Hyponatremia Due to an Interaction Between Hydromorphone and Desmopressin in a Patient with Central Diabetes Insipidus: A Case Report

Gillian Mazzetti MD, Oren Steen MD, Ameen Patel MD, Natalia McInnes MD

Abstract

There are case reports of opiate-induced hyponatremia thought to be mediated by increased secretion of antidiuretic hormone. We report a case of hyponatremia in a woman with central diabetes insipidus treated with desmopressin after receiving large doses of hydromorphone which suggests a different mechanism of opiate action.

A 55-year-old woman with central diabetes insipidus presented to hospital with an asthma exacerbation, later complicated by intestinal perforation requiring surgery. She received hydromorphone for pain for 3 weeks before surgery, but her requirements increased after surgery. Her serum sodium subsequently decreased, reaching a nadir of 119 mmol/L. Hydromorphone and desmopressin were discontinued, and she was managed with fluid restriction, a 3% saline infusion and intravenous vasopressin.

This suggests that hydromorphone may interact with desmopressin to potentiate its antidiuretic effect. Furthermore, hydromorphone may contribute to hyponatremia by another mechanism rather than by increasing production of antidiuretic hormone.

Résumé

Selon certaines observations cliniques, l’hyponatrémie provoquée par l’administration d’opiacés pourrait être modifiée par l’augmentation de la sécrétion de l’hormone antidiurétique. Nous présentons un cas d’hyponatrémie chez une femme atteinte de diabète insipide par carence en hormone antidiurétique et traitée à l’aide de desmopressine après avoir reçu d’importantes doses d’hydromorphone, ce qui nous amène à réfléchir à la possibilité d’un mécanisme d’action des opiacés qui serait différent.

Une femme de 55 ans atteinte de diabète insipide par carence en hormone antidiurétique se présente à l’hôpital faisant une crise d’asthme, qui sera ultérieurement compliquée d’une perforation intestinale nécessitant une chirurgie. Elle prend de l’hydromorphone contre
la douleur durant trois semaines avant la chirurgie, mais ses besoins augmentent après l’intervention. Son taux de sodium sérique décroît par la suite pour atteindre un nadir de 119 mmol/L. L’hydromorphone et la desmopressine sont alors interrompues, et la patiente est mise sous restriction liquidienne, perfusion de solution saline 3 % et vasopressine intraveineuse.

Ces éléments laissent à penser que l’hydromorphone peut interagir avec la desmopressine pour potentialiser son effet antidiurétique. De plus, il se peut que l’hydromorphone contribue à l’hyponatrémie par un mécanisme autre que l’augmentation de la production de l’hormone antidiurétique.

**Background**

Hyponatremia is defined as a serum sodium (Na) of less than 136 mmol/L. Symptoms from hyponatremia include headache, nausea, vomiting, and confusion; however, severe hyponatremia (Na < 120 mmol/L) can result in seizures, coma, and death. There are multiple etiologies of hypotonic hyponatremia (Table 1) with medications being a frequent contributing factor (Table 2).

There are case reports of patients developing hyponatremia while on opiates (Table 3), which are thought to increase antidiuretic hormone (ADH) secretion. We report a case of severe hyponatremia in a woman with central diabetes insipidus (DI) treated with desmopressin while receiving large doses of hydromorphone, which suggests that opiates’ effects on water balance may not be centrally mediated.

**Case Report**

A 55-year-old woman with central DI secondary to resection of a non-functioning pituitary macroadenoma presented to the hospital with an asthma exacerbation. She also had central adrenal insufficiency and hypothyroidism. Her medications on admission were desmopressin 0.8 mg PO TID, prednisone 10 mg PO qAM and 7.5 mg PO qPM, levothyroxine 0.1 mg PO daily, diclofenac/misoprostol 75/0.2 mg PO BID, rabeprazole 20 mg PO daily, domperidone 10 mg PO QID and salbutamol, ipratropium and budesonide/formoterol inhalers. She was admitted and treated with bronchodilators and high-dose corticosteroids. Her serum sodium on admission was 124 mmol/L. This was thought to be due to excessive desmopressin, which was confirmed by serum and urine osmolality measurements (267 mOsmol/kg and

