Format for ANSWERING REVIEWERS

March 24, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8990-review.doc).

Title: A Case of Inappropriate ADH syndrome: Hyponatremia due to Polyethylene Glycol Preparation

Author: Sun-Hye Ko, Chul-Hyun Lim, Jae-Young Kim, Seung Hun Kang, Myong Ki Baeg, Hyun Jin Oh

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8990

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Thank you for submitting a well organized report with interesting case. I finished the review process of this case report. This case report states a case of SIADH which seems to be associated with ingestion of PEG as a precolonoscopic preparation. I think this manuscripts is worthy of publication in that it is a rare case which can give several lessons to the readers. And the linguistic expression is simple and easy to understand. However, there are several points which to be considered.
Major point: 1. Please comment about the possible mechanisms of PEG to induce SIADH. 2. Isn't there any possibility for medicine (anti diabetics, antihyperlipidemics) to induce SIADH?
Minor point: 1. Please use MeSH term for SIADH.

Thank you for the thorough review.

1) We had included nonosmotic stimuli as a possible cause of increased ADH on page 6, line 18-20. However, as further clarification would help the readers, we have added "nonosmotic stimuli due to PEG" on page 7, lines 11.

2) While we could not find any reports of antihyperlipidemics associated with SIADH, there was one report of rosiglitazone being associated with SIADH. However, as her medical history did not include this drug, we believe that anti-diabetics can be ruled out as a cause. Also, as it is customary to stop taking anti-diabetics when fasting for fear of hypoglycemia, it is unlikely that these were the cause.

3) This has been corrected.

(2) The authors present a case report of a patient with a complication related to the colon cleansing

preparation for colonoscopy. The patient was admitted to the hospital after PEG colon cleansing preparation for colonoscopy because of an acute reaction leading to stupor requiring intensive care admission and was finally diagnosed with a syndrome of inappropriate secretion of antidiuretic hormone. PEG colon cleansing is considered safe and this is a rare condition induced by PEG colon cleansing for colonoscopy in a middle aged patient needing intensive care. The description of this exceptional complication is interesting and it is convenient to have knowledge in this regard. The presentation, the diagnostic work-up and the Discussion are adequate and supported by updated bibliographic data

Thank you for your thoughtful review and your positive comments.

(3) #1.Does the patient have excess fluid during bowel preparation that can cause the hyponatremia ? #2.The table 2 can be avoided. Instead, the authors may summarize the reported cases of hyponatremia during PEG use as table 2.

Thank you for your excellent comments.

1) While excess fluid during bowel preparation has been associated with hyponatremia in previous cases, our patient denied taking any excess fluids besides the prescribed 4 L.

We have clarified this on page 4, line 27 as, the patient ingested 4 L of a standard bowel preparation solution containing an isosmotic solution of PEG without any further fluid consumption.

2) We thank the reviewer for this excellent suggestion and we have changed table 2 in the revised manuscript as your comment.

(4) The authors report a case of acute symptomatic hyponatremia following bowel preparation with polyethylene glycol. This is and interesting report that merits reporting. Some further details and clarifications are needed. In the abstract is says that the patient was treated with normal saline. In the case report it says that the patient was treated with 3% sodium chloride. The abstract should be changed to 3% sodium chloride. More details about the evaluation of SIADH should be given. The serum potassium should be reported. Urine electrolytes with a fractional excretion of sodium and fraction excretion of urate should be reported if available. The exact cortisol value should be reported. A cortisol level should be high with hyponatremia, so normal or low normal value may be inappropriate. Additional history should be provided if she had symptoms of nausea, vomiting and headache preceding her hyponatremic seizure. They are almost universal findings of hyponatremic encephalopathy, so she may have had them. The patients weight should be included in the report. Mention of a dietary history, alcoholism should be provided if available. Alcoholics and patient with malnutrition are at increase risk for hyponatremia. It may be worth specifically mentioning that she was not on a thiazide diuretic or SSRI. Some details should be given as to how she was treated with hypertonic saline, the rate of correction in serum sodium.

Thank you for the thorough and enlightening review.

