group and the controls could be explained in terms of a higher incidence of physical disability due to angina and dyspnoea in the VF group, the patients' attitudes to their disease, or overcautiousness on the part of their general practitioners. These explanations must be speculative since we could not obtain evidence to support or refute them in view of the retrospective manner in which some of the information was collected about the patients in the VF group. Within 10 months of leaving hospital, however, these differences between the two groups had disappeared.

Recognising that unsuccessful rehabilitation after myocardial infarction could be due as much to psychological as to physical factors,[4] it might be expected that patients whose heart attacks were complicated by ventricular fibrillation would be most adversely affected psychologically by their illness. They commonly believe, quite inaccurately, that their "Heart attack had been very severe" and often comment, "I had actually died and was brought back to life."[7] As a result they may harbour fear of sudden death or recurring ill health—fears that should have been allayed by sympathetic and informed medical counselling before and after they were discharged from hospital. Our 10-month follow-up figures do not suggest that anxiety alone explains the failure to return to work in either group of patients. Age seemed to be the most influential factor. The only two patients in the VF group who were below the age of 58 and had not returned to work by 10 months (table III) had experienced a further acute myocardial infarction and were incapacitated by severe angina and dyspnoea.

Since age was the most useful factor in distinguishing between patients who returned to work within 10 months of their discharge from hospital and those who did not, it may be advisable to consider early retirement after acute myocardial infarction in patients who are in or around their early 60s, especially if they wish to leave manual occupations and have understanding employers. A similar opinion has been expressed by Biorck.[6]

Though the controls were not ideal in that they were consecutive admissions after 1973, this selection was unlikely to have prejudiced the results of our study since VF patients admitted before 1973 behaved in the same way as those admitted after this date.

In conclusion, primary ventricular fibrillation after a myocardial infarction, though initially slowing rehabilitation, does not itself ultimately adversely affect the resumption of work and normal living.

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Lactic acidosis complicating treatment of ketosis of labour

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Summary

Hypertonic glucose, fructose, and sorbitol solutions were given intravenously to women in the first stage of labour who had ketonuria and ketonaemia as evidenced by a raised blood acetoacetate and 3-hydroxybutyrate. There was no difference in the antiketogenic action of these, which was rapid and effective, but when compared with a control group who were given normal saline they had a high incidence of hyperlactataemia, and nine out of 28 patients developed lactic acidosis after the infusions. The "lactatogenic" effect was shared by all three substrates, and when they are used in the treatment of ketosis of labour, and the mother develops lactic acidosis, they might exacerbate pre-existing lactic acidosis and precipitate fetal distress.

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Introduction

The detection of ketonuria during labour is usually the first indication that ketosis exists. The combination of starvation and vomiting with depletion of carbohydrate reserves stimulates ketogenesis and ketonaemia caused by the accumulation of the ketone bodies acetoacetic acid, 3-hydroxybutyric acid, and acetone. If ketoacidosis develops and is untreated it may induce a fetal acidosis or enhance an acidosis already present as a consequence of intrauterine anoxia and also cause deterioration in the general maternal condition.

Treatment aims to provide sufficient carbohydrate intravenously to prevent further ketogenesis and correct the acidosis together with adequate rehydration. Intravenous solutions of glucose, fructose, and the polyol sorbitol are readily available for this purpose but attention has recently been drawn to the potential danger of lactic acidosis complicating intravenous fructose infusions.[1] Lactic acidosis has been reported in mother and fetus during labour after intravenous fructose,[2] and sorbitol might be expected to have a similar effect as it is converted by the liver to fructose.

This investigation was designed to compare and evaluate the antiketogenic action of fructose, sorbitol, and glucose with particular reference to the incidence of hyperlactataemia and lactic acidosis after infusion.

Patients and methods

Fifty women admitted in the first stage of labour with ketonuria, as indicated by a positive Ketostix test result, were divided at random into four groups, which were given either dextrose, fructose,

sorbitol, or normal saline (control group) intravenously. Most women had a normal uncomplicated first stage but there was one twin pregnancy, two cases of mild pre-eclamptic toxaemia, two trials of labour, and five cases of artificial rupture of membranes, including two cases of slight ante-partum haemorrhage. All patients were delivered several hours after the infusions were completed. Fetal scalp vein sampling was not performed, but immediately after delivery the babies were examined by a paediatrician and the Apgar score assessed.

BIOCHEMICAL INