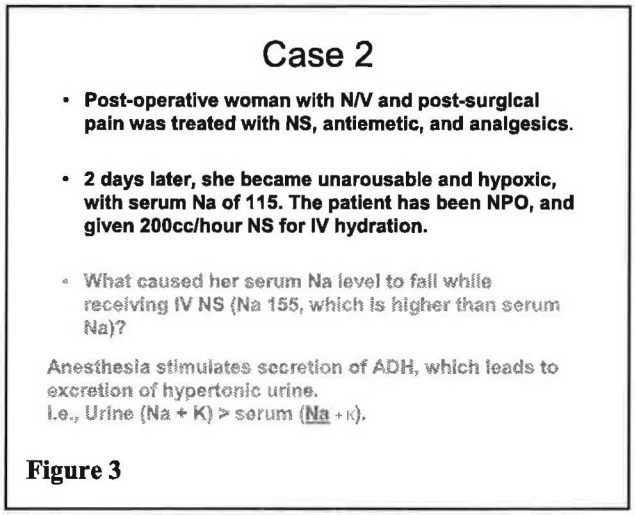


Figure 3

A post-operative woman had N/V, and post-surgical pain (Figure 3). She was treated with N/S, antiemetics, and analgesics. She remained NPO. 2 days later, she was found to be unarousable and hypoxic. Serum sodium was 115. What caused the dilution of her serum sodium when she had received nothing but N/S, a solution isotonic to the serum?

When ADH release is from non-osmolal stimuli, such as from surgery, nausea, vomiting, urine can be quite hypertonic. Whenever the sum of urine sodium and potassium concentrations exceeds that of the intake fluid, the plasma sodium will be diluted from the process. This has been termed the desalination phenomenon, and has the implication that in the treatment of hyponatremia from SIADH, N/S not only may not be effective, but can also be detrimental in situations when the sum of urinary sodium and potassium concentrations exceeds that of the infused N/S.

The bottom line is that the concentration of serum sodium is determined by the in and out balances of water, sodium and potassium. When we balance the in and out of all these elements, we will find that the change of sodium concentration to be from the changes in these balances.

This concept is well illustrated by a study by Steele et al, Ann. Int. Med. 126:20-25, 1997(3). The study is a prospective cohort study including 24 women who underwent uncomplicated surgeries under general anesthesia. On average, ~5 liters NS (or Ringer lactate) was administrated over 24 hr. Plasma (Figure 4) and urine (Figure 5) electrolytes measured at induction of anesthesia and 24 hrs later showed that hyponatremia occurred quite commonly due to production of highly concentrated urine.

Plasma Levels	Before Anesthesia	24 Hours after Anesthesia
Sodium, *mmol/L*	140 ± 0.5	136 ± 0.5†
Potassium, *mmol/L*	4.1 ± 0.1	3.8 ± 0.1
Chloride, *mmol/L*	106 ± 0.4	104 ± 0.5
Bicarbonate, *mmol/L*	22 ± 0.4	22 ± 0.5
Anion gap, *mEq/L*	12 ± 0.5	10 ± 0.3
Creatinine, *μmol/L (mg/dL)*	62 ± 2 (0.7 ± 0.02)	59 ± 3 (0.7 ± 0.02)
Blood urea nitrogen, *mmol/L (mg/dL)*	3.5 ± 0.2 (10 ± 0.6)	2.5 ± 0.3 (7 ± 0.8)
Glucose, *mmol/L (mg/dL)*	4.8 ± 0.1 (86 ± 2)	5.3 ± 0.4 (95 ± 8)

* Values are the mean ± SE.
† $P < 0.01$ by paired observations.

Figure 4

Balance study showed that the hyponatremia was due to a greater retention of infused fluid than the retention of accompanying infused electrolytes.

