Reversible lactic acidosis associated with repeated intravenous infusions of sorbitol and ethanol

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Summary
Infusions of fructose or sorbitol are used commonly in parenteral nutrition and may cause lactic acidosis. A case is reported in whom blood lactate concentration was monitored frequently over a 5-day period during intravenous feeding with a sorbitol-ethanol-amino acid mixture. During the first five infusions blood lactate rose only moderately, but with the final infusion lactate rose to 11.1 mmol/l and the patient had a severe metabolic acidosis. In retrospect the patient had shown deterioration in renal and hepatic function tests during the preceding 24 hr. On terminating the infusions the blood lactate concentration fell rapidly. It is suggested that great care should be exercised when using such infusions in ill patients and acid base status and renal and hepatic function should be monitored frequently.

Introduction
Sorbitol, fructose and ethanol are widely used as carbohydrate calorie sources for intravenous nutrition.

Lactic acidosis has been reported during infusions of fructose (Woods and Alberti, 1972) and sorbitol with ethanol and has generally been associated with severe hepatic or renal dysfunction or septicaemia. Reports have usually been of cases following single prolonged administration of these compounds. A case is now reported in which repeated short-term administrations of a sorbitol/ethanol/amino acid mixture caused only mild elevations in blood lactate until the final infusion, at the same rate, caused lactic acidosis. On discontinuing the infusion, in association with insulin, glucose and bicarbonate therapy, the blood lactate concentrations and arterial blood pH returned towards normal values.

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Methods
Arterial blood pH, Po2 and Pco2 were estimated by the standard Astrup technique. Arterial blood glucose, lactate, pyruvate, sorbitol and fructose were estimated by automated fluorometric enzymatic techniques (Lloyd, Buckle and Alberti, in preparation) after rapid de-proteinization of blood in ice cold 5% (vol/vol) perchloric acid.

Case history
A 70-year-old male, was admitted to hospital with abdominal pain, nausea and vomiting. He had previously been operated on for a perforated duodenal ulcer and 2 years before admission had suffered a myocardial infarction. Laparotomy revealed a perforation of the duodenum, which was oversewn. Postoperatively he was treated with intravenous fluids, penicillin and streptomycin. Further surgery was undertaken 8 days later because of gastric stasis and bleeding, and vagotomy, pyloroplasty and gastroenterostomy were performed. Over the next month he received parenteral nutrition, had intermittent pyrexia, a further period of gastric bleeding and continued gastric stasis. He was operated on again and an isoperistaltic retrocolic gastroenterostomy fashioned. Postoperatively respiratory assistance was required and he was transferred to the intensive care unit.

At this time blood pressure was 100/80 mmHg, pulse 140/min, central venous pressure + 1 cm H2O and there was sacral oedema. ECG showed occasional ectopic beats and myocardial ischaemia. In view of his poor nutritional state intravenous feeding was re-instituted. This comprised 1 litre Aminoplex 5 (Geistlich) alternating every 6 hours with 500 ml plasma or saline, 154 mmol/l. On this regime nitrogen balance was positive. He was also given heparin, digoxin, vitamin supplements, phenoperidine and sodium carbenicillin, which was later...
changed to gentamicin, ampicillin and cloxacillin. Four days after admission to the intensive care unit he started having intermittent periods of hypotension. A blood culture taken during one of these episodes subsequently grew *Candida albicans*. On the fifth day the patient's condition had deteriorated and he was found to have a severe metabolic acidosis (pH 7.16, PaCO₂ 3.8 kPa; base deficit, 17 mmol/l) which was attributed to lactic acidosis due to the sorbitol-ethanol content of the Aminoplex 5. This infusion was discontinued and a 6-hour infusion of glucose (0.3 g/kg/hr) and insulin (0.085 u./kg/hr) instituted together with a 2-hr infusion of 125 mmol sodium bicarbonate. The patient showed a good metabolic recovery and was clinically improved but 12 hr later blood pressure fell, renal function deteriorated and 24 hr later he died. Post-mortem examination revealed pneumonia, empyema, pulmonary emboli, renal abscesses, peritonitis and severe coronary atherosclerosis.

**Results**

Metabolic investigations were carried out during six of the ten 6-hr infusions of Aminoplex 5 during the 5 days leading up to and including the episode of metabolic acidosis. The mean blood lactate concentration before Aminoplex 5 infusion was 1.35 mmol/l. On all occasions blood lactate rose during infusion (Fig. 1) reaching a mean concentration of 3.90 mmol/l by 6 hr. On the occasion when the metabolic acidosis was detected, the lactate level was 11.1 mmol/l. Blood sorbitol and fructose concentrations rose to 2.3 and 0.9 mmol/l in the first five infusions studied but to 3.6 and 2.5 mmol/l respectively with the final infusion.

When the severe lactic acidosis was detected blood pyruvate concentration was only 0.10 mmol/l and the lactate/pyruvate ratio was 105. Arterial blood pH was 7.16; PaCO₂ 3.8 kPa; PaO₂ 7.2 kPa; HCO₃⁻ 9.4 mmol/l; standard bicarbonate, 10.6 mmol/l; base deficit, 17.0 mmol/l and blood glucose, 16.6 mmol/l. Blood pressure was 135/60 mmHg.

Two hours after corrective therapy was instituted arterial blood pH was 7.35; PaCO₂ 6.2 kPa; PaO₂ 7.6 kPa; HCO₃⁻ 27.0 mmol/l; standard bicarbonate 26.0 mmol/l; base excess 1.5 mmol/l; glucose 22.2 mmol/l, lactate 5.7 mmol/l and the lactate/pyruvate ratio was 60 (Fig. 2). At 6 hr glucose was 7.9 mmol/l, fructose 0.6 mmol/l, sorbitol 0.2 mmol/l, lactate 3.4 mmol/l and lactate/pyruvate ratio 40. Plasma electrolytes remained stable through this period. However, during the 24 hr leading up to lactic acidosis blood urea concentration had risen from 18 to 24 mmol/l (reference range 3.6-6.6 mmol/l), plasma asparate aminotransferase had increased from 44 to 283 i.u./l (reference range 5-40 i.u./l) and plasma bilirubin from 33 to 68 µmol/l (reference range 0-17 µmol/l). During the six hours of treatment for lactic acidosis there was a further increase in all three parameters.

**Discussion**

This patient is typical of many who routinely receive intravenous nutrition. He had a stormy post-operative course and was extremely ill, 'catabolic' and malnourished at the time of study. Fructose,
sorbitol and ethanol are popular calorie sources for such patients. The main advantage is that, unlike glucose, insulin is not required for their metabolism and they are said to be less damaging to veins, although this has been questioned (Woods and Alberti, 1972). Sorbitol is metabolized first to fructose and the major route thereafter is to lactate. In normal man lactate is cleared rapidly by the liver but in severely ill patients, particularly those with hepatic dysfunction, lactate accumulates and lactic acidosis may supervene (Cohen and Woods, 1976). Ethanol, by its effect of increasing the hepatic NADH : NAD ratio, compounds the problem.

The notable point about the present patient is that he received sorbitol with ethanol on ten occasions and on five of these where measurements were made only moderate elevations of blood lactate concentration occurred. It was only on the final infusion that lactic acidosis developed. In retrospect there was marked deterioration in renal and hepatic function before the final infusion but the change in clinical state gave no real indication of pending metabolic disaster. Obviously this type of response should be avoided if at all possible. It might be reasonable in the very ill patient either to infuse fructose/sorbitol/ethanol solutions at a lower continuous rate (a rather high infusion rate was used in this patient) or for shorter periods. Alternatively checks on blood acid/base status should be made or, if measurement is available, blood lactate should be measured after the first few hours of infusion. It would also be sensible to check renal and hepatic function frequently. In the present case both hyperglycaemia and advancing renal impairment may have contributed independently to the persistent acidosis. If renal function is impaired sorbitol and fructose will accumulate more rapidly while hepatic dysfunction will enhance lactate accumulation. Alternatively a different intravenous feeding regime could be used such as lipid and/or glucose and insulin with amino acids.

The lactate concentration in blood decreased rapidly after the sorbitol/ethanol infusion was stopped, indicating clearly that lactate could be metabolized although not rapidly enough to cope with the load derived from sorbitol. Lactic acidosis from other causes has an immediate mortality of about 75% (Cohen and Simpson, 1975). Correction of acidosis is undoubtedly desirable, as in acidaemia the liver switches from lactate consumption to lactate production (Lloyd et al., 1973), although in this case only partial correction of acidosis with bicarbonate was necessary. In the present case the removal of sorbitol was almost certainly the major factor in recovery.

In summary, lactic acidosis may develop at any time during parenteral nutrition of patients with sorbitol, fructose and ethanol, particularly in the presence of hepatic and renal dysfunction. Careful monitoring is required, particularly as in this situation the acidosis should be reversible.

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