A woman with hyponatraemia, acidosis, aneuria and terminal ileostomy

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Introduction

It is not uncommon for more than one electrolyte and/or acid base disorder to be present simultaneously. In such a setting, determining the aetiological and pathophysiological factors involved can represent a real challenge. Failure to identify these factors thoroughly may lead to a disastrous outcome either from improper fluid and electrolyte management or from the ongoing consequence of an underlying illness left untreated. Here, we report the case of a patient who developed pronounced hyponatraemia, metabolic acidosis and hyperazotaemia. These manifestations were associated with true volume depletion and a severe decline in urine output. Rapid correction of plasma Na (PNa) was avoided by recognizing the important role played by hypovolaemia and high plasma urea (Purea) in free water excretion. In addition, a definitive cure could be offered to the patient after identifying the underlying illness responsible for the clinical manifestations.

Case

On March 21, 2000, a nephrological evaluation was requested for a 53-year-old woman with hyponatraemia and decreased consciousness. Her main past medical history consisted of: (i) an adenocarcinoma of the uterus in 1994, treated by hysterectomy and radiotherapy; (ii) a Dukes 2A adenocarcinoma of the colon in 1998, treated by total colectomy with terminal ileostomy; and (iii) a rectocutaneous fistula that closed spontaneously in 1999.

The patient was evaluated for cloudy urine, dysuria and suprapubic pain in another centre on March 10, 2000. Ciprofloxacin was initiated after obtaining a voided urine specimen. Three days later the patient was re-evaluated because of ongoing urinary symptoms. Analyses of the urine specimen collected on March 10 were consistent with contamination and, accordingly, the antibiotic was discontinued. An abdominal ultrasound later revealed mild hydronephrosis that was more pronounced on the left side. On March 16, 2000 the patient was transferred to the L'Hôtel-Dieu de Québec Hospital for further evaluation.

On March 21, 2000 she developed clouding of consciousness. Physical examination showed a body weight of 45.3 kg (normally 47 kg), a blood pressure of 114/65 mmHg supine and 80/30 mmHg standing, and an increased skin turgor. The jugular veins were non-distended, the heart and lungs were normal, and no abdominal mass or pain were noted. Review of hospital charts showed that the patient was oliguric between March 16 and March 20, and that she was anuric by March 21. Blood and/or urine tests were obtained between March 10 and March 21. As shown in Table 1, Purea increased several-fold between March 16 and March 21, and PNa decreased concomitantly from 128 to 110 mM. Plasma creatinine (Pcreat) values were also higher in March 2000 compared with a value obtained in November 1999.

1. What is the cause of the abnormally high urea-to-creatinine ratio seen in this patient on 21 March 2000?

Several conditions can lead to a high urea-to-creatinine ratio, as listed in Table 2. Our patient has clear evidence for dehydration. However, the 3-fold increase...
in P\textsubscript{urea} between March 15 and March 21 (Table 1),
accompanied by a decrease in P\textsubscript{creat} while the patient
was oligoanuric, indicates that other factors probably
account for the very high urea-to-creatinine ratio (480)
on March 21.

2. How would you classify the patient’s hyponatraemia?

As mentioned above, physical examination suggests
dehydration. Thus, hyponatraemia occurred in the
setting of hypovolaemia. A urinary osmolality (U\textsubscript{osm})
of 463 mOsm on March 13 (see Table 1), indicating
high levels of antidiuretic hormone (ADH) at the
collecting duct, and a urinary [Na] (U\textsubscript{Na}) < 5 mM,
which is consistent with hyperaldosteronism, both con-
firm that the effective circulating volume is reduced—
presumably by > 10\% considering non-osmotic
stimulation of ADH release.

It is pertinent to note that even if the patient has
normoosmolar hyponatraemia (calculated plasma
osmolality (P\textsubscript{osm}) 291 mOsm) she should be treated
for hypoosmolar hyponatraemia. Here, the P\textsubscript{osm} is
normal because of high P\textsubscript{urea}, which is an ineffective
osmole. Thus, the patient has true hyponatraemia and
rapid correction of this condition would place her at
risk for centropontine myelinolysis.

