30231-Answering reviewers

Dear Editor,

We have finally completed our responses to the reviewers with revisions have that have been identified in red letters in the revised manuscript. Changes made in the original manuscript have been identified by red letters. We feel we have adequately responded to the comments made by each reviewer and hope it will be acceptable for publication. Some comments have materially improved the quality of the manuscript and we thank the reviewers for spending their valuable time to offer many helpful comments.

Reviewer #1

In this paper Maesaka et al., starting from the observation that clinical examination is not a valuable tool to assess volume status, propose the use of FEurate as an additional strategy to differentiate SIADH to CSW/RSW. I think that the initial observation is correct and the introduction on new tools for managing hyponatremia might be useful for clinicians. Nevertheless, although the reported approach seems interesting, I found some points that, in my opinion, should be clarified: Major considerations 1. The authors state that they adopt a pathophysiological approach, but they don't explain the pathophysiological mechanisms underlying the relationship between natremia and FEurate. Indeed, they report a case series that, in their opinion, should sustain their hypothesis but there is not a clear explanation of any mechanism. I think that a new paragraph on this specific issue could add important information for the readers.

Response:

These are excellent comments that we have struggled with over the years. We decided to eliminate discussions on mechanisms of sodium transport abnormalities in RSW from our recent publications for many reasons and have not adequately addressed the very troublesome relationship between natremia and FEurate in RSW and SIAD in the present manuscript. As suggested, we will add a separate paragraph to address these intriguing questions.

Comments on natriuresis in RSW and relationship between natremia and urate transport.

Natriuresis in RSW. The syndrome of renal salt wasting has been clearly established from a clinical perspective but the mechanism by which this occurs has not been resolved. The consistency with which we were encountering urate transport abnormalities in RSW suggested that a circulating natriuretic factor, if present, would have its major effect on proximal tubule sodium transport. But because of the ability of the distal tubule to increase sodium transport, we reasoned that sodium excretion induced by a factor affecting proximal sodium transport might be minimized or nullified. To this end we elected to study lithium transport in rats exposed to plasma from neurosurgical patients who have been reported to have RSW and high FEurates. (24,45,46,51) Without entering into the controversy whether or not lithium is exclusively transported in the proximal tubule, lithium is known to be transported on a 1:1 basis with sodium almost

exclusively in the proximal tubule under ambient conditions. (52) We injected the plasma from 21 neurosurgical patients, 14 of whom had FEurates exceeding 10%, and 14 age and gender-matched controls into rats and demonstrated a significant increase in FENa from 0.29 to 0.59% and FElithium from 24 to 36.6%, in controls and neurosurgical patients, respectively). (53)

We extended our interest in patients with increased FEurate with normonatremia by investigating patients with Alzheimer's disease (AD) who have been reported to be hypouricemic. (54). We studied 18 patients with advanced AD, mini-mental examination (MMSE) scores of <10, and compared them to 6 patients with multi-infarct or vascular dementia (MID) and 11 normal age and gender-matched controls. All patients were normonatremic except for one hyponatremic patient with AD, FEurate being significantly higher and serum urate lower in AD as compared to the other groups. Infusion of the sera from all groups of patients resulted in FENa of 0.33, 0.38 and 0.63% and FElithium 27.2, 31.2 and 41.7% in control, MID and AD, respectively. FENa and FElithium were significantly increased in AD as compared to control and MID. In both the neurosurgical and AD rat studies, the distal sodium load of 36.6 and 41.7% as determined by the FElithium, had a significant sodium uptake by the distal nephron to account for the FENa of only 0.59 and 0.63% in the final urine. The RSW patient with B cell lymphoma obstructing the inferior vena cava had a similarly high distal sodium load that was inhibited by furosemide to generate an exaggerated diuresis that resulted in profound hemodynamic instability. (31) Interestingly, there were no differences in blood pressure or inulin clearances throughout both studies. In a third group of studies, proteins were purified from ammonium sulfate precipitates of urine proteins and placed in transwells to determine transport of radioactive sodium, ^{22}Na, across cultured porcine proximal tubule cells, LLC-PK1 cells, grown to confluency on a semipermeable membrane. Urine proteins from normonatremic neurosurgical patients with increased FEurate inhibited ^{22}Na transport across cultured LC=PK1 cells as compared to those with normal FEurate. (55)

These studies demonstrate the presence of a natriuretic factor in the plasma and urine of normonatremic neurosurgical patients with increased FEurate and in sera of normonatremic AD patients with increased FEurate. The natriuretic factor has its major effect on proximal tubule sodium transport to support our proposal that a high FEurate in the presence of normonatremia might be a marker of RSW without going through a phase of hyponatremia, [figure 1]. Future studies must address this interesting possibility. Atrial or brain natriuretic peptides are extremely unlikely as the natriuretic factor in RSW because their main site of action is in the inner medullary collecting duct. (56)

Relationship between natremia and FEurate

The intriguing relationship between serum sodium and FEurate has been uniquely coupled in many hyponatremic and non hyponatremic conditions such as RSW. Because the natriuretic factor present in the plasma of patients with RSW affect sodium transport mainly in the proximal tubule, it would be interesting to speculate that the natriuretic factor might also affect reabsorbing and/or secretory transporters or anion exchangers for urate in the proximal

tubule. (40) This circulating factor can have effects on the sodium and urate transporters regardless of whether the patient is hyponatremic or normonatremic.

The relationship between sodium and urate in SIAD continues to elude any rational explanations. It can be readily understood why FEurate remains persistently increased in the presence of normonatremia in RSW, but in SIAD, normalization of FEurate after correction of hyponatremia has not been fully explained. Some have implicated the V1 receptor activity of pitressin to explain the increase in FEurate in SIAD but others were able to induce SIAD with increased FEurate in healthy volunteers by dDAVP which lacks any V1 activity. In addition, the V1 activity of pitressin is an unlikely cause of the increase in FEurate in SIAD because pitressin levels are still increased when FEurate normalizes after correction of hyponatremia. (57) The same group has made commendable efforts to explain the increase in FEurate in SIAD by implicating chronic hyponatremia, but the normal FEurate reported in psychogenic polydipsia and reset osmostat where hyponatremia has been documented for up to 10 years do not support such an hypothesis. (32) At the present time, the relationship between serum sodium and FEurate remains unexplained in SIAD.

We also added the following on page 9, line 12 to explain the brisk diuresis in a patient with RSW who was given furosemide:

Because the proximal tubule is the main site of natriuretic activity in RSW, see below, the large sodium load that would ordinarily be transported by the distal nephron was inhibited by furosemide resulting in a markedly increased urine output and hemodynamic instability that required large volumes of saline to attain hemodynamic stability.

2. Because of its structure (a collection of case reports) the paper might be difficult to follow and in some cases it is repetitive.

Response:

We have elected to be repetitive on certain points because there has been a recurrent misconception among reviewers and readers of previous manuscripts.

3. I don't understand how they set 11% as a threshold to differentiate SIADH from CSW/RSW. Was it derived from case reports or from more structured studies? Equally, I don't understand the relation between normonatremia and FEurate > 11% (table 2-which is actually a figure). Is it supported by some data? What does it mean?

Response:

The delineation of normal values for FEurate has been somewhat elusive from our perspective and the question raised is a very good one. We initially started using FEurates of 5-10% as being normal but we encountered normal controls

and patients with established reset osmostat to have FEurates in the 4-5 and 10-11% ranges. We feel that setting the normal range from 4-11% has been most effective for clinical purposes as we have gained more experience with it over the years. We would prefer not to include a section to explain this as it appears to have taken hold in several of our recent publications.

4. There is a general lack of references in tables and figures (especially table 3- what are the sources of that data? and figures 3,5,6). 5. Figure 1 is adapted from Robertson GL Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. Am J Med 2006;119(7 Suppl 1):S36-S42. I think that authors should clearly indicate this reference and require permission to publish that figure.

