Case report

A 35-year-old woman was admitted for relapse of acute lymphoblastic leukaemia (FAB grade L 2). Full remission had been achieved after 28 months' treatment with OPAL (vincristine, prednisone, doxorubicin, and L-asparaginase (colaspase)). The relapse proved resistant to OPAL, and high-dose combination chemotherapy with TACC (cyclophosphamide 45 mg/kg/day intravenously, cytosine arabinoside (cytarabine) 100 mg/m²/day intravenously in divided dosage 12-hourly, and 6-thioguanine 100 mg/m² by mouth 12-hourly for four days, with lomustine 200 mg/m² by mouth on the second day)³ resulted in bone marrow aplasia. Autologous bone marrow transplantation was therefore performed. The period of total aplasia was complicated by septicaemia (*Klebsiella aerogenes*), which was treated with intravenous broad-spectrum antibiotics (gentamicin 240 mg and cefuroxime 6 g daily for three weeks and (because of poor response) carbenicillin 30 g/day for two weeks). Intercurrent gastrointestinal candidiasis was treated with antimycotic drugs (miconazole 1.5 g/day by mouth and 1.5 g/day intravenously for four days, and 5-fluorocytosine (flucytosine) 10.0 g/day as continuous intravenous therapy).

About three weeks after onset of the septicaemia nausea, vomiting, and right upper abdominal pain appeared. Serum alkaline phosphatase and aspartate and alanine aminotransferase activities remained normal. γ -Glutamyltransferase activity was 83 U/l (normal 3-30 U/l) and conjugated bilirubin concentration 8 μ mol/l (0.5 mg/100 ml) (normal 0-5 μ mol/l (0-0.3 mg/100 ml)). The gall bladder was not opacified on oral cholecystography. Computed tomography disclosed multiple, small (0.5-2.5 cm diameter) non-capsulated lesions of low attenuation (6 Hounsfield units) in liver and spleen (fig (a)). Sonography showed soft-tissue aggregates in some of the lesions in

(a) Tomogram of upper abdomen showing small multiple lesions in liver and spleen (arrowed). (b) Real-time sonogram of right lobe of liver showing cystic lesion containing soft-tissue aggregate (arrowed)—?candidoma.

the liver. Under guidance of real-time sonography the largest of these lesions was punctured with a 0.8 mm needle (fig (b)). Smears of the aspirate stained with May-Grünwald-Giemsa and dried in air contained fungal mycelia and spores. Culture of the main part of the aspirate for bacteria and fungi grew a strain of *Candida albicans*.

5-Fluorocytosine 10.0 g/day intravenously and amphotericin B up to 25 mg/day intravenously produced a poor response, and three months later the patient still had symptoms of disseminated candidiasis with abscesses evident on sonography and computed tomography.

Comment

The candida abscesses in this patient's liver and spleen had the sonographic and radiological appearances of multiple cysts. There was no capsule formation, and the lesions contained little debris. This may be explained by her lowered resistance to infection. In addition, sonography showed aggregates of fungus in some larger lesions. Such candida ball formation has been described in bile ducts.^{4,5} Invasive disseminated fungal infection should be diagnosed as soon as possible in a patient undergoing immunosuppression, since early antifungal treatment may be life saving. The diagnosis, however, is seldom achieved before death.¹

Our findings show that candida microabscesses in liver and spleen may be imaged by sonography and computed tomography. A liver lesion containing a soft-tissue aggregate is suggestive of a candida abscess (candidoma). Under sonographic control biopsy material may be obtained for microscopy and culture.

¹ Krick JA, Remington JS. Opportunistic invasive fungal infections in patients with leukaemia and lymphoma. *Clin Haematol* 1976;5:249-310.

² Suzuki H, Harada K, Higashi F, Fujimori I, Fukuda J. Detection of liver microabscess due to *Candida albicans* by liver biopsy in a patient with leukaemia during complete remission [authors' transl]. *Kansenshogaku Zasshi* 1979;53:23-8.

- ³ Gorin NC, Najman A, Salomon Ch, *et al.* High dose combination chemotherapy (TACC) with and without autologous bone marrow transplantation for the treatment of acute leukaemia and other malignant diseases. *Eur J Cancer* 1979;15:1113-9.
- ⁴ Marcucci RA, Whitely H, Armstrong D. Common bile duct obstruction secondary to infection with candida. *J Clin Microbiol* 1978;7:490-2.
- ⁵ Magnussen CR, Olson JP, Ona FV, Graziani AJ. Candida fungus balls in the common bile duct. Unusual manifestation of disseminated candidiasis. *Arch Intern Med* 1979;139:821-2.

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Hypokalaemia due to salbutamol overdosage

Salbutamol, a beta₂-adrenergic agonist, is used mainly to treat bronchial asthma but has also been advocated for use in severe cardiac failure, congestive cardiomyopathy, and premature labour. We report a case of self-poisoning with salbutamol associated with pronounced hypokalaemia.

