Lesson of the Week

Acetazolamide and symptomatic metabolic acidosis in mild renal failure

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Acetazolamide is widely used to treat glaucoma because it reduces the rate of formation of aqueous humour.¹ It should be remembered, however, that acetazolamide inhibits carbonic anhydrase in the renal proximal tubular epithelium, which results in a bicarbonate diuresis. Indeed, acetazolamide was first introduced to treat glaucoma because of this diuretic action.² We report on two patients in whom acetazolamide induced a symptomatic metabolic acidosis. Both patients were elderly and had mild renal impairment.

Case reports

Case 1—An 82-year-old woman presented with acute glaucoma three months after a central retinal vein thrombosis occurred and was treated with acetazolamide 250 mg twice a day. Eight days later she was admitted to hospital in a severely confused state, complaining of breathlessness, weakness, and dizziness. She had a tachypnoea of 35/min. Her finger nails showed the pigmentation of chronic renal failure.

The arterial hydrogen ion concentration was 62 nmol/l (pH 7.21), actual bicarbonate 6 mmol(mEq)/l, and base excess -19 mmol(mEq)/l. Blood gas tensions and venous electrolyte concentrations are shown in the table. The plasma chloride concentration was 114 mmol(mEq)/l and the calculated anion gap was 17.6 mmol(mEq)/l. Despite this definite metabolic acidosis the urine pH was 6. There was no ketonuria, and blood glucose concentrations were normal. There was no clinical or bacteriological evidence of infection. Treatment with acetazolamide was discontinued and a total of 250 mmol of 1.4% sodium bicarbonate was given intravenously. The following day the arterial hydrogen ion concentration had fallen to 35 nmol/l (pH 7.46), bicarbonate

Acetazolamide treatment for glaucoma may cause serious symptoms owing to metabolic acidosis if the patient has unrecognised renal impairment

was 15.0 mmol(mEq)/l, and base excess -6 mmol(mEq)/l. Her clinical condition rapidly improved, although the plasma creatinine concentration fell only slightly (table). A normocytic normochromic anaemia of 8.7 g/dl was noted, and an intravenous pyelogram showed small kidneys, suggesting end-stage nephritis.

Case 2—A 92-year-old man with mild senile dementia was admitted to hospital with a four-day history of acute narrow-angle glaucoma. The plasma electrolyte concentrations on admission are shown in the table. He was treated with pilocarpine eye drops and acetazolamide 500 mg at first, followed by 250 mg three times a day. One week later he became very confused and restless and had a tachycardia of 120/min and a tachypnoea of 40/min. He had a mild fever of 37.4°C but no clinical or bacteriological evidence of infection. The arterial hydrogen ion concentration was normal at 41 nmol/l (pH 7.39), but the actual bicarbonate of 12 mmol(mEq)/l and base excess of -10 mmol(mEq)/l indicated an underlying metabolic acidosis. The urine pH was 7.

Treatment with acetazolamide was withdrawn, and he made a rapid clinical recovery interrupted two days later by an attack of pyrophosphate crystal arthropathy in the right knee, which was confirmed by polarised light microscopy of the synovial fluid. The table shows that plasma electrolyte concentrations returned to normal for him.

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Discussion

Both patients suffered acute confusion one week after starting treatment with acetazolamide, which was associated with biochemical evidence of a metabolic acidosis. In the patient in

Blood gas tensions and venous electrolyte concentrations in two patients

Day	Venous plasma concentration of					Arterial blood concentration of			Arterial gas tension	
	Na ⁺ (mmol/l)	K ⁺ (mmol/l)	HCO ₃ ⁻ (mmol/l)	Urea (mmol/l)	Creatinine (μmol/l)	H ⁺ (nmol/l)	HCO ₃ ⁻ (mmol/l)	Base excess (mmol/l)	PaO ₂ (kPa)	Paco ₂ (kPa)
Case 1										
1	135	4.6	8.0	32.4	552	62	6.0	-19	17.5	2.2
2	140	4.3	18.3	34.7	573	35	15.0	-6	13.6	3.0
19	127	4.7	21.0	15.7	410					
Case 2										
1	137	3.7	28	9.5	186	41	12	-10	12.1	2.7
8	136	3.3	19	11.8	176					
15	139	3.5	27	13.3	162					

Conversion: SI to traditional units—Na⁺, K⁺, HCO₃⁻, base excess: 1 mmol/l = 1 mEq/l. Urea: 1 mmol/l ≈ 6.0 mg/100 ml. Creatinine: 100 μmol/l ≈ 1.13 mg/100 ml. PaO₂, Paco₂: 1 kPa ≈ 7.5 mm Hg. pH = -log₁₀ H⁺ concentration in mol/l.

case 2 the acidosis was compensated for by hyperventilation to correct the arterial hydrogen ion concentration, but presumably cerebral acidosis stimulated this.³ A poor correlation between hydrogen ion concentration in the blood and cerebrospinal fluid has been described in acetazolamide-induced acidosis.⁴ Recovery from the acidosis coincided in both patients with clinical recovery.