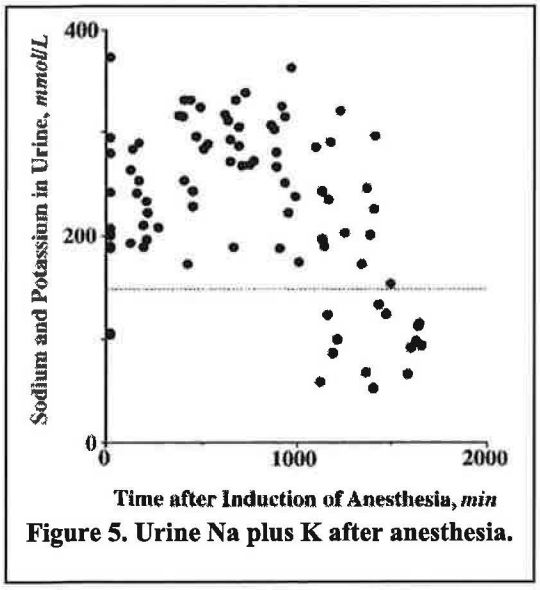


Figure 5. Urine Na plus K after anesthesia.

Treatment of Hyponatremia:

Treatment of hypoosmolal hyponatremia can be quite challenging (4). This is because overly aggressive correction of hyponatremia can result in osmotic demyelination with potentially devastating consequence to the patients. On the other hand, hyponatremic encephalopathy can be equally fatal. Initially, the brain swells in the setting of hyponatremia as water moves into tissue to equilibrate the ECF and ICF tonicities. However, within minutes, the brain starts losing its interstitial fluid, and the brain cells lose their electrolytes. This process is followed by extrusion of organic osmoles from the brain cells (Figure 6). When hyponatremia is

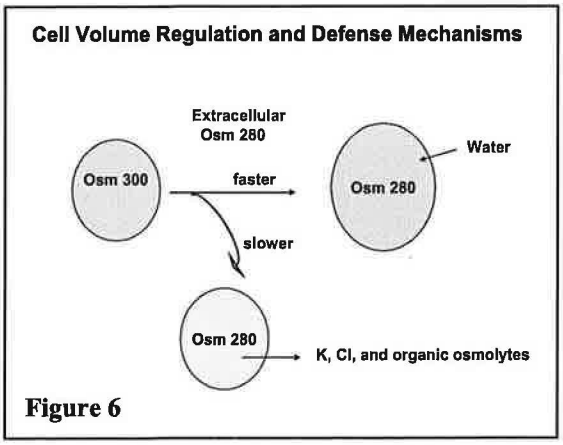


Figure 6

chronic, brain has already undergone the above mentioned volume regulation, and is normal or near normal in size. Overly rapid correction of hyponatremia at this time can induce brain cell dehydration as the rising serum sodium pulls fluid from ICF before the lost organic osmoles can be reclaimed by the brain cells (Figure 7). This can lead to the feared consequence of osmotic demyelination. These patients usually show an initial neurological improvement upon the correction of hyponatremia, only to be followed by neurological deterioration days or weeks later. The diagnosis is made by MRI. There is no known effective therapy, although re-induction of hyponatremia has been suggested.