### Table 1: Etiologies of hypotonic hyponatremia (modified from Adrogue et al. 2000 and Halperin et al. 1999)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive water intake or inappropriately low solute intake</td>
<td>Psychogenic polydipsia, beer potomania, “tea-and-toasters”</td>
</tr>
<tr>
<td>Hemodynamically mediated secretion of ADH</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td></td>
<td>Decreased intravascular volume - Congestive heart failure, cirrhosis, renal failure</td>
</tr>
<tr>
<td></td>
<td>Third spacing – bowel obstruction, peritonitis, pancreatitis</td>
</tr>
<tr>
<td>Excessive loss of solutes</td>
<td>Renal losses - Diuretics, adrenal insufficiency, osmotic diuresis</td>
</tr>
<tr>
<td></td>
<td>Extrarenal losses – vomiting, diarrhea, blood loss, excessive sweating</td>
</tr>
<tr>
<td>Inappropriate secretion of ADH (SIADH)</td>
<td>Malignancy – pulmonary tumours, mediastinal tumours</td>
</tr>
<tr>
<td></td>
<td>CNS disorders – stroke, hemorrhage, mass lesions, trauma, demyelinating disorders</td>
</tr>
<tr>
<td></td>
<td>Non-malignant pulmonary conditions – acute respiratory failure, infections, positive pressure ventilation</td>
</tr>
<tr>
<td></td>
<td>Drugs – refer to Table 2</td>
</tr>
<tr>
<td></td>
<td>Other – postoperative state, pain, nausea, HIV infection</td>
</tr>
</tbody>
</table>
Table 2: Examples of medications causing hyponatremia (modified from Adrogue et al. 2000 and Halperin et al. 1999)\(^{1,3}\)

<table>
<thead>
<tr>
<th>Affecting sodium and water homeostasis</th>
<th>Thiazides, indapamide, amiloride, loop diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affecting water homeostasis</td>
<td>Antidepressants (tricyclic antidepressants, SSRIs, monoamine oxidase inhibitors), antipsychotics (phenothiazines, haloperidol), antiepileptics (carbamazepine, oxcarbazepine, valproic acid), anti-neoplastic agents (platinum based, vinca alkaloids, cyclophosphamide), opiates</td>
</tr>
<tr>
<td>Increased hypothalamic production of ADH</td>
<td>NSAIDs, antiepileptics (carbamazepine, lamotrigine), cyclophosphamide, desmopressin</td>
</tr>
<tr>
<td>Potentiation of ADH effect</td>
<td>Venlafaxine, carbamazepine</td>
</tr>
<tr>
<td>Reset osmostat</td>
<td>ACE inhibitors,amlodipine,IVIG, ecstasy, sulfa, ciprofloxacın, rifabutin, amiodarone, propafenone, proton pump inhibitors, bromocriptine, bupropion</td>
</tr>
<tr>
<td>Rare causes (case reports)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Opiate-induced SIADH - Case reports\(^{4,7}\)

43 year old woman with a pulmonary neuroblastoma admitted with pain crisis from spinal metastases, on hydromorphone. Developed SIADH and hyponatremia (Na 119 mmol/L) with seizures two days after hydromorphone was exchanged for a fentanyl patch. The hyponatremia resolved with fluid restriction and discontinuation of fentanyl patch\(^{4}\).

79 year old woman admitted for elective knee replacement surgery, started on acetaminophen and tramadol postoperatively for pain management. Developed SIADH and hyponatremia (Na 110 mmol/L) with confusion and seizures on postoperative day #2. Hyponatremia resolved with fluid restriction, 3% saline and discontinuation of tramadol\(^{5}\).

92 year old woman, started on tramadol for pain control in hospital. Developed SIADH and hyponatremia (Na 117 mmol/L) three days after starting tramadol. Hyponatremia resolved with fluid restriction and discontinuation of tramadol\(^{6}\).

56 year old man admitted to hospital with intentional mixed acetaminophen, codeine and tramadol overdose. Developed hyponatremia (Na 119 mmol/L) and confusion on day 2 of admission. Mental status improved with fluid restriction, but patient signed out against medical advice before further studies could be completed\(^{7}\).

734 mOsmol/kg, respectively). Her desmopressin dose was decreased to 0.6 mg PO BID and her serum sodium normalized.

