Metabolic consequences of salbutamol poisoning reversed by propranolol

Administration of salbutamol, a β_2 -adrenoreceptor agonist, is associated with several metabolic consequences including disturbances of carbohydrate, lipid, and potassium homeostasis.¹ Although the importance of these effects during therapeutic use of the drug is not clear, severe hypokalaemia has been reported after salbutamol poisoning.² As evidence suggests that the metabolic effects are due to β_2 -adrenoreceptor stimulation³ it seems logical to treat these results of salbutamol poisoning with a β_1 -adrenergic antagonist. We report a case in which salbutamol-induced hypokalaemia was managed successfully with propranolol.

Case report

A previously healthy 17-year-old girl was admitted having taken an unspecified quantity of salbutamol 2 mg tablets (Ventolin) three hours previously. On admission she was agitated and tremulous and had a tachycardia of 156 beats/minute: an electrocardiogram showed the rhythm to be sinus. Blood pressure was 110/60 mm Hg. Gastric lavage was performed with no appreciable tablet return. Initial investigation showed a plasma potassium concentration of 2.3 mmol (mEq)/l. Arterial pH was 7.46 and plasma glucose concentration 7 mmol/l (126 mg/100 ml).

She was given 10 mg propranolol intravenously at a rate of 1 mg/minute every three minutes. Throughout this period cardiac rate and rhythm were monitored. Serial venous blood samples were withdrawn with minimal stasis and without forearm compression via an indwelling cannula. Plasma was separated within 30 minutes and stored at 4°C until analysis. Plasma potassium concentration was measured by flame photometry and plasma glucose concentration by a glucose oxidase method (YS1 model 23A; Yellow Springs, Ohio).

Changes in plasma potassium and glucose concentrations and heart rate during administration of propranolol (1 mg/minute every three minutes).

The figure shows the changes in plasma potassium, glucose concentrations, and heart rate. Plasma potassium concentration rose during administration of propranolol (2.3 to 2.8 mmol/l) while plasma glucose concentration fell (7.0 to 5.3 mmol/l; 126 to 96 mg/100 ml). A significant inverse correlation between these variables was found ($r = -0.896$, $p < 0.001$). Heart rate fell promptly during the initial stages of administration of propranolol, but further dose increments did not produce a continued fall. No significant changes in systolic or diastolic blood pressure were noted either during or after the procedure. Plasma potassium concentration remained satisfactory: two hours after administration of propranolol it was 4.08 mmol/l and eight hours later 3.52 mmol/l. The subsequent clinical course was uneventful. At no stage was potassium supplementation given.

Comment

Although the therapeutic action of salbutamol depends on selective action on β_2 -adrenoreceptors, at higher doses the drug loses specificity and also acts on β_1 -adrenoreceptors.⁴ Hypokalaemia seems to be due to a shift in potassium from extracellular to intracellular space, possibly secondary to direct β_2 -adrenoreceptor-mediated alteration in membrane permeability.⁵ Other metabolic effects (for example, glycogenolysis) may reflect a β_1 -agonist effect.³

Thus it seems reasonable to use a non-selective β -agonist to treat the metabolic consequences of salbutamol poisoning: we have shown this to be safe and effective. The hypokalaemia responded rapidly to administration of propranolol and plasma potassium concentrations remained satisfactory thereafter.

An alternative explanation for changes in potassium concentration during administration of salbutamol is increased cell membrane sodium/potassium exchange induced by β_1 -adrenoreceptor-stimulated changes in circulating insulin and glucose concentrations: evidence that practolol, a predominantly β_1 -adrenergic antagonist, can prevent the hypokalaemia induced by salbutamol has been cited in favour of this.³ The close correlation between changes in plasma glucose and potassium concentrations seen during non-selective β -adrenergic blockade in our patient suggest that these metabolic effects of salbutamol may share a similar mechanism. Although statistical relations based on data derived from one person must be viewed with caution, this finding may offer some support to the concept that the changes in potassium concentration seen with salbutamol are secondary to changes in carbohydrate metabolism.

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(Accepted 18 June 1982)

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Aminophylline toxicity in the elderly

In the past four months I have encountered three cases of drug toxicity in medical wards in Leicester that were due to aminophylline overdose.

Case reports

Case 1 was a 67-year-old woman who had been found by the police wandering in the streets and was admitted to a medical bed from the accident and emergency department and initially diagnosed as having chronic organic syndrome of unknown type. It was then found that she had an empty bottle labelled aminophylline, and though concentrations could not be measured it was felt that she was possibly a case of overdose. On examination she appeared feverish, with poor attention and concentration, loss of retention, vague ideas of persecution, and some loss of remote memory.¹ She was given supportive treatment only, and four days later had made a complete recovery, well within the normal range for her age. She admitted that she had taken the medication deliberately. There was evidence of reactive depression, mainly since the marriage of her son, who had left home, leaving her alone. She responded well to supportive help and counselling.