3. What is the cause of the aneuria?

Aneuria is often caused by urinary tract obstruction
and is then usually associated with hydronephrosis.
Here, interestingly, the progression to aneuria occurred
without any fall in the glomerular filtration rate
(GFR); P\textsubscript{creat} even declined slightly during the same
period. Hence, hydronephrosis in our patient could
have only occurred in the setting of mild urinary tract
obstruction and preserved diuresis; the symptom of
‘aneuria’ in such a context must indicate that urine is
not being excreted through the normal collecting
system. It appears very likely, therefore, that the
patient had a fistula between the urinary tract and a
hollow organ, e.g. the gut. Previous abdominal irradiation
for uterine carcinoma is a major risk factor for
internal fistula.

4. How would you demonstrate the fistula?

The hypothesis of an enteric fistula can be verified by
determining whether the volume of the ileostomy
drainage has changed, and by analyzing its content.
The presence of creatinine in the stools, for example,
would suggest the presence of an enterourinary
fistula. A radionuclide scan of the kidney showing
partially preserved renal function with abnormal urine
distribution would also suggest a fistula.

Review of the patient’s chart revealed that the
ileostomy bag had to be emptied more frequently in
the past week, and laboratory studies indicated that
creatinine was excreted in the gastrointestinal tract
(see Table 3). A radionuclide scan (shown in Figure 1)
and a retrograde cystography (Figure 2) confirmed the
presence of a fistula between a segment of the small
intestine (somewhere from the proximal jejunum to the
proximal ileum) and the bladder.

During the afternoon of March 21, an indwelling
bladder catheter and double J ureteral stents were
inserted by retrograde canulation. A perfusion of
isotonic saline (154 mM NaCl) was also started at
100 ml/h, providing a means of restoring the extra-
cellular volume. After these treatments, the amount
of urine excreted through the bladder increased
greatly. Serum and urine tests were obtained on
repeated occasions during the following 24 h (see
Table 4).

5. What is your main concern regarding the correction
of hyponatraemia?

The main concern is correcting P\textsubscript{Na} too rapidly
(> 0.5 mM/h). In this particular case, there are two
reasons why the risk for rapid correction is high. First,

We refer to Table 1 for the Blood and urine tests obtained between November 1999 and March 21, 2000.

We refer to Table 2 for the Causes of high urea-to-creatinine ratio.
the patient has non-osmotic ADH secretion due to volume depletion. Once this stimulus is no longer present as a result of proper rehydration, suppression of ADH will lead to aqueous diuresis. Secondly, the patient has high Purea (60 mM before treatment) with partially preserved GFR. As the circulating volume is re-established, the increase in urine output will lead to a higher than expected loss of free water because of urea-induced osmotic diuresis.

6. How would you prevent a rapid correction of the PNa?

The key to managing the water disorder in this patient is to administer free water or prevent excessive water diuresis as the effective circulating volume is being restored. Based on the data in Table 4, the saline perfusion led to loss of volume-mediated ADH secretion, sometimes before 6 p.m. when U_osm fell to 355 mOsm (had the patient not been azotemic, U_osm would have been < 100 mOsm).

Table 3. Tests performed on bladder urine and on ileostomy drainage fluid

<table>
<thead>
<tr>
<th></th>
<th>Na (mM)</th>
<th>K (mM)</th>
<th>Cl (mM)</th>
<th>Osm. (mOsM)</th>
<th>Creat. (μM)</th>
<th>Urea (mM)</th>
<th>NH₄⁺ (mM)</th>
<th>HCO₃⁻ (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urineb</td>
<td>50</td>
<td>19</td>
<td>81</td>
<td>576</td>
<td>1200</td>
<td>413</td>
<td>&gt; 12</td>
<td>0 or higher</td>
</tr>
<tr>
<td>Ileostomyc</td>
<td>44</td>
<td>34</td>
<td>44</td>
<td>277a</td>
<td>1900</td>
<td>119</td>
<td>0 or higher</td>
<td>&gt; 34</td>
</tr>
<tr>
<td>Ileostomyd (calculated)</td>
<td>28</td>
<td>21</td>
<td>28</td>
<td>174a</td>
<td>1200</td>
<td>75</td>
<td>0 or higher</td>
<td>&gt; 21</td>
</tr>
</tbody>
</table>

*These represent calculated values; direct measurements, here, were not available. aAnion gap in urine = Na + K – Cl = – 12 mM; osmolar gap = 576 – 552 = + 24 mM. Anion gap = + 34 mM. dAfter correction for water reabsorption based on the urine to ileostomy creatinine ratio. Here, the anion gap = + 21 mM. Osm., osmolality; Creat., creatinine. See Appendix 1.

Fig. 1. Radionuclide scan of the kidney using mercapto-acetyl-(glycine)³. A fast and intense uptake of the radioisotope is observed (a and b), followed by a rapid transit from cortex to medulla (b–g). Tracer also appears precociously in the pelvis (b) and the bladder (c); the collecting system, however, appears slightly dilated and there is stagnation of the isotope in the upper urinary tract, suggesting mild or partial obstruction. From (d) to (f), an abnormal shadow appears in the region of the vesical dome (see white arrows). From (f) to (g), an intensifying dark spot is seen on the right side of the bladder dome (see black arrow) and probably indicates a site of fistulization. From (e) to (h), another shadow (see open arrows) shows that an increasing amount of urine follows a ‘paraureteral’ route.

Fig. 2. Retrograde cystography. Note the significant amount of contrast material in the small intestine. The site of probable fistulization is marked with an arrow.

Free water can be administered as dextrose 5% but high infusion rates may lead to dextrose-induced osmotic diuresis. Free water can also be administered as enteric tap water, which is safe and effective. The initial rate of administration is estimated by calculating the ongoing free water loss by the kidney, which is equal to the urinary volume \((1–((UNa_\text{out})/C0_{Na}))\). Once a target \(P_{Na}\) is reached (maximum rise in \(P_{Na}\) 10–12 mM/day and 0.5 mM/h), the equation used to calculate the rate of free water administration will have to include all of the active osmoles given to the patient; this equation represents the net free water loss and is equal to the urinary volume \((1–((UNa_\text{out})/C0_{Na}))\). Another means of preventing rapid \(P_{Na}\) correction is, as mentioned above, to decrease free water diuresis. This may be done by administering desmopressin, which is safe and will effectively counteract water loss induced by urea and decreased ADH secretion. Free water diuresis can also be abated by using a loop diuretic to promote solute excretion. This type of intervention would only be effective if \(U_{\text{osm}}\) is > 350 mOsM.

To prevent rapid \(P_{Na}\) correction in our patient on March 21, it was decided to administer enteric tap water, furosemide and desmopressin all together because of very high \(P_{urea}\) and urinary urea (\(U_{urea}\)) at 2 p.m. (see Table 4) and at 6 p.m.; here, an osmolar gap of +216 mM, including only 11 mM of unmeasured cations (see Appendix 1), suggests that \(U_{urea}\) was very elevated. This treatment effectively prevented a rapid correction of the hypoosmolar disorder; as illustrated in Table 4, \(P_{Na}\) increased from 108 to 115 mM (+7 mM or approximately 1 mM/h) in the first 6 h and remained stable for the next 20 h.

### 7. How would you interpret and explain the acid–base disorder in this case?

After the nephrological evaluation on March 21, blood gas and urinary measurements were ordered (the result is shown in Table 4, line 1). Clearly, the patient has hyperchloremic metabolic acidosis. The calculated plasma anion gap, assuming normal albumin levels, is 15 mM, and the urinary anion gap is −12 mM. These calculated values suggest that \(NH_4\) is being excreted in the urine and that the cause of acidosis is extrarenal (see Appendix 1).