Her hospitalization was complicated by diverticulitis with an intra-abdominal abscess 3 weeks after admission. She was treated with antibiotics, stress dose corticosteroids and percutaneous drainage of the abscess. Hydromorphone was ordered on an as needed basis for analgesia. She became moderately hyponatremic (Na = 129 mmol/L), necessitating a reduction in her desmopressin to 0.4 mg PO BID. Five weeks after her admission, she developed acute abdominal pain with hemodynamic instability. A CT scan revealed perforation of a jejunal diverticulum requiring a laparotomy with a bowel diversion and drainage of intra-abdominal abscesses. She required a vasopressin infusion at 1 unit/hr for hypotension. Hydrocortisone 100 mg IV q8h was also started. She was nil per os (NPO) postoperatively, and her oral desmopressin was held. Her sodium on the vasopressin infusion was 145 mmol/L. Once she stabilized, vasopressin was discontinued and intranasal desmopressin was initiated.

Despite a rapid increase in the intranasal desmopressin to 10 \(\mu\)g every 4 hours, she developed polyuria and her serum sodium rose to 154 mmol/L, requiring a D5W infusion and re-initiation of vasopressin. She resumed oral desmopressin (0.8 mg PO BID) 5 days later after her sodium corrected. Hydrocortisone was weaned and she was restarted on prednisone 7.5 mg PO daily seven days after her laparotomy. She was transferred to the ward 9 days after surgery on a 2/3 D5W and 1/3 normal saline infusion at 75 mL/h. She was given regular doses of long acting hydromorphone along with subcutaneous doses prn. Her total daily doses of hydromorphone are detailed in (Figure 1).

Her sodium was 133 mmol/L upon transfer to the ward and continued to decrease despite reducing the dose of oral desmopressin (Figure 1). Her prednisone was increased to her preadmission dose of 10 mg PO qAM and 7.5 mg PO qPM. At this time, there was suspicion that her hyponatremia was related to her hydromorphone. Her intravenous fluids were...
Figure 1: Patient's serum sodium levels, total daily hydromorphone and desmopressin doses during her hospitalization. Total daily doses of hydromorphone were calculated as PO equivalency using a ratio of 1:2 (IV/SQ:PO).
changed to normal saline at 75 mL/h, her desmopressin dose was rapidly titrated down, and a suggestion was given to hold the prn hydromorphone. However, she continued to receive regular and prn doses of hydromorphone for pain, and her sodium reached a nadir of 119 mmol/L even after her desmopressin was held. At this time, her serum osmolality was 243 mOsmol/kg and her urine osmolality was 408 mOsmol/kg, suggestive of excessive ADH. Her hydromorphone and normal saline infusion were discontinued, and she was transferred back to the intensive care unit. She was fluid restricted to 500 mL/day and her desmopressin remained on hold. A 3% saline infusion was given at 10-20 mL/h for 7 hours until her sodium rose to 122 mmol/L, after which a vasopressin infusion at 1.0-1.5 U/hr was started for controlled correction of sodium over the next 24 hours. She was subsequently restarted on oral desmopressin. Two days later, her sodium was 136 mmol/L on desmopressin 0.8 mg PO BID with no intravenous fluids. Her serum sodium was stable for the remainder of her hospitalization. She was discharged home on desmopressin 0.7 mg PO BID with a serum sodium of 141 mmol/L.

Discussion

Upon presentation to the hospital, this patient’s initial episode of hyponatremia was likely related to excessive desmopressin dose. Her episode of severe hyponatremia occurred approximately 10 days after her laparotomy for intestinal perforation (Day 51 of admission). During the patient’s initial episode of hyponatremia, she was on several medications that could have contributed to hyponatremia (Table 2), including diclofenac/ misoprostol and rabeprazole.9 Diclofenac/ misoprostol was discontinued on Day 21 of admission, almost 1 month prior to the laparotomy. Rabeprazole was changed to pantoprazole shortly after admission, and since her dose was stable throughout her hospitalization, it is unlikely that this contributed to the subsequent severe hyponatremia.

