Case Report

Intensive care treatment of severe mixed metabolic acidosis

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We report a case of severe metabolic acidosis associated with acute renal failure and septicaemia following treatment with maximal therapeutic doses of metformin and diclofenac. On the second day of intensive care the patient deteriorated with respiratory insufficiency and abdominal pain during continuous renal replacement therapy. A laparoscopy revealed a perforated cholecystitis with abscess formation. The patient regained renal function and recovered.

Intake of diclofenac 5 days before this episode could have been the main cause of renal insufficiency and metabolic acidosis in this patient and could also have delayed surgical treatment by masking early clinical signs of perforated cholecystitis. The renal failure may also have caused metformin and lactate to accumulate, contributing to the mixed pattern of metabolic acidosis.

Acid-base balance and electrolyte changes were rapidly normalized by continuous renal replacement therapy.

Accepted for publication 8 September 2004

Key words: Acute renal failure; continuous renal replacement therapy; diclofenac; metabolic acidosis; metformin; non-steroidal anti-inflammatory drugs.

Profound and rapidly emerging metabolic acidosis, often indicating severe underlying disease or injury, is not uncommon in modern intensive care. There are two major forms of metabolic acidosis with different therapeutic strategies. Organic metabolic acidosis is caused by metabolizable anions, whereas non-organic or mineral metabolic acidosis results from non-metabolizable anions.

We report a case of mixed organic and non-organic profound metabolic acidosis associated with acute renal failure (ARF) and septicaemia in a patient under treatment with metformin and diclofenac.

Case report

Abdominal pain and diclofenac
A 75-year-old woman was brought to the hospital with a 7-day history of increasing upper abdominal pain, nausea, anorexia and mental confusion, and 2 days of anuria. Her medical history included a gall-stone disease, mild hypertension and type 2 diabetes mellitus, treated with 1 g of metformin three times daily, i.e. maximal therapeutic dosage. Serum creatinine was 80 μmol l⁻¹ 6 months ago.

Five days earlier, a general practitioner had prescribed oral diclofenac, a non-steroidal anti-inflammatory drug (NSAID), 50 mg three times daily, i.e. maximal therapeutic dosage, for suspected cholecystolithiasis and had also arranged for an ultrasound investigation. Earlier the same day the patient had made a second visit to her general practitioner because of increased abdominal pain, and rectal diclofenac was added to her ongoing oral diclofenac treatment. Before arrival she deteriorated and fainted.

Severe metabolic acidosis
In the emergency room the patient was unable to answer simple questions. The respiratory rate was 40 min⁻¹, heart rate 40–50 min⁻¹, and due to peripheral vasoconstriction and hypothermia of 34.8°C the peripheral saturation of oxygen was unmeasurable and there was no palpable peripheral pulse.

Arterial blood gas analysis revealed a severe combined organic and non-organic metabolic acidosis with a pH of 6.9, and BE −30, lactate 10, sodium 119,
Potassium 8.4, chloride 89 and bicarbonate 4.8 mmol l\(^{-1}\). The observed Anion Gap (AG\(_o\)), defined as \(((\text{Na}^+)+[\text{K}^+])-(\text{Cl}^-+[\text{HCO}_3^-])\), was 34 mmol l\(^{-1}\).

The blood glucose level was 25 mmol l\(^{-1}\). A low PaCO\(_2\) of 1.8 kPa indicated considerable respiratory compensation. A high PaO\(_2\) of 43 kPa resulted from administration of oxygen by a face mask. The patient was anuric with a plasma potassium of 8.5 mmol l\(^{-1}\), and the ECG showed flattened P-waves, wide QRS complexes and peaked T-waves.

In the intensive care unit (ICU) the serum creatinine was 980 µmol l\(^{-1}\), serum urea 35 mmol l\(^{-1}\), platelet count 335 \(\times 10^9\) l\(^{-1}\), and C-reactive protein (CRP) 69 mg l\(^{-1}\). Invasive systolic blood pressure was 50–60 mmHg.

