PAPERS AND SHORT REPORTS

Metabolic acidosis induced by carbonic anhydrase inhibitors and salicylates in patients with normal renal function

R A COWAN, G G HARTNELL, C P LOWDELL, I McLEAN BAIRD, A M LEAK

Abstract

Two young patients with unimpaired renal and hepatic function were found to have developed metabolic acidosis after treatment for glaucoma and joint pain with a combination of salicylates and carbonic anhydrase inhibitors in normal doses.

Carbonic anhydrase inhibitors appear to interact with salicylates to produce serious metabolic acidosis in patients without the predisposing factors generally considered to constitute risks. It is recommended that treatment combining salicylates and carbonic anhydrase inhibitors is either kept to a minimum or avoided.

Introduction

Acetazolamide is commonly used to treat glaucoma but may cause metabolic acidosis in the elderly,[1] patients with renal or liver failure,[2-4] and diabetics.[5] Severe acidosis has not, however, been described in young patients with normal renal and hepatic function who take carbonic anhydrase inhibitors. We describe two such patients who developed metabolic acidosis during treatment combining normal doses of salicylates and carbonic anhydrase inhibitors. Both patients had juvenile chronic arthritis with antinuclear antibodies and chronic bilateral iridocyclitis, which had led to the development of cataracts, secondary glaucoma, and partial loss of vision.

Department of Medicine, West Middlesex University Hospital, Isleworth, Middlesex

R A COWAN, MB, BS, senior house officer
G G HARTNELL, BSC, MRCP, registrar
C P LOWDELL, BSC, MRCP, registrar
I McLEAN BAIRD, MD, FRCP, consultant physician

Rheumatology Unit, Canadian Red Cross Memorial Hospital, Taplow, Bucks

A M LEAK, BSC, MRCP, senior registrar

Correspondence to: Dr G G Hartnell.

Case reports

Case 1—The symptoms of an 8 year old boy with juvenile chronic arthritis had been well controlled with prednisolone, indomethacin, and aloxiprin 3 g daily. The carbonic anhydrase inhibitor dichlorphenamide 25 mg thrice daily was added to control recurrent episodes of glaucoma. Serum salicylate concentration was stable at around 150 mg/l. Aloxiprin was increased to 3·6 g daily to control worsened joint pain. One month later he was admitted to hospital because of drowsiness, vomiting, and hyperventilation. Serum electrolyte concentrations were: urea 5 mmol/l (30 g/100 ml); sodium 143 mmol (mEq)/l; potassium 3·6 mmol(mEq)/l; bicarbonate 10 mmol(mEq)/l; and salicylate 250 mg/l. The hospital where he was treated did not have facilities for measuring arterial blood gas tensions. Dichlorphenamide and aloxiprin were stopped. The acidosis was corrected with intravenous saline and sodium bicarbonate, and he made a complete recovery. Subsequently, he began more treatment with dichlorphenamide and naproxen, but no further acid base abnormalities occurred.

Case 2—A 22 year old woman with an 18 year history of juvenile chronic arthritis had been treated for several years with prednisolone, indomethacin, salsalate 3·5 g daily, and, intermittently, acetazolamide. After an exacerbation of her arthritis the dose of salsalate was increased to 4 g/day and acetazolamide 250 mg four times daily was added for glaucoma. Ten days later she was admitted to hospital unconscious and hyperventilating (respiratory rate 38 breaths/min). No localised neurological signs were present, and the results of a lumbar puncture to investigate neck stiffness were normal. Serum electrolyte concentrations were: sodium 143 mmol/l, potassium 4·2 mmol/l, and bicarbonate 3·8 mmol/l. Arterial blood gases had a pH of 7·33; carbon dioxide tension was 1·04 kPa (7·8 mm Hg), oxygen tension 17·4 kPa (131 mm Hg) with a base deficit of 17·6 mmol(mEq)/l. Salicylate concentration was 262 mg/l. The metabolic acidosis was corrected with intravenous saline and sodium bicarbonate, and she made a good recovery. Acetazalomide was continued to control her glaucoma but salicylates were stopped, and she remained well.

Discussion

We believe that this is the first report of an interaction between salicylates and carbonic anhydrase inhibitors causing serious metabolic acidosis in patients with normal renal function. Previous reports of carbonic anhydrase inhibitors causing severe acidosis have been of patients in whom other predisposing factors have been present.[1-5] In fact, acetazolamide has been used to treat salicylate poisoning.[6]

The mechanism of this interaction, though not clear, may be related to hypocapnia induced by salicylate leading to a reduction in the carbon dioxide available for production of bicarbonate. Carbonic anhydrase inhibitors produce metabolic acidosis by their action on carbonic anhydrase in the proximal and distal renal tubules. This blocks excretion of hydrogen ions, producing an alkali urine. As acidosis develops, however, an increase occurs in the resorption of bicarbonate, which is independent of the activity of carbonic anhydrase; this limits the degree of acidosis that can be attributed to inhibition of carbonic anhydrase alone.[7] In cases of renal failure the blocking of carbonic anhydrase activity leads to increasing acidosis because the capacity of the tubules to resorb bicarbonate is inadequate. Toxic doses of salicylates that result in metabolic acidosis are likely to have a detrimental effect in combination with carbonic anhydrase inhibitors. Serum salicylate concentrations of over 300 mg/l are required to produce a metabolic acidosis,[8] and in our two patients salicylate concentrations were below this at the time of presentation. Therapeutic doses of salicylates cause limited respiratory alkalosis, but this fall in carbon dioxide tension has little effect on the production of bicarbonate unless the action of carbonic anhydrase is blocked, when the production of bicarbonate is much lower than if either mechanism were operating in isolation. The lack of bicarbonate ions would prevent excretion of hydrogen ions, thus causing increasingly severe acidosis.

Therapeutic doses of salicylates and carbonic anhydrase inhibitors given together seem to be capable of inducing potentially fatal metabolic acidosis in patients with normal renal and hepatic function. In such patients the doses should be kept to the minimum or salicylates replaced by an unrelated anti-inflammatory agent. Serum bicarbonate concentrations should be estimated regularly and especially after any increase in the dosage.

These cases have been reported to the Committee on Safety of Medicines.

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Trends in sales of drugs for asthma in New Zealand, Australia, and the United Kingdom, 1975-81

G KEATING, E A MITCHELL, R JACKSON, R BEAGLEHOLE, H REA

Abstract

As part of an investigation into the recent epidemic of deaths from asthma in New Zealand, trends in the sales of drugs for asthma in New Zealand, Australia, and the United Kingdom during 1975-81 were examined. Data on sales of drugs were obtained from an international pharmaceutical market research organisation. A striking increase in sales of sympathomimetic aerosols, steroid aerosols, and theophylline per caput occurred in all three countries, with the greatest increase occurring in New Zealand. Sales of sodium cromoglycate also increased in New Zealand and the UK but fell in Australia. By 1981 New Zealand had the highest sales of all these drugs per caput.

Explanations for the rising mortality from asthma in New Zealand despite large increases in drug sales need to be explored. Although the temporal association between mortality and sales of drugs suggests that direct drug toxicity is unlikely, there may be more subtle adverse effects of drug use.

Department of Health, Wellington, New Zealand
GABRIELLE KEATING, MB, DCOMH, registrar in community medicine

School of Medicine, University of Auckland, Auckland, New Zealand
E A MITCHELL, FRACP, DCH, senior lecturer, department of paediatrics
RODNEY JACKSON, MB, DCOMH, Medical Research Council training fellow in epidemiology, department of community health
ROBERT BEAGLEHOLE, MD, FRACP, associate professor of epidemiology, department of community health

Chest Medical Unit, Greenlane Hospital, Auckland, New Zealand
HAROLD REA, MD, FRACP, physician

Introduction

New Zealand is experiencing a new epidemic of fatal asthma that is not occurring in other developed countries.[1] Between 1974 and 1980 the mortality from asthma in people aged 5-34 almost doubled in New Zealand but remained relatively stable in five other countries including Australia and the United Kingdom. Admissions to hospital and sales of drugs for asthma have also increased in New Zealand over the past two decades.[2] In children under 15 admissions to hospital increased about 10-fold during 1964-80; in people aged 15-44 there was a fourfold increase during this period. The concern that the increasing use of aerosol bronchodilators may have contributed directly or indirectly to an epidemic of deaths from asthma in the 1960s[3-5] led to a sug-