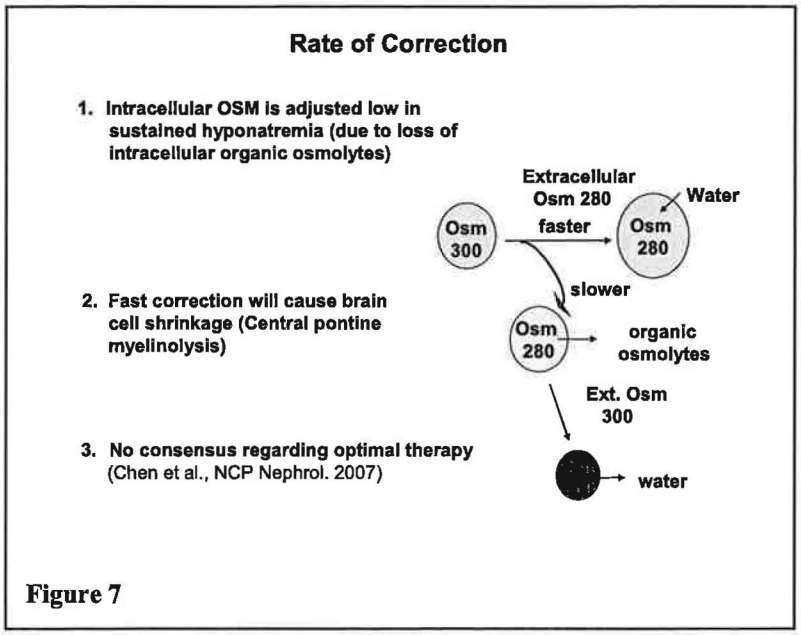


Figure 7

So what is the safe rate of correction? This remains controversial. Too slow a correction risks the patient to brain herniation, too rapid correction risks the patient to demyelination. Although there is no black and white answer to this dilemma, there is a generally accepted principle that the treatment should be guided by the patient's hyponatremic symptoms, not by the level of serum sodium concentration (5). For severely symptomatic patients at risk for brain herniation, 3% saline should be used at 1 to 2cc/Kg/hour to aim at an initial correction rate of 1 to 2 meq/l/hour. The correction should not exceed 10 to 12 meq/l/hour in the first day, or 18meq/l/hour in the first 48 hours. In general, 3% saline should be discontinued once serum sodium level has been corrected to 120 unless the hyponatremia is hyperacute (usually an iatrogenic situation). For mildly symptomatic, the treatment is fluid restriction and other measures, but no hypertonic saline should be used. Again, it is the severity of hyponatremia symptoms, not the level of sodium that dictates the intensity of treatment (5-10).

Case #3:

Homeless man with mental disorder was found unresponsive, reportedly drinking lots of water, followed by several emesis and seizures. Serum sodium is 108. Is this urgent? The renal fellow decided it was urgent, and wanted to correct it at a rate of 2meq/l/hour using 3% saline to raise the sodium to a target of 120. How much sodium to give?

The sodium needed is the (target sodium concentration- the patient's sodium concentration) x TBW=(120-108)X (70X 0.6)=504meq sodium.

This is equivalent to give 1 liter of 3% saline over 6 hours, or about 170cc/hour. However, when he went to see the patient, he found the patient's Foley bag overflowing with very dilute urine. He decided to hold off the 3% saline order.

In the situation of psychogenic polydipsia, there is very often a transient and erratic release of ADH which when it ends, can result in rapid self-correction. Because the dynamic of this process is unpredictable, in order to avoid excessive correction of hyponatremia, no amount of calculation can replace the need for frequent monitoring of serum sodium, urine electrolytes and the patient as the guide in therapy. It is not infrequent that we find the serum sodium to correct at a rate faster than we have planned based on calculation.

In addition to giving 3% saline, another way to correct hyponatremia is to compel the kidneys to excrete electrolyte-free water in spite of ADH. This can be accomplished by using loop diuretic, osmoactive particles, or the V2 antagonists. We will use the next two cases to illustrate the concept of electrolyte-free water clearance.

Case #4 (ref. 9):

50Kg man with SIADH from lung cancer was admitted with MS change. Sodium concentration was 110, Usom 500. You want to increase sodium concentration from 110 to 120 in 10 hours by making the kidney excrete electrolyte-free water. How to do this?

First, we determine how much electrolyte-free water needs to be excreted to raise sodium concentration from 110 to 120, assuming a TBW of 30 liters.

The new TBW is estimated to be (110X30)/120=27.5 liters

Target loss of water in order to raise the sodium to 120 is therefore 2.5 liters.

Target rate is therefore 250cc/hour of negative water balance.

In order to achieve this, we first induce hypotonic urine by giving 40mg IV Lasix. In the first hour post Lasix, UOP is 1 liter, with sodium concentration of 75 and potassium of 20. Since we only want 250cc of free water excretion, we should give the patient back

750cc of water, 75meq of sodium, and 20meq of potassium. This can be done by giving the patient 500 N/S + 20meq of KCl/ 250cc of D5W.

Let us say that in the next hour, UOP dropped to 800cc, with sodium concentration of 75, and potassium concentration of 30. Again, since we only want 250cc per hour of free water excretion, we need to give the patient back 550cc of water, 60meq of sodium (75X0.8), and 24meq of potassium (30x0.8). This can be done with 400cc N/S (use the ratio of 60/150), and 24meq of KCl/150cc of D5W. As the effect of Lasix wears off, repeat the Lasix.

Case #5 (ref. 9):

A man with SIADH has serum sodium of 124, fixed Uosm of 500 (Figure 8). His daily Osm load is 500, dietary sodium 100meq/day, potassium 40meq/day. How to make his kidneys excrete more free water?