Response:

The reviewer is absolutely correct in pointing out the deficiencies in adequately referencing tables and figures, especially the figure adapted from the work of Robertson. We were aware of this adaption in this and previous publications and made no corrections until now and will refrain from making the same mistake in future publications.

Minor considerations: 1. It should be noticed that some authors prefer the term SIAD (syndrome of inappropriate antidiuresis) instead of SIADH.

Response:

We have noticed this difference in referring to the syndrome as SIAD instead of SIAD in recent publications. In order to provide some uniformity in this and future publications, we will be happy to use SIAD instead of SIADH. The changes have been executed in this manuscript.

Reviewer #2.

In brief the authors of the review article seek to highlight key points in pathophysiology of SIADH, reset osmostat and RSW and present an engagingly readable article on the faulty assumption of the existence of cerebral salt wasting syndrome while giving a simple algorithmic approach to diagnosis of hyponatremia giving a prominent role to FEurate in this process. I think the concept is very original and would definitely consider the article to be published with minor revision on some specific points.

1. Introduction needs to be limited to one paragraph. 2. Reference for case of hyponatremia with bronchogenic carcinoma in first paragraph on subheading on “evolution of new algorithm” is missing.

Response:

The subject to be covered has been difficult to codify in one paragraph so we would respectfully like to maintain the same format. The entire description of the 5 cases later included in reference 21 includes the case of bronchogenic carcinoma but in order to avoid any confusion, we have added the reference at the end of the third line on page 6.

3. Some information on mechanism of why Feurate is not reduced with volume expansion in RSW would be instructive

Response:

FEurate is not reduced with volume repletion or even volume expansion in RSW. This raises an interesting question whether a volume depleted patient with RSW might have a "normal FEurate" at baseline and increase dramatically with volume repletion. We saw this with the hip fracture patient, reference 12, who happened to have a very high FEurate at baseline but increased to over 60% with volume repletion.

4. What about the rule of fractional excretion of phosphate in diagnosis of RSW?

Response:

The suggestion to include FEphosphate determinations to differentiate SIAD from RSW is an interesting one as we have previously proposed, that when FEphosphate is increased to >20%, it would favor the diagnosis of RSW. I spent several years studying phosphate transport by renal micropuncture and clearance studies in rats and have come to appreciate how saline infusions can rapidly increase FEphosphate by decreasing serum calcium and magnesium to increase PTH secretions The phosphaturia due to saline could be nullified by thyroparathyroidectmy, suggesting that the acute saline-induced phosphaturia was PTH mediated. In order to address this interesting question we have added the following to the manuscript starting at the bottom of page 23.

FEphoshate

We have previously stated that an increased FEphosphate >20% at baseline is consistent with RSW. (21) We have encountered only one patient with an increased FEphosphate with RSW, but while it might be potentially useful in differentiating SIAD from RSW, there are pitfalls that can alter it's value. We have demonstrated in a previous renal micropuncture study that phosphate transport is very sensitive to saline infusions, because parathyroid hormone (PTH) increases rapidly as calcium and possibly magnesium decrease in serum to stimulate PTH release. (66) Since saline is frequently administered to patients with hyponatremia, determinations of FEphosphate must be performed at baseline or analyzed according to whether or not the patient was receiving saline at the time the test was performed.

5. A little bit on the historical concept of CSW and the pitfalls in initial descriptions of cases of CSW may be given to underline the fallacious assumptions leading to this diagnosis

Response:

We point out in the first sentence under "Cerebral/renal salt wasting" that Peters et al did not prove RSW in their first report and refer the reader to our chapter, reference 49, for a more complete discussion of this interesting history of RSW. The manuscript is long enough as it is and we would prefer to introduce the idea but not provide a lengthy discussion of it. However, we provide sufficient data to rectify this fallacious assumption to prove convincingly that RSW does exist.

6. References in Table 3 are missing

Response:

The correction has been made to this inadvertent error.