1) The abstract has been changed to 3% hypertonic saline per your suggestion on page 2, line 19.

2) The evaluation of SIADH including medical history and physical examination are on page 4, line 21 to page 5, line 6. Tests and their results are on page 5, line 7-16. The serum potassium, urine electrolytes, fraction excretion of sodium and urate have been added to Table 1.

3) The basal cortisol level had been reported on Table 2 with a value of 32.47 (μg/dL, normal range : 9.41–26.06). We have changed the text on page 5, line 11-12 to to the basal cortisol level was increased, which was consistent with hyponatremia. Also, as per the suggestion of reviewer #3, we have combined Table 2 into Table 1.

4) The patient complained of nausea and headache as well but did not have any history of vomiting. This has been added to the text on page 5, line 1.

While the patient was waiting for colonoscopic examination, she began complaining of nausea, headache, generalized weakness and sweating.

5) The weight has been added to the manuscript on page 4 line 21 as weighing 48kg.

6) Alcohol and nutrition history have been added to page 4, lines 22-23 as was well-nourished and did not have any history of alcoholism.

7) Her medical history has been updated on page 4, line 24 as but no history of thiazide diuretics or selective serotonin reuptake inhibitors.

8) Her hypertonic saline infusion rate and the times for checking her electrolytes have been added to page 5 line 18 and line 20. Her daily sodium levels can be found in Table 1.

(5) The manuscript reports an interesting severe complication of colonic cleansing with a PEG solution. There are two points that need clarification: (a) Even with elevated serum ADH levels, hyponatremia will nod develop unless there is substantial intake of water. It is probable that a part of the 4 liters consumed was absorbed. (b) PEG absorbed into the blood will cause an elevation in serum osmolality, some degree of hyponatremia from osmotic water transfer out of cells and an increase in osmolar gap (difference between serum osmolality measured by depression of freezing point, or by another colligative property measurement, and calculated osmolarity, which is the sum of the osmotic equivalents of sodium, urea and glucose). The measurement unit for osmolality is mOsm/kg and for osmolarity mOsm/L. Effective osmolarity (not osmolality) is the sum of the osmotic equivalents of sodium plus glucose. There is no laboratory measurement for effective osmolality avalailable to clinicians. The text states that the patient had a decreased effective serum osmolality of 233 mOsm/kg. The authors need to clarify whether the serum osmolality values represent direct measurement of osmolality (in which case it is total, not effective serum osmolality) or estimated effective osmolarity. In the second case, it is possible that total osmolality was initially higher if PEG were present in the serum. I also suggest strongly addition of serum glucose levels to Table 1. On another point of interest, if there were measurements of serum sodium concentration prior to the ingestion of PEG solution, they should be mentioned.

Thank you for the insightful and detailed comments.

1) While we agree with your analysis that part of the 4L of water may have been absorbed, relevant references show conflicting results. One study comparing PEG with OSP reported that the PEG group showed a slight but significant decreased serum creatinine levels, consistent with free water absorption. However, another study has reported that only 190-250mL of water are absorbed when 3-4L of PEG are ingested, which would be insufficient for hyponatremia to occur. We agree with your analysis that some of the fluid may have been ingested but that this may happen in only selected susceptible patients. What type of patients are susceptible needs more large-scale studies. This has been added to the discussion on page 6, lines 24-26 as below.

While some studies have reported absorption of water during PEG preparation, the amount has been reported to be small and not enough to cause symptomatic hyponatremia.

2) We agree with your point that this needed further clarification. The osmolality in the manuscript is direct osmolality and we have clarified this in the text on page 5, line 7 as total.

3) We thank the reviewer for this excellent suggestion and we have in the revised manuscript added the serum glucose level in Table 1.

4) Unfortunately, data regarding the patient's sodium levels prior to PEG ingestion were unavailable.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Chul-Hyun Lim, MD, PhD
Department of Internal medicine
College of Medicine
The Catholic University of Korea
505, Banpo-Dong, Seocho-Gu, Seoul, 137-701, Korea
E-mail: diluck@catholic.ac.kr
Tel; +82-2-2258-2045 / Fax; +82-2-2258-2055