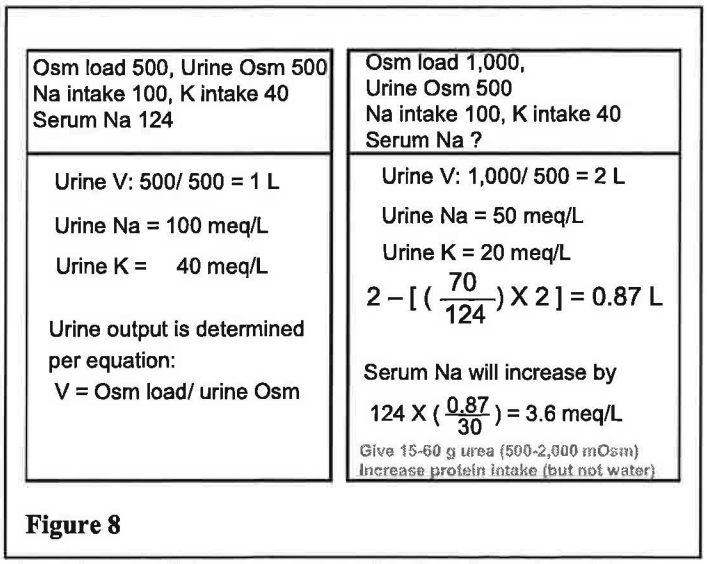


Figure 8

The urinary output is determined by the urinary osmolal load and the urinary osmolality as shown in this formula: urinary volume = the osmolal load / Uosm. Our patient therefore will have a UOP of 1 liter based on his osmole intake and fixed urine osmolality. If we increase the osmolal load in this patient from 500 to 1000/day, we will then increase the obligatory water loss. This increase in UOP will effectively dilute urine electrolytes, and therefore increase electrolyte-free water clearance (the amount of EFW excreted by kidneys is the total urine volume minus the amount of urine that is iso-osmotic to the plasma).

In the case of the patient above, if we increase his Osm load from 500 to 1000msom, given the fixed Uosm of 500mosm/l, he will have 2 liters of UOP instead of the previous UOP of 1 liter. His urine is now dilute with urinary sodium concentration of 50meq/l, and potassium concentration 20meq/l. His electrolyte-free water clearance is (1-70/124) x2=0.87 liter. His serum sodium will rise accordingly with the positive value of electrolyte free water clearance.

New Treatments on the Horizon (ref. 11)

Finally, V2R antagonists are being used for treatment of hyponatremia. Vasopressin has three types of receptors (Figure 9)(11). V1aR mediates the effect of vasoconstriction, platelet aggregation, inotropic stimulation and myocardial protein synthesis. V1bR mediates the effect of pituitary ACTH secretion. V2R mediates the effect of water permeability in the principal cells of renal collecting tubles, and the release of vWF and factor 8 by the vascular endothelium.

Vasopressin Receptor Subtypes

Receptor Subtype	Site of Action	Effects
V_{1a}	Vascular smooth muscle Platelets Lymohocytes Hepatocytes	Vasoconstriction Platelet aggregation Coagulation factor release Glycogenolysis
V_{1b}	Anterior pituitary	ACTH and endorphin release
V_2	Renal collecting ducts	Free water reabsorption

Figure 9

Among the V2R antagonists (also known as vaptans) (Figure 10) (11), only Conivaptan has been approved by the FDA for treating euvolemic and hypervoelmic hyponatremia. It is not to be used for hypovolemic hyponatremia, and is probably contraindicated for cirrhotic patients due to its potentially harmful V1aR vasodilatory effect in this population. Conivaptan is both a substrate and an inhibitor of CYP 450. The other vaptans appear to have less effect on the CYP 450. Because of the significant inhibition of cytochrome P450 by Conivaptan, its use is presently restricted to a maximal of 4 days and as an IV drugs used in hospital settings. The availability of vaptans may make it more feasible to treat patents with chronic hyponatremia who are currently treated with fluid restriction alone.

AVP Receptor Antagonists

	Conivaptan*	Tolvaptan	Lixivaptan	Satavaptan
Receptor	V_{1a} and V_2	V_2	V_2	V_2
Route	IV	Oral	Oral	Oral
Urine volume	↑	↑	↑	↑
Urine osmolality	↓	↓	↓	↓
Urine lytes	↔	↔	↔ low dose ↑ high dose	↔
Company	Astellas	Otsuka	Cardiokine	Sanofi-Aventis

* FDA approved for treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients

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