Reviewer #3

I thoroughly enjoyed reading this manuscript. An idea presented is well backed-up by facts, literature and clinical reasoning. Well written with unnecessary details, physiologic concepts are well explained. The graphs are self-explanatory and clinically useful. Algorithms have a nice and logical flow. Much needed publication do decrease the existing confusion in this area of nephrology. I have only one suggestion to add another name for SIADH type D, "nephrogenic syndrome of inappropriate antidiuresis (NSIAD)", as this name is also used in the literature for gain-of function disorder. Excellent work.

Response:

We have incorporated the suggestion to add: "nephrogenic syndrome of inappropriate antidiuresis (NSIAD)".

We thank the reviewer for the favorable comments, which we greatly appreciate, given the nature of our conclusions. It is our hope that this manuscript will generate the same enthusiasm and open-mindedness to pursue and question present practices and pursue new insights into our approach to hyponatremia. We are not saying that our approach is the final answer, but we hope we have generated enough interest to improve our approach to hyponatremia and RSW.

Reviewer #4

In this review, Maesaka et al. propose differentiating SIADH to CSW/RSW by the use of FEurate.

Response: This manuscript emphasizes the difficult task of differentiating SIADH from C/RSW by providing an algorithm with supporting data to diagnose with greater ease reset osmostat, Addison's disease and prerenal causes of hyponatremia and different ADH responses to saline in SIAD and RSW.

Hyponatremia is a very common finding that needs a methodical approach for both diagnosis & therapy: on the first hand, water restriction and/or vaptans are necessary, on the other, salt infusion is. Here, authors suggest deciphering both diseases not only by clinical clues but by using FEurate. To support this point of view, they argue many case reports and pathophysiological evidences. This manuscript arose several questions/remarks I would like authors to answer. Self-citation ratio is unusually high: 15/59 quotes (about ?). I do realize authors are very involved in diagnosis & treatment of hyponatremia: self-citation is not evidence, it is only consistency

Response:

We have been aware of the number of publications which utilize FEurate in hyponatremic patients for a long time. The number of "self-citation" merely reflects our contribution to this area and the paucity of data from other investigators. We would have included other publications if they were available and would urge others to expand our efforts as stated in the last sentence of this manuscript.

"We feel we have accumulated enough data to support these final comments and to encourage others to expand our efforts to derive the true prevalence of RSW in a broad population of hyponatremic and normonatremic patients."

It is with this spirit that we are approaching our efforts to understand the intricacies of hyponatremia and we invite others to test our hypotheses or provide a better approach to hyponatremia.

Moreover, self-references are mostly case reports leading to make this review appear as a case reports collection and make it not suitable and easy to read (many repetitions). So, case reports are more illustrations than demonstration. In details:

Response:

There is some concern about the definition of "case reports". Reference 12 included a single case in Kidney International. This case unequivocally proved the existence of RSW. We proved its existence by demonstrating decreased intravascular volume by the gold standard radio-isotope dilution methods, using radio labeled serum albumin and chromium ^{51} labeled RBCs, plasma renin, aldosterone and ADH levels were all increased at baseline and when saline eliminated the more potent volume stimulus for ADH secretion, the coexistent hypo osmolality inhibited ADH secretion, which was undetectable at the time the urine became dilute and increased serum sodium to normal within 48 hours. This proves the appropriateness of ADH secretion in volume depleted patients such as RSW as noted in figure 4. UNa at baseline of only 6 mmol/L proved by actual data that a salt waster can have a low UNa if salt intake is reduced. The Uosm at baseline of 320 mosm/kg increasing to 590 four hours after initiation of saline therapy supports our contention that the low salt diet weakened the medulla for urine concentration and increasing after medullary packing with

sodium, figure 5. We have long believed that salt wasting can occur without cerebral disease but we now had enough data to prove the existence of RSW in a patient without cerebral disease to propose changing CSW to RSW for very important clinical reasons. In addition, the misdiagnosis with fluid restriction for 10 days before our consultation increased morbidity with loss of appetite, reduced salt intake and low UNa and provided evidence to support others, including ourselves, who reported fluid restriction being harmful to patients with RSW. This single case report unequivocally proved the existence of salt wasting and permitted us to make comments about UNa, misdiagnosis and mistreatemt of RSW by fluid restriction, the appropriateness of ADH secretion in RSW and a BUN to creatinine ratio that was not different from proven cases of SIAD. We now have the data to make credible conclusions in this and other papers. This "case report" is certainly not uninformative as it provides some valuable data to support conclusions that shed light on the evaluation of patients with RSW.

