Hyperpnoea and ketonuria in an HIV-infected patient

Quiz

A 32-year-old HIV-infected man of African origin presented to our emergency department with a 3-day history of nausea, vomiting, abdominal pain and muscular pain. The patient was alert and oriented. He denied alcohol, tobacco and illicit drug use. His current medications were lopinavir, Epivir, stavudine and trimethoprim-sulfamethoxazole.

In the emergency room, he was afebrile; blood pressure 110/70 mmHg and pulse rate was at 110/min. Kussmaul breathing at a frequency of 32 breaths/min was noted. The patient’s pulse oximetry revealed a saturation of 99% on room air, and capillary blood sugar was 150 mg/dl. Electrocardiogram showed normal sinus rhythm. The patient had lost 5 kg in weight during the previous 3 months. The abdominal, lung, cardiovascular, neurological examinations were all unremarkable. Laboratory investigations on admission revealed the following abnormalities: pH: 7.49; PaCO2: 18 mmHg; PaO2: 125 mmHg; bicarbonates: 10 mmol/l; potassium: 3.7 mmol/l; calcium: 2.1 mmol/l; sodium: 125 mmol/l; lactates: 8 mmol/l (normal value <2.0 mmol/l); glucose: 2.4 mmol/l; CK: 3195 UI/ml (controls <220 UI/l); ASAT: 59 UI/l (normal range 5–35 UI/l) and ALAT: 35 UI/l (normal range 5–40 UI/l). Other pertinent labs were blood urea of 33 mg/dl and creatinine of 1.3 mg/dl. HbA1c was normal. Urinary dipstick analysis was unremarkable, except for an important ketonuria (4+) without glycosuria.

The patient received intravenous glucose and L-Carnitine. Highly active anti-retroviral therapy (HAART) was discontinued. The metabolic abnormalities gradually normalized over the following 2 days. However, the patient’s lactate level remained elevated at 2–3 mmol/l.

Questions

What is your diagnosis?
Answer to the quiz on the preceding page

In this case, arterial blood gases showed severe alkalosis with decreased serum bicarbonate level and elevated lactic acid level. This data suggested three possibilities: primary respiratory alkalosis with compensatory decrease of bicarbonate and elevated lactates, primary lactic acidosis with compensatory decrease in respiratory CO^2_2 tension, and mixed disorder involving respiratory alkalosis and metabolic acidosis.

First hypothesis: primary respiratory alkalosis with compensatory decrease of bicarbonate and elevated lactates

At any given moment, the extracellular pH may be predicted on the basis of the Henderson–Hasselbach formula: pH = pK_a + log (bicarbonate/CO^2_2). The buffering response to acute hypocapnia is biphasic. First, hypocapnia in the extracellular fluid results in an immediate decrease in the intracellular fluid CO^2_2 concentration, resulting in the transfer of chloride ions from the intracellular fluid to the extracellular fluid compartment. This chloride ion efflux, accompanied by a decrease in the concentrations of bicarbonate ions in extracellular fluid, is called tissue buffering [1]. Secondly, the renal response (inhibition of renal tubular reabsorption of bicarbonate) can begin within minutes and takes effect over a period of hours to days [1]. With long-term exposure, in the presence of normal renal function, the bicarbonate-ion level begins to fall, and the pH decreases but does not reach the normal value of 7.40 with an increase in arterial blood pH of 0.1–0.3 units.

Hypocapnia may increase the metabolic demand of tissue through cellular excitation or contraction. Finally, alkalosis—especially respiratory alkalosis—inhibits the usual negative feedback by which a low pH limits the production of endogenous organic acids such as lactate [2,3]. Alkalosis raises blood lactate concentration by a pH-mediated effect on the enzyme phosphofructokinase, which converts fructose-6-phosphate to fructose-1,6-bisphosphate, an intermediary in the glycolytic pathway [4]. In vivo, this rise is usually mild, with lactate levels usually around 1.5 to 3 mEq/l [5,6]. Therefore, alkalaaemia explains only partially the significant serum lactate elevation in our patient. Furthermore, elevated lactate level persisted, despite arterial blood gases normalization. Hyperventilation results from increased afferent drives from the chemical receptors in the lung or arterial walls. In our case, however, evidence of pneumonia, pulmonary oedema or heart chamber enlargement was not seen on chest X-ray nor electrocardiogram. Furthermore, there was no apparent dyspnoea and the arterial oxygen tension was normal. Cerebral MRI was also normal. The patient had not received any respiratory-stimulating drugs, and the abnormal respiration rate persisted during sleep. On the other hand, the hypothalamus is considered a metabolic centre, and it controls ketone metabolism [7]. This may explain high ketonuria in our patient. However, there was no hypothalamus lesion on CT scan in our patient.

In conclusion: primary respiratory alkalosis per se does not explain all abnormalities.

Second hypothesis: primary lactic acid acidosis (complicating NRTIs therapy) with compensatory decrease in respiratory CO^2_2 tension

Nucleoside reverse transcriptase inhibitors (NRTIs) in use some months earlier and persistently elevated lactate levels despite correction of acid–base abnormalities, were arguments in favour of this hypothesis. Indeed, this was confirmed by the improvement of clinical condition following withdrawal of anti-retroviral drugs and administration of L-Carnitine [8]. The reported incidence rate of lactic acidosis, an uncommon but serious complication of anti-retroviral therapy, vary from 1.3 to 10/1000 person-years on HAART [9,10]. Carnitine is derived from γ-hydroxy-β-butyric acid. Although a regular diet is the primary supply of carnitine, endogenous synthesis is possible from sulphated amino acids [11]. Carnitine levels are decreased in HIV-infected patients through several mechanisms, including malabsorption, increased excretion, over-consumption of energy in fatty acids metabolism and the use of drugs, including NRTIs [11,12]. Carnitine is an important compound for the mitochondria bio-energetic system that may modulate apoptosis. It has also been observed that carnitine could reverse the mitochondrial toxicity of NRTIs in vitro and in vivo [11–14]. Finally, a nomograph of acid–base equilibrium showed that the actual PaCO^2_2 level was extremely low, below the standard deviation of the estimate of PaCO^2_2 at the given bicarbonate level (18 instead to 23 mmHg) [15]. This means that the decrease in PaCO^2_2 was not due only to respiratory compensation for metabolic acidosis.

In conclusion: lactic acidosis can explain most of the presenting features. However, the blood alkalosis with the associated important decrease in CO^2_2 remains unexplained.

Third hypothesis: the acid–base disturbances in this case represent a mixed disorder of metabolic acidosis and respiratory alkalosis

Krendel et al. [16] suggested that local cerebrospinal fluid (CSF) acidification resulted in an increase in hydrogen ions and stimulated chemosensitive respiratory neurons inducing respiratory alkalosis. Although we did not measure the CSF lactate level, we supported the CSF lactic acidosis theory, as there were no classic causes for respiratory alkalosis found in our patient (see subsequently). CSF lactic acidosis may explain medullary chemoreceptor stimulation and cause the associated hyperventilation and CO^2_2 wash.

In conclusion: metabolic lactic acidosis is induced by NRTIs and a mixed respiratory alkalosis is related to compensatory decrease in respiratory CO^2_2 tension and CSF lactic acidosis in our patient.
Conflict of interest statement. None declared.

References


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