**Therapeutic strategies**

In the ICU the vital signs rapidly deteriorated with falling blood pressure and mental confusion. No full patient history was yet available, and the preliminary diagnosis was a severe mixed metabolic acidosis, probably due to ARF and possibly also to metformin-associated lactic acidosis (MALA) with intravascular volume depletion as a contributing factor (Table 1).

Solutions of albumin 20% and acetated Ringer’s solution were rapidly infused to increase intravascular volume. Calcium chloride was given together with rapid-acting insulin to counteract and reduce the hyperkalaemia.

For removal of potassium, lactate and metformin from the circulation, continuous veno-venous hemodiafiltration, (CVVHDF; Prisma™, Gambro, Sweden) was started with a blood flow of 180 ml min\(^{-1}\), a dialytic fluid (Haemosol®; Hospal) flow (Qd) of 2500 ml h\(^{-1}\) and a substitution fluid (Haemosol®; Hospal) flow of 2000 ml h\(^{-1}\).

The metabolic acidosis (Fig. 1), ECG pattern and systemic haemodynamic values almost normalised during the initial 12 h of continuous renal replacement therapy (CRRT).

**Septicaemia and abdominal exploration**

Progressive respiratory insufficiency resistant to non-invasive ventilation followed, and shortly after an endotracheal tube was inserted for mechanical ventilation. The clinical picture and haemodynamic parameters sampled from a PiCCO® catheter (Pulsion Medical, Munich, Germany) resembled those of early septicaemia, and colloidal and vasopressor therapy with norepinephrine was instituted. Imipenem was chosen for initial therapy, and blood cultures later revealed a bacillus strain. Increased upper abdominal tenderness was revealed on clinical re-examination, and a laparoscopy revealed abscess formation from a perforated gall-bladder, which was removed.

Postoperatively the patient improved and regained urine production within 36 h. Mechanical ventilation was continued for 3 days and CRRT for 5 days. Recovery was uneventful following a period of polyuria. Twenty-eight days after the event, creatinine and urea levels were normalized at 75 µmol l\(^{-1}\) and 5.4 mmol l\(^{-1}\), respectively.

**Discussion**

Differentiation between organic acidosis, reflecting underlying metabolic pathology, and non-organic acidosis, where protons are accumulated due to renal failure, is important for adequate management, but AG\(_o\) cannot be used to differentiate between these entities. An increase in AG\(_o\), i.e. high-anion-gap acidosis (in this case 34 mmol l\(^{-1}\)), is found in organic acidosis (in this case caused by circulatory failure and septicaemia), but also in non-organic acidosis with retention of mineral anions, apart from chloride, commonly due to ARF, as in this patient. Hypoalbuminaemia, a common finding in ICU patients, may confound interpretation of acid-base data, e.g. AG\(_o\), since anion properties of albumin should be considered in these calculations. The actual albumin level has been recommended (1) to be included for calculation of an adjusted anion gap value, AG\(_{adj}\) according to the formula AG\(_{adj}\) = AG\(_o\) + 0.25 \(\times\) (normal albumin) - [observed albumin]. In this patient, with an actual plasma albumin of 28 g l\(^{-1}\) and an assumed normal value of 36 g l\(^{-1}\), her moderate hypoalbuminaemia would have little impact on her adjusted anion gap compared with the observed value.

**Table 1**

<table>
<thead>
<tr>
<th>Possible causes of metabolic acidosis</th>
<th>Type of acidosis</th>
<th>Potassium level</th>
<th>Lactate level</th>
<th>Anion gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin-associated lactic acidosis (MALA)</td>
<td>Organic</td>
<td>N/(+)</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Splanchnic ischaemia</td>
<td>Organic</td>
<td>N/(+)</td>
<td>+/++</td>
<td>++</td>
</tr>
<tr>
<td>NSAID-induced acute renal failure</td>
<td>Non-organic</td>
<td>++</td>
<td>N</td>
<td>+/++</td>
</tr>
<tr>
<td>Acute renal failure induced by septicaemia or hypovolaemia</td>
<td>Non-organic</td>
<td>++</td>
<td>+/++</td>
<td>+/++</td>
</tr>
</tbody>
</table>
Metabolic acidosis in the ICU

Fig. 1. Changes in plasma potassium (●), lactate levels (▲), base excess (○) and pH (△) during continuous renal replacement therapy (CRRT) from early after admission and during the next 5 days in the case of severe metabolic acidosis, renal insufficiency and extensive hyperkalaemia reported here. The periods of mechanical ventilation (MV), CRRT and surgery are also indicated.