To respond further to the comment about case reports, it should be pointed out that reference 20, the first report of persistent increases in FEurate after correction of hyponatremia included 5 cases, suggesting that these patients represented a group of patients that were pathophysiologically different from SIAD. Reference 22 included 73 patients and reference 23 included 96 patients with AIDS. Reference 24 included 29 patients with intracranial diseases and 21 controls, reference 29 had 14 consecutive patients with normal FEurate who had a reset osmostat. 8 had spontaneously excreted dilute urines and 6 had a normal water-loading test with all 5 who had ADH determined at a time when the urine was dilute had unmeasurable levels of ADH. Reference 31 had 4 illustrative cases of how determinations of FEurate brought greater clarity to identifying the causes of hyponatremia. Reference 33 was a single case of psychogenic polydipsia to document a normal FEurate seen in this chronically hyponatremic patient due to psychogenic polydipsia. Reference 59 will have 62 patients and not included in the paper were 18 patients with Alzheimer's disease, 6 with vascular dementia and 11 controls.

In reference 13, we reported a case of RSW in a patient with pneumonia without cerebral disease. He had increased FEurate and also diluted his urine after initiation of saline infusion with correction of hyponatremia within 48 hours. This case was the impetus to prove inhibition of ADH secretion by saline in a volume-depleted hyponatremic patient with a hip fracture. Both cases diluted their urines at 3 AM in the morning so we missed our opportunity to determine plasma ADH levels in this patient. However, a normal water-loading test after volume repletion proved he did not have SIAD. We also reported two cases of SIAD in whom we performed blood volume studies by the same radio isotope dilution method to prove we were dealing with cases of SIAD and showed the inability of saline to dilute the urines or correct the hyponatremia, figure 6. The blood volumes were increased in these patients with SIAD which is consistent

with other studies in SIAD and the source for our data-driven comment that the term "euvolemic hyponatremia" to characterize patients with SIAD is incorrect. It should also be noted that the BUN to creatinine ratios were virtually identical in the two patients with RSW and SIAD which is contrary to proposal by others that this ratio is increased in RSW, but without supporting data. This may happen in a volume depleted patient with normal kidneys but as we have pointed out in a number of publications, you cannot generate a sufficient urea gradient in salt wasting to increase BUN in serum. It should be pointed out that all of our conclusions, many to correct misconceptions or clarify pathophysiologic phenomena, are based on data without conjecture.

FEurate also has been shown to be extremely helpful in the identification of patients with Addison's disease, a diagnosis that has been proposed by others to be very difficult to make when evaluating a patient with hyponatremia. The case of B cell lymphoma with edema and high FEurate is extremely important and interesting by possessing many instructive features of how RSW can occur in the presence of edema, ascites and pleural effusion.

Our "case reports" have always provided data that gave us the opportunity to arrive at some important conclusions and contributions to our approach to hyponatremia. We have gathered a large volume of data to:

1. ***support the proposal of a new algorithm that we feel is superior to the current volume approach.***
2. ***Provide a better method to differentiate SIAD from RSW***
3. ***Unequivocally reporting on patients with RSW without clinical evidence of cerebral disease to propose changing CSW to RSW for very important clinical reasons where outcomes should thus improve as the increase in morbidity and mortality associated with hyponatremia may in part be iatrogenic. The mini review on this subject published in Kidney International has received very favorable feedback. If anything, it should be stated that based on these reports of RSW occurring without evidence of cerebral disease the prevalence of RSW must be determined to improve clinical outcomes. It can no longer be considered "rare" until future studies come up with a true prevalence of RSW in a general population of hyponatremic patients.***
4. ***The value of determining FEurate in hyponatremic conditions is gaining acceptance and utility.***
5. ***RSW can occur in edematous conditions as we have done in several patients***
6. ***The ease by which a reset osmostat can be diagnosed and because of the normal FEurate and predictable response to water-loading, it should be eliminated as a subtype of SIAD and regarded as a separate entity.***
7. ***Eliminating reset osmostat as a subtype of SIAD would require and simplify the definition of SIAD, i.e. concentrated Uosm but not Uosm>100 mosm/kg..***