### 8. Is it possible to determine how the gut modified the urine to bring about the electrolyte and acid–base disorder?

To do so, one can compare the composition of the urine in the bladder with that of the urine in the ileostomy drainage bag. One is then comparing the urine before it enters the intestine and after it exits the intestine. Consequently, change in urine composition will result from transport processes between the entry and the exit sites. These assumptions, however, are only valid if minimum back leak of urine occurs from gut to bladder and if there is minimum contamination from fluid formed above the level of the fistula. Here, it was possible to obtain simultaneous measurements on both bladder and ileostomy specimens when the patient had had empty stomach for several hours (see Table 3). In addition, anemia at the time the specimens were collected suggests that significant gut-to-bladder back leak is unlikely.

### 9. What was the effect of the small intestine on urine composition with regard to water handling?

A 63% increase in creatinine (see Table 3) probably indicates that water is reabsorbed through the intestine’s epithelium. However, because the gut is also able to reabsorb creatinine [1], water reabsorption must have been higher than that predicted by the change in creatinine from bladder to ileum. Based also on the increase in \([Na]+[K]\) from bladder to ileum (69 vs 78 mM, respectively), it can be said that more water is being reabsorbed than effective osmoles. Interestingly therefore, the gut is able to extract additional free water from that formed by the kidney.
10. What was the effect of the small intestine on electrolyte handling?

After partial correction for water loss, it is seen in Table 3 (line 3) that [Na] and [Cl] decreased by > 40% in the ileostomy drainage, indicating partial reabsorption of these solutes. Therefore, the gut is not causing net salt wastage at this particular time. It is important to note, however, that 50% more Cl is reabsorbed compared with Na, indicating that an unmeasured anion is secreted in the intestinal lumen and/or that an unmeasured cation other than K is reabsorbed along with Cl. A positive anion gap of 21 in the stools confirms that an unmeasured anion is being secreted. High levels of urea in the ileostomy drainage also indicate that an unmeasured cation, namely NH₄ generated by urea-splitting bacteria, could be present in the intestinal lumen and partially reabsorbed with Cl. All these changes in the electrolyte composition of the urine are consistent with NH₄Cl/H-HCO₃ exchange.

Another abundant urinary solute, urea, is being reabsorbed as it comes into contact with the intestinal mucosa. In Table 3, for instance, a marked decrease in [urea] from bladder to small intestine (82% reduction) is observed. In interpreting this result, however, it is important to remember that some urea is probably reabsorbed as NH₃ following degradation by intestinal ureases, and that water reabsorption may have been underestimated (as mentioned above). In this patient, therefore, it appears that the gut avidly reabsorbed urea, thereby contributing to hyperazotaemia.

The last important urinary solute, K, remained at the same concentration after its passage down the small intestine. Although incomplete correction for water reabsorption may have also overestimated [K] in the ileostomy drainage, relatively normal P_K between March 16 and March 21 suggests that the gut had a minimal effect on net K transport.

11. What are the main electrolyte and acid–base disorders resulting from urinary diversions?

Ureteroileostomies commonly cause an increase in urinary acidification with or without mild hyperchloremic acidosis. The pathophysiology of this complication has been reviewed by McDougall et al. [3] and it appears to involve the Na/H and the HCO₃/Cl antiporters, which enable the parallel reabsorption of NH₄ and Cl in exchange for H and HCO₃ [4–11]. Severe metabolic acidosis is infrequent because rapid drainage of urine into a collecting bag limits the contact time between urine and intestine.

Hyperazotaemia has not been described frequently with urinary diversions using ileal segments; this may also have to do with the relatively small surface of intestinal mucosa to which urine is exposed with this type of diversion. For example, animal models in which long ileal diversions are performed do tend to accumulate urea in their plasma, presumably from hepatic detoxification of the reabsorbed ammonium [5].

Jejunal conduits are now seldom used because of an unacceptably high frequency of complications. Indeed, 40–65% of the patients develop hypernatraemia, hyperkalaemia, acidosis and azotaemia, the so-called ‘jejunal conduit syndrome’. The severity of these abnormalities in this syndrome also appears to correlate with the length of the conduit [12,13]. The pathophysiological basis of this syndrome has not been rigorously determined but there is some evidence for NaCl wasting leading to a reduction in the extracellular volume and for high levels of potassium reabsorption [13,14]. Transport systems that may be involved include K channels, K–Cl symporters and the Na pump.