Case report

The patient, a 76-year-old widow, was admitted two hours after taking a total of 40 salbutamol (4 mg) and Distalgesic tablets. On admission she was conscious, agitated, sweating, and tremulous. There was regular tachycardia of 140 beats/min, blood pressure was 90/50 mm Hg, respiratory rate 40/min, and temperature 37.5°C. There was no evidence of muscular weakness. Gastric lavage was performed and debris of pink tablets obtained.

Investigations yielded the following results: plasma sodium 140 mmol(mEq)/l, potassium 2.3 mmol(mEq)/l, chloride 100 mmol(mEq)/l, bicarbonate 27 mmol(mEq)/l, urea 5.7 mmol/l (34 mg/100 ml), and glucose 7.7 mmol/l (139 mg/100 ml). Haemoglobin was 11.7 g/dl with a white cell count of 16.4 × 10⁹/l (neutrophils 94%). Serum paracetamol concentration on admission was 55 mg/l. Plasma renin activity was 0.15 mmol/l/h (0.2 ng/ml/h) (normal supine range 0.77-1.54 mmol/l/h (1.0-2.0 ng/ml/h)) and plasma aldosterone 386 pmol/l (13.9 ng/100 ml) (normal supine range 100-500 pmol/l (3.6-18.0 ng/100 ml)). An electrocardiogram showed sinus tachycardia without the characteristic changes of hypokalaemia.

She was treated with 80 mmol (6 g) potassium chloride in an intravenous infusion of 2 l physiological saline given over 24 hours. A 1.84 l urine collection over this period contained 197 mmol sodium and 59 mmol potassium. One day after admission the plasma potassium concentration had risen to 4.4 mmol/l, and it subsequently remained normal without further supplementation.

Comment

Agitation, tremor, tachycardia, and hypotension are typical features of salbutamol overdosage,¹ and neutrophil leucocytosis is consistent with adrenergic stimulation. The effect of salbutamol on the metabolism of potassium is complex. In common with catecholamines and other sympathomimetic agents, salbutamol directly stimulates transfer of potassium from extracellular to intracellular fluid by activating sodium-potassium-dependent adenosinetriphosphatase. In addition, secretion of insulin, which has a similar effect on the transfer of potassium, is stimulated by salbutamol.² The hypokalaemic effect of intravenous salbutamol in insulin-dependent diabetics and normal subjects, however, is comparable,³ suggesting that insulin may not contribute greatly to the induced hypokalaemia.

Intravenous salbutamol causes a fall in plasma potassium concentration in normal subjects, patients with asthma, and patients

with premature labour without affecting urinary potassium excretion. Standard doses by mouth and via aerosol have no appreciable effect on plasma potassium concentrations. Inhalation of salbutamol is effective, however, in reducing exercise-induced hyperkalaemia and as prophylaxis against hyperkalaemic familial periodic paralysis.

In the present case there was no history of diuretic treatment, vomiting, or diarrhoea and no other cause of hypokalaemia could be identified. Renal mechanisms are unlikely to have played a part as neither plasma aldosterone concentration nor urinary potassium excretion was raised. The low aldosterone concentration may have resulted from a direct inhibitory effect of hypokalaemia on the zona glomerulosa cells combined with a low level of circulating renin. This low plasma renin activity may have resulted from an inhibitory adrenergic mechanism; a reduced renin response to tilting has been shown after salbutamol in man.⁴

Hypokalaemia is a potentially serious consequence of adrenergic agonist overdosage. Propranolol, a non-selective beta-blocker, prevents tachycardia and hypokalaemia induced by intravenous salbutamol⁵ and thus would seem to be an appropriate form of treatment.

¹ Morrison GW, Farebrother FW. Overdose of salbutamol. *Lancet* 1973; ii:681.

² Clausen T, Flatman JA. The effect of catecholamines on Na-K transport and membrane potential in rat soleus muscle. *J Physiol (Lond)* 1977; 270:383-414.

³ Gungodogdu AS, Brown PM, Juul S, Sachs L, Sonksen PH. Comparison of the hormonal and metabolic effects of salbutamol infusion in normal subjects and in insulin-requiring diabetics. *Lancet* 1979; ii:1317-21.

⁴ Wiggins R, Davies R, Basar I, Slater JHD. The inhibition of adrenergically provoked renin release by salbutamol in man. *Br J Clin Pharmacol* 1978; 5:213-5.

⁵ Berend N, Marlin GE. Characterization of the β adrenoceptor subtype mediating the metabolic actions of salbutamol. *Br J Clin Pharmacol* 1978; 5:207-11.

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Interaction of ethinyloestradiol with ascorbic acid in man

Ethinyloestradiol is the oestrogen most often present in combined oral contraceptive steroid preparations. We have shown that this steroid has a mean bioavailability of only 40%¹ owing to extensive first-pass metabolism. A large proportion of this first-pass metabolism occurs in the gut wall during absorption with the formation of a sulphate conjugate.² Sulphate conjugation of other drugs such as paracetamol is inhibited by ascorbic acid,³ a drug that also undergoes sulphate conjugation in the gut wall. In a preliminary study four out of six women showed an increase in plasma ethinyloestradiol concentrations when a single dose of ethinyloestradiol was administered with ascorbic acid.⁴ We therefore studied the effect of ascorbic acid in women receiving long-term treatment with oral contraceptive steroids.