8. ***Other important contributions are the lesser importance of UNa in evaluating hyponatremic patients and BUN to creatinine ratio that has been erroneously stated as a means to differentiate SIAD from RSW.***

It is evident from the above data-driven conclusions and contributions that they are not trivial and the comment by this reviewer,

"So, case reports are more illustrations than demonstration"

Does not agree with our conclusions and contributions.

This reviewer has offered significant negative conclusions to our publications that have many paradigm shifting data-supported proposals, but this reviewer has not provided any data to support the negative comments. We will change our course immediately if this reviewer provides data to prove errors in our data and conclusions. It would not be possible for us to respond without the inclusion of data that support these negative comments.

We find it difficult to respond to and interpret the comment:

"self-references are mostly case reports---- So, case reports are more illustrations than demonstration"

Page 6: "this unique relationship between FEurate & natremia" What should be the pathophysiologic relationship?

Response:

This question has been addressed in the revised manuscript, which also includes a section on natriuretic factor in plasma of patients with RSW.

In nephron, natremia (= water balance) is mostly regulated by AVP in collecting duct, whereas uricemia (& FEurate) is in proximal tubule… This should be clearer in the manuscript. Page 7: the patient mentioned (ref 31) is told to exert hyponatremia (119mM) with spontaneous hypotonic urine (92 mOsm/kgH2O): so, it's not SIADH, it's water intoxication and normal renal response…I bet ADH secretion would have been close to…undetectable, as Uosm and ADH secretion are very closely correlated.

Response:

On page 7 lines 16-20 states the following:

"While a normal FEurate has effectively identified patients with RO, patients with psychogenic polydipsia also have a normal FEurate, but differentiating RO from psychogenic polydipsia can be readily made by the large volumes of water ingested and polyuria with dilute urines in psychogenic polydipsia, [table 2]. (33)"

We are well aware of this differentiation and by definition, patients with a reset osmostat dilute their urine with undetectable levels of ADH after a water load,. (suggest reading reference 29 carefully to note that 6 patients underwent water-

loading with undetectable levels of ADH at the time when the urine became dilute during a standard water-loading test.) Yes, it is not SIAD and it is water intoxication and normal renal response of the kidneys but patients with a reset osmostat develop hyponatremia with much less water intake because their osmostat has been reset at a lower osmolality. ADH was undetectable in reset osmostat but it required much less water to develop hyponatremia than in psychogenic polydipsia.

Page 8 & Figure 2: do you correlate ADH secretion and FEurate? If so, ADH could directly act on FEurate (i.e. proximal tubule PT)? What should be the physiological mechanism? Have ADH receptor been reported to be expressed by PT? Shouldn't it be mediated only by the correction of extracellular compartment? I'm not completely convinced by the figure 2: was FEurate measured at the same time all days?

Response:

It is unfortunate that figure 2 is being misinterpreted. We never state that ADH controls FEurate. We are well aware of where ADH acts and where urate is being transported. Figure 2, now figure 4, is extremely important because it demonstrates saline has a meager effect on FEurate. This reviewer is missing the point of this figure. FEurate decreased despite the volume of saline being administered, supporting the experimental data that saline does not affect urate transport very much. This has been demonstrated by very respectable investigators such as Steele, Diamond and Canon, as referenced, and a summary of their data is included in table 3.

Many complain that patients with hyponatremia are given saline so FEurate determinations are not very meaningful. This graph clearly demonstrates how saline only has a meager effect on FEurate and is consistent with published datas noted in table 3. We are unable to understand the meaning behind the following statement.

"Shouldn't it be mediated only by the correction of extracellular compartment?"