Corticosteroids have been shown to inhibit an inducible cyclooxygenase in mice, which inhibits prostaglandin synthesis.10 Prostaglandins enhance both sodium and water excretion at the level of the kidney; therefore, inhibition of prostaglandins can lead to increased water retention and hyponatremia.11 NSAIDs, which inhibit prostaglandins, have been shown to induce hyponatremia in case reports independently12 and in combination with desmopressin,13 so it is possible that corticosteroids could contribute to hyponatremia by decreasing prostaglandin levels. However, our patient’s prednisone was either at the maintenance dose or lower during her severe episode of hyponatremia, and previous larger increases in her corticosteroids did not cause hyponatremia. We therefore concluded that corticosteroids were unlikely to have contributed to her severe hyponatremia.

During her severe episode of hyponatremia, urine and serum osmolality were suggestive of excessive ADH. New medications at the time of the severe hyponatremia included piperacillin/tazobactam, amiodipine, atorvastatin, intravenous heparin, and oral hydromorphone. Hydromorphone had been initiated several weeks prior to her laparotomy, and she became moderately hyponatremic requiring a decrease in her desmopressin dose. After her laparotomy, she received large daily doses of hydromorphone, and despite significant reductions in the desmopressin, she became severely hyponatremic. Since none of the other medications she was taking after her laparotomy had a temporal relationship with her hyponatremia, the most probable culprit medication to trigger the severe hyponatremia was hydromorphone.

Opiates have been theorized to cause ADH related antidiuresis for over 40 years. In 1968, a study on rats demonstrated that morphine produced a dose–response related decrease in urine flow.14 However, other animal-based studies have shown that chronic exposure to morphine actually caused increased urine output in rats.15 In humans, a fentanyl infusion in healthy male volunteers was shown to increase plasma ADH concentrations, but there were no urine volume or sodium measurements in the participants, and it is difficult to extrapolate if this could cause significant hyponatremia.16 A review article by Sezen (2003) reported that administration of a mu opioid agonist caused antidiuresis in some experimental conditions and diuresis under other conditions.17 Administration of kappa or delta opioid agonists appeared to cause a diuretic effect.17 An extensive review article by Vuong et al (2010) summarized that opiates can either stimulate or suppress endogenous ADH secretion, and these effects may be related to the fluid status of the subject.17 The theorized mechanism was that endogenous opioids act directly on the neurohypophysis to influence ADH secretion, likely mediated by mu and kappa opioid receptors.8

However, when rats congenitally lacking ADH were injected with morphine, they had decreased urine output, which suggests that morphine has an antidiuretic effect that is not ADH mediated.18 These mechanisms of action of opiates are unknown, but may involve opioid receptors in the kidney. When Kapusta et al (1991) infused a mu opioid receptor agonist directly into the left kidney of anesthetized rats, it resulted in decreased urinary flow rate and decreased sodium excretion from the left kidney compared to the right.19 It was hypothesized that this was due to the effects of the mu opioid receptor agonist on the renal sympathetic nerves. However,
a similar study by the same group using a different opioid agonist had shown that the antidiuretic effect of opioid agonists was independent of the renal sympathetic nervous system. Although the exact mechanisms of the antidiuretic effects of opiates have not been established, they likely involve both central and peripheral mechanisms.

**Conclusion**

This is a case report of opiates interacting with synthetic ADH to cause hyponatremia. At this time, mechanisms of this interaction remain unclear, but in this case of a woman with central DI, the effects of hydromorphone are likely mediated by a mechanism independent of central secretion of ADH. Given the potential consequences of severe hyponatremia, physicians need to be aware of this interaction between opiates and desmopressin.

**Competing Interests**

Authors GM, OS and AP have nothing to declare. Author NM has received research funding from Merck and AstraZeneca.

**References**


Message du rédacteur en chef (suite de la page 5)

Par conséquent, si l’on se doit d’agir en réaction à des articles comme celui d’Allen et coll., on devrait surtout veiller à enseigner aux étudiants en médecine et aux médecins résidents à mieux comprendre la façon d’interpréter l’ensemble des paramètres et des termes qu’ils rencontreront dans la documentation médicale ou au fil de présentations offertes lors de congrès ou de tables-ronde. Pour réussir, les apprenants/médecins dont la formation se poursuit tout au long de la vie devront améliorer leurs compétences en interprétation des données, en même temps qu’ils veillent à maintenir leurs connaissances à jour.

Mitch Levine