36 vs. 34 mmol l\(^{-1}\). Approximately 6 h after the start of CRRT, the AG\(_o\) had been reduced from 34 to 21 mmol l\(^{-1}\). Simultaneously, the strong ion difference (SID), i.e. the total anion concentration of bicarbonate (in mmol l\(^{-1}\)), albumin (g l\(^{-1}\)) and phosphate (mmol l\(^{-1}\)), calculated according to the formula \([HCO_3^-] + 0.28\cdot[Alb] + 1.8\cdot[Pi]\) (2), was 24, i.e. approximately 15 mmol l\(^{-1}\) less than the normal value (2). This difference of 15 mmol l\(^{-1}\) corresponds to the concentration of unidentified strong anions [XA\(^-\)], including lactate, and cannot be directly measured in plasma. Nevertheless, as shown here, this difference is easily approximated from the gap between cations and anions, including SID and chloride, in the individual patient. Considering the plasma lactate of 4.3 mmol l\(^{-1}\), the remaining anion gap of 11 mmol l\(^{-1}\) mainly reflects the accumulation of non-organic acids due to ARF. Although a mixed pattern of metabolic acidosis in this patient – indicated by the considerable difference between [XA\(^-\)] and lactate levels – was obvious already early in the clinical course, we consider the Stewart approach (3) partially outlined above to be useful in selected cases of metabolic acidosis (2, 4).

As with other NSAIDs, diclofenac inhibits the constitutive non-inducible isoenzyme COX-1 with possible adverse effects like platelet and renal dysfunction. Any NSAID, regardless of COX isoenzyme selectivity, may contribute to ARF with non-organic metabolic acidosis (5, 6).

Metformin is an oral antidiabetic drug frequently used by patients with type 2 diabetes mellitus. A serious adverse effect of metformin treatment, with a mortality rate of approximately 50% (7), is the development of lactic acidosis of type B, characterized by a blood lactate greater than 5 mmol l\(^{-1}\), decreased blood pH and an increased AG\(_o\). Lactate is a small molecule (molecular weight 90 Da) and can readily be removed from the circulation by intermittent haemodialysis (IHD). However, no increased risk for lactic acidosis under metformin treatment for type 2 diabetes mellitus could be statistically confirmed in a recent meta-analysis, concluding that the main determinant for lactic acidosis is the underlying systemic dysfunction rather than the treatment (8).

In intensive care patients with ARF, CRRT is considered superior to IHD with respect to haemodynamic stability (9). The IHD utilizes a Qd of 500 ml min\(^{-1}\), and apart from removing ions or molecules like H\(^+\), K\(^+\) and lactate, also adds bicarbonate.

The use of CRRT with lactate-free replacement fluid has been reported to be successful in lactic acidosis (10). In this case we used the highest possible Qd of our equipment, 2500 ml h\(^{-1}\), corresponding to 42 ml min\(^{-1}\). Already after 3 h of CRRT our patient had a significant decline in lactate levels and in base deficit, and after 6–8 h these variables were almost normalized.

In conclusion, we present a case report of profound mixed metabolic acidosis and ARF, presumably resulting from a regular intake of metformin for diabetes mellitus and of diclofenac for cholecystolithiasis. The case also highlights the risk of using an NSAID for pain relief in a patient with possibly compromised cardiovascular function and/or septicemia. A therapeutic observation worth considering is the rapid normalization of electrolyte and acid-base balance by CRRT despite its lower clearance properties compared with IHD.

Acknowledgements

We are indebted to Hilding Gnoûters for inspiration, and to Gifinformationscentrale (Swedish Poisons Information Centre) Stockholm, and the staff at the Medical Library of Helsingborg Hospital for professional assistance.

References


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