FEurate in SIAD remains an enigma for us as compared to FEurate in RSW. We have included a section on plasma natriuretic factor in RSW and the relationship between natremia and urate transport to shed some light on the status of FEurate in SIADH and RSW as noted above in response to reviewer #1.

Page 12: all over the manuscript, authors argue that "extracellular status cannot be accurately assessed by usual clinical criteria" but illustrate their case reports by such "clinical criteria" as of orthostatic hypotension and/or tachycardia…

Response:

It is unfortunate that the postural hypotension and reflex tachycardia has been taken out of context because there are so many other findings that collectively

prove the diagnosis of RSW. It was included in the case summary because we had such strong evidence for RSW, postural BP and pulse changes being consistent with it. We would be very hesitant to use this single finding without more compelling evidence for RSW in this patient. Instead, the reviewer should appreciate the manner in which the diagnosis of RSW was made and how the volume approach failed miserably. The high FEurate is against the diagnosis of CHF and other classic prerenal causes of hyponatremia. We are acutely aware of the failure of postural hypotension to be diagnostic of volume depletion. The case of SIAD with increased blood volume alluded to earlier, reference 13, had postural hypotension due to autonomic dysfunction.

Water restriction should not be an aim; the true one should be water balance negativation: the amount of water restriction should be correlated to osmotic ballast daily load… Page 17: what does mean SAH? SIADH?

Response:

The reviewer is correct. We failed to identify SAH as subarachnoid hemorrhage. This was corrected on line 3, page 17 as subarachnoid hemorrhage (SAH)---

Page 20: hyponatremia is the most common electrolyte disorder Page 29: table 2 starts with hyponatremia, if FEurate is >11% that leads to "normonatremia"…something is weird and should be corrected and/or clarified.

Response:

The dotted line connecting normonatremia and FEurate >11%, RSW does not include hyponatremia. There is no connection to hyponatremia. The legend states that this relationship has yet to be verified.

Page 30 table 3: where are the data from? How were them collected? Authors should distinguish sex, age, dietary salt intake and many other cofounders that could make the interpretation of FEurate hazardous (cf. Steinhauslin JASN 1994 & Cappuccio JAMA 1993).

Response:

The source of the data for table 3 is clearly placed in the right hand column under references. Based on these data, "dietary salt intake" appears to be irrelevant. We have not been able to implicate age and sex as major influences in determining FEurate. It is interesting that this reviewer is citing this situation where dietary salt intake is presumed to be making a difference in FEurate when we present ample experimental data by extremely competent invesrtigators showing very little effect of saline on FEurate. FEurate only increased to a meager 9.78 and 5.8% when FENa was very high at 4.43 and 8.2%, respectively. Figure 2 also illustrates how saline does not affect FEurate much but in SIADH, there is an intriguing relationship between FEurate and serum sodium, a mechanism which escapes us.

Moreover, un unpublished work has shown nycthemeral modifications of FEurate during a swiss (Lausanne) study in the general population. Authors should attenuate the importance of FEurate. Page 32 figure 1: regarding to the poor reproducibility of plasma AVP measurements, authors should refer (also) to Uosm. Do we really need AVP measurement for the diagnosis of SIADH?

Response:

The reviewer is misinterpreting the reason for including figure 3. It represents the work by Robertson et al where the 4 types of SIAD were proposed based on determinations of ADH levels and serum osmolality in hyponatremic patients. Unfortunately, these authors established the diagnosis of SIADH by being euvolemic by tenuous clinical criteria without determining volume. We comment on this shortcoming in the manuscript to support our proposal to eliminate type C as a subtype of SIAD. We do not advocate ADH determinations as being of much clinical value, especially in trying to differentiate SIAD from RSW at a time when they are hyponatremic. We determined ADH levels in salt wasters who diluted their urines while receiving isotonic saline infusions to prove the appropriateness of the increase in ADH levels in RSW and during a water-loading test in 6 patients with a reset osmostat.

We hope our responses are clear and answers each comment satisfactorily. We look forward to a favorable response.

Sincerely,

John K. Maesaka, MD