Patients, methods, and results

We studied five female volunteers aged between 22 and 33 years who were taking oral contraceptive preparations containing 30 μ g of ethinyloestradiol (Ovranette in two, Eugynon 30 in three). Written informed consent was obtained from each volunteer and approval for the study given by the Mersey regional ethical committee.

The volunteers were studied in two consecutive menstrual cycles during the last week of oral contraceptive administration. In random order one of these weeks served as a control and in the other the contraceptive preparation was given with a 1 g dose of effervescent ascorbic acid (Ascorbef, Cox-Continental Ltd). Blood samples (10 ml) were obtained six and 24 hours after the oral contraceptive preparation had been taken on three consecutive days at the same stage in each cycle. The plasma was separated by centrifugation and stored at -20°C until analysis for its ethinyloestradiol content by a

sensitive radioimmunoassay.¹ Statistical analysis was by Student's *t* test for paired samples.

The table shows the mean of the three plasma ethinyloestradiol concentrations obtained in each volunteer in each study period six and 24 hours after dosing. During treatment with ascorbic acid the mean concentrations were raised at six and 24 hours in all patients, and this difference was statistically

Mean ($\pm$ SE) plasma ethinyloestradiol concentrations (ng/l) six and 24 hours after a 30 μ g dose of ethinyloestradiol with and without ascorbic acid. Each value is the mean of samples taken on three consecutive days

Case No	Six hours			24 hours		
	Control	With ascorbic acid	% increase	Control	With ascorbic acid	% increase
1	60 $\pm$ 5	70 $\pm$ 4	16.7	27 $\pm$ 2	43 $\pm$ 6	59.3
2	85 $\pm$ 5	95 $\pm$ 6	11.8	34 $\pm$ 5	56 $\pm$ 7	64.7
3	20 $\pm$ 3	24 $\pm$ 3	20.0	4 $\pm$ 1	8 $\pm$ 2	100
4	42 $\pm$ 2	53 $\pm$ 7	26.2	27 $\pm$ 7	33 $\pm$ 5	22.2
5	37 $\pm$ 6	41 $\pm$ 3	10.8	12 $\pm$ 2	16 $\pm$ 5	33.3
Mean	49 $\pm$ 11	57 $\pm$ 12	16.3	21 $\pm$ 5	31 $\pm$ 9	47.6
Significance	p < 0.01			p < 0.05		

significant. The table also shows the percentage increases in the concentrations. The mean concentrations for the group as a whole were raised at six hours from 49 ng/l to 57 ng/l, an increase of 16.3%, and at 24 hours from 21 ng/l to 31 ng/l, an increase of 47.6%. No adverse effects were experienced by the volunteers throughout the study.

Comment

Concurrent administration of ascorbic acid with combined oral contraceptive steroid preparations clearly causes the plasma concentration of ethinyloestradiol to rise. The dose of ascorbic acid used is one that is often taken to prevent the common cold. The increased concentrations at six hours might be due to an interaction in the intestinal mucosa, since the ability to produce sulphate conjugates may be swamped by a 1 g dose of ascorbic acid. This would reduce the first-pass effect of ethinyloestradiol, thus increasing its systemic bioavailability and plasma concentration. The plasma concentrations of ethinyloestradiol 24 hours after dosing were increased by 47.6%, rather more than the increase seen at six hours, which may be due to the reduced conjugation of ethinyloestradiol that is absorbed after enterohepatic circulation.¹

The increase in plasma concentrations of ethinyloestradiol during treatment with ascorbic acid might be of some benefit in permitting wider use of the very-low-dose ethinyloestradiol preparations. Ascorbic acid at this dose level is generally free of side effects.⁵

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¹ Back DJ, Breckenridge AM, Crawford FE, *et al.* An investigation of the pharmacokinetics of ethinyloestradiol in women using radioimmunoassay. *Contraception* 1979; 20:263-73.

² Back DJ, Bates M, Breckenridge AM, *et al.* The in vitro metabolism of ethinyloestradiol, levonorgestrel and mestranol by human jejunal mucosa. *Br J Clin Pharmacol* 1980; 9:281-2P.

³ Houston BJ, Levy G. Drug biotransformation interactions in man. VI. Acetaminophen and ascorbic acid. *J Pharm Sci* 1976; 65:1218-21.

⁴ Back DJ, Bates M, Breckenridge AM, *et al.* Drug metabolism by gastrointestinal mucosa—clinical aspects. In: Prescott LF, Nimmo WS, eds. *Drug absorption*. Australasia: ADIS Press, 1980:80-7.

⁵ Briggs MH, Garcia-Webb P, Johnson J. Dangers of excess vitamin C. *Med J Aust* 1973; 2:48-9.

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