12. Can you identify the site of fistulization: proximal ileum or jejunum?

Our patient underwent a fistulectomy within the following weeks. During surgery, cement-like adhesions were found throughout the abdominal cavity and around the posterior wall of the bladder dome. These retroperitoneal adhesions were probably responsible for mild urinary tract obstruction seen in this patient. Because of the distorted anatomy, it was not possible to identify the exact site of fistulization, although the surgeons felt that the enteric opening was in the middle part of the small intestine.

Based on the preoperative evaluation, and because the phenotype of electrolyte complications did not fit that of either type of urinary diversion described earlier, it is possible that our patient had a mixed jejunal and ileal ‘conduit-like’ syndrome. Such a syndrome may have occurred from fistulization of the bladder into the jejunum, forcing urine to come into contact with the mucosa of both jejunum and ileum. Presumably, the very large surface of mucosa to which the patient’s urine was exposed would account for the severity of the hyperazotaemia.

13. Based on the available information, can you propose a pathophysiological chain of events that led to the complications presented by the patient?

To explain the electrolyte disorders in our case, the following scenario can be proposed: NH₄Cl and urea excreted by the kidney were reabsorbed throughout the jejunum and the ileum; NH₄Cl/H-HCO₃ counter-transport led to hyperchloremic metabolic acidosis, stimulating renal NH₄ excretion further, while pure urea absorption (and also hepatic NH₄ production) led to hyperazotaemia. High P_urea, in turn, caused osmotic diuresis with secondary dehydration, accentuating azotaemia further. Dehydration led to increased thirst and ADH hypersecretion, causing dilution of the extracellular fluid and hyponatraemia. It is also interesting to point out that in this case, the gut was able to extract additional free water from that formed in the kidney, which probably contributed to the
hypoosmolar disorder. To explain the absence of hyperkalaemia in our case, we propose that the effect of a jejunal diversion was counteracted by the effect of an ileal diversion.

Several lessons can be drawn from this unique case:

1. An increase in the urea-to-creatinine ratio is not always caused by prerenal azotaemia.
2. Normoosmolar hyponatraemia in the presence of hyperazotaemia should be treated as hypoosmolar hyponatraemia.
3. If associated with hypovolaemia, the latter condition carries a high risk for overly rapid correction of $P_{Na}$.
4. Administration of desmopressin or urinary electrolyte enrichment with furosemide are two options to prevent excessive water diuresis.
5. Patients with intestinal conduit and vesicointestinal fistulae are prone to electrolyte disorders, the severity of which varies according to the length of the gut exposed to urine.
6. $NH_4\text{-Cl}$ reabsorption in exchange for $H\text{-HCO}_3^-$, and urea reabsorption are important mechanisms for the development of acidosis and dehydration in patients with urinary diversions.
7. The small intestine has high capabilities for net free water reabsorption.

Conclusion

The case presented here offers unique insights into the role of the gut in water and electrolyte handling, and into the pathophysiology of complications related to urinary conduits. To our knowledge, a combined jejunoileal conduit-like syndrome resulting from an acquired vesicojejunal fistula has not been described previously, although a similar case without hyponatraemia was published recently [15].

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References


Appendix 1

The urine anion gap and the osmolar gap are often used as surrogate measures of urine $NH_4^+$ [16]. They may also indicate the presence of $HCO_3^-$ which is another unmeasured urinary solute that can be excreted in substantial quantities under specific circumstances. It is important to mention, however, that these indirect determinations may represent poor substitutes for direct measurements. Indeed, a recent study by Kirschbaum et al. [16] showed that in addition to $NH_4^+$, $SO_4$ and $PO_4$ urinary excretion could also be quite variable in patients with metabolic acidosis. Thus, the difference between $[Na^+ + K]$ and $[Cl]$ may not correspond only to the difference between $[HCO_3^-]$ (as the unmeasured anions) and $[NH_4^+]$ (as the unmeasured cations). The results of the urine anion gap and the osmolar gap must be interpreted with caution.