There was clinical, haematological, and radiological evidence of pre-existing renal failure in the patient in case 1, and direct biochemical evidence of pre-existing renal failure in the other patient. Acetazolamide treatment was associated with worsening acidosis only and little or no deterioration in other aspects of renal function and no evidence of acute renal failure.⁵ The acidosis in the second patient may have precipitated the attack of pyrophosphate arthropathy by reducing the activity of synovial alkaline phosphatase, which may metabolise pyrophosphate.⁶ This has not been reported, though a case of acute gout (the type of crystal was not confirmed) after treatment with acetazolamide has been reported.⁷ Acetazolamide normally produces a mild self-limiting acidosis.⁸⁻¹⁰ A few cases of serious acidosis have been reported in elderly patients, diabetic patients, and patients with renal disease.^{4, 11-14} One patient who had liver damage in addition to acidosis died.¹⁵

Acetazolamide is excreted by the kidneys, and the frequency of the dose should be adjusted for patients in renal failure.^{16, 17} In short-term studies of acetazolamide treatment in renal failure definite retention of hydrogen ions was found in patients with urea concentrations that were comparable to those in our patients.^{18, 19} In the only long term-study of acetazolamide treatment in renal failure a serious acidosis frequently developed.²⁰ It is not clear how the acidosis develops in these patients. It has been suggested that in some patients with renal failure excessive bicarbonate may be lost by the tubules.²¹ Acetazolamide would be expected to inhibit the partial reabsorption of this bicarbonate.

The manufacturers of acetazolamide warn that it should not be given to patients with "idiopathic renal hyperchloraemic acidosis," but few doctors would relate this obsolete phrase to their elderly patients with mild, acquired renal failure. Many elderly patients have unrecognised mild renal failure, and we recommend that before treatment is started with acetazolamide urea and electrolyte concentrations should be measured—as was indeed suggested when acetazolamide was introduced.² If renal function is impaired then further estimations should be carried out and the bicarbonate concentration watched carefully. If this

should fall to 20 mmol(mEq)/l or below, oral sodium bicarbonate may be given¹⁰ or, preferably, acetazolamide should be discontinued.

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What might cause excessive belching? Can air entrapment in the oesophagus cause difficulty in swallowing or cardiac extrasystoles? What treatment is advised?

Excessive belching can result only from abnormal entry of air into the oesophagus or stomach. Fermentation in the stomach is not enough, and intestinal air does not travel backwards. Entry is by aerophagy, in which the upper oesophageal closing mechanism is opened and negative intrathoracic pressure sucks air into the oesophagus. Only rarely does it enter the stomach, and probably only when hiatal herniation can occur. The air is expelled by contraction of the thoracic cage. The stimulus to aerophagy is a sensation of abdominal distension that is a paraesthesia, not a reality, and the patient tries to help up the phantom gas, inadvertently letting it in first. Any obstruction in the oesophagus may produce a sensation of an "air lock" or air entrapment that is not a reality. Occasionally, air swallowed with a bolus will pass down through a stricture ahead of the bolus, which plugs the hole momentarily. Many patients with an obstructed oesophagus from stricture or achalasia belch a small bubble after each swallow. Air is not entrapped above an obstruction because it can be instantly released into the mouth, nor is it entrapped in aerophagy. Extrasystoles may cause a sensation that is misinterpreted as wind needing to come up, leading to aerophagy. There is no good evidence that aerophagy or oesophageal obstruction causes extrasystoles. Treatment is to

remove the stimulus to aerophagy. Sometimes holding the chin on to the chest stops the aerophagy sequence because it is then difficult to open the upper oesophageal closing mechanism.—D A W EDWARDS, reader in gastroenterology, London.

Correction

Lithium treatment and preoperative fluid deprivation

An error appeared in this article by Professor M Schou (7 November, page 1253). The lesson should have read: If patients with lithium-induced polyuria must abstain from drinking before an operation because of the narcosis they should be given intravenous fluids the night before the operation.

ABC of Alcohol: Alcohol in the body

We regret that an error occurred in this article by Drs J B Saunders and A Paton (21 November, p 1380). In the table showing the alcohol content of and peak blood concentration after various drinks the peak blood concentration after 12 single measures of spirits should have read 240 mg/100 ml, not 140.