Case 2 was a 62-year-old woman who was referred to the psychiatric outpatient unit by her general practitioner and was receiving Navidrex-K (cyclopenthiazide and potassium) and aminophylline orally. She showed disorientation, loss of attention and concentration, loss of retention, and poor remote memory. She also showed some disinhibition. All medication was discontinued and within four days she had improved, showing some residual loss of attention and concentration and some little loss of retention, which has now almost totally cleared. She denied any deliberate overdose, but on questioning and examination of her drug schedules it became clear that she had been consuming increasingly large amounts of aminophylline, taking about six times the recommended dosage—that is, about 1200 mg daily.²

Case 3 was an 83-year-old widow who had alarmed her family by increasing signs of depression after her husband's death. She was found one morning in a very disorientated state by her niece and was rushed to the accident and emergency department and admitted as a case of self-induced poisoning with aminophylline; two empty prescription bottles for the substance were found in her house. She showed disinhibition, aggressiveness, suspicious feelings, lack of attention and concentration, and a lack of retention; she was also disorientated. She had fever and a fine tremor. These symptoms continued despite the use of thioridazine 25 mg as required (about 75 mg used) and then four days after admission her state suddenly cleared completely, leaving a remarkably well-orientated, articulate, elderly lady, who described her feelings of grief over the death of her husband and who has since responded to psychiatric help.

Comment

These cases all have a remarkably similar presentation, but it must be noted also that they mimic closely organic reactions to such things as urinary infection or hypoglycemia and also the most common chronic organic syndromes such as multi-infarct dementia. The problem is, of course, that serum concentrations of aminophylline may be difficult to obtain, so if there is any suspicion of toxicity by aminophylline it might be best simply to give supportive treatment and observe for three or four days and delay any investigations. There are few published reports on aminophylline toxicity³ and no previous description of what appears to be a discrete and specific response, at least in the elderly.

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(Accepted 18 June 1982)

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Steatorrhoea after tetracycline

Tetracycline is regularly used to label the bone mineralisation front before bone biopsy.¹ Having observed transient steatorrhoea in several patients undergoing bone biopsy, we investigated the relationship between steatorrhoea and oral tetracyclines by measuring faecal fats shortly after the patients had received oral tetracycline.

Subjects, methods, and results

All 27 patients studied were under investigation in a metabolic ward for either osteoporosis or osteomalacia. Of these, four were Asian and 23 white; 12 were men and 15 women, aged 19-68. All individual diet and drug regimens except tetracycline were kept unchanged. Daily fat content of the diets was maintained between 176 mmol/day (50 g/day) and 246 mmol/day (70 g/day) for all patients. None complained of bowel disturbance, and renal function was normal in all patients. Oral tetracycline or demethylchlortetracycline were given as bone markers. Thirteen patients were given single doses of 2 g tetracycline; 14 were given demethylchlortetracycline in doses of 150 mg six hourly for between two and four days.

Faecal fats were collected over either three or four days and estimated from 10 ml of homogenates using the method of King,² the normal faecal fat per 24 hours being up to 21.1 mmol (6 g). Collections were started between one and six days after tetracycline or demethylchlortetracycline had been given, and at least one collection was made again subsequently in those patients showing steatorrhoea. Nineteen patients had faecal fat estimations within normal limits. Six patients had pronounced steatorrhoea, which subsequently disappeared (figure). Two further patients had borderline steatorrhoea (24 mmol/day, 6.8 g/day and 22.9 mmol/day, 6.5 g/day), which disappeared (not shown in the figure). Other tests of malabsorption including estimation of vitamin B12 concentrations, jejunal biopsy, glucose tolerance test, measurement of serum amylase activity, and faecal cultures gave normal results.

Comment

At least six (22%) of 27 patients undergoing investigation for osteoporosis or osteomalacia had transient steatorrhoea after taking a tetracycline drug for the purpose of bone biopsy. The effect persisted for variable periods after the drug had been discontinued. The cause is uncertain. Tetracyclines are absorbed irregularly from the gastrointestinal tract owing to their low solubility and to chelation with calcium; a large proportion of oral tetracycline remains in the gut causing a high local concentration which may modify the gut flora or may cause direct toxicity to the gut wall. Since in most patients with blind loop syndrome, however, the steatorrhoea improves after a

Faecal fat estimations in six patients after single dose of 2 g tetracycline (cases 1-4) or demethylchlortetracycline 150 mg six hourly for four days (case 5), or demethylchlortetracycline 150 mg six hourly for two days (case 6).

Conversion: SI to traditional units—Faecal fat: 1 g/24 hr = 3.52 mmol/24 hr.

course of tetracycline,³ the effect in our patients may possibly have been due to a direct toxic effect rather than to an alteration in flora. Administration of the drug to rats has impaired fat absorption.⁴ In man tetracycline can cause oesophageal ulcers,⁵ but steatorrhoea has not been reported. If our findings in patients with a healthy small bowel apply to patients with blind loop syndrome then tetracycline may actually produce the steatorrhoea for which it was intended as treatment.

We thank Miss E Stainthorpe, Sister Dunsdon, and staff of the metabolic unit for assistance in this study and Mrs L Hewat for typing the manuscript.

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(Accepted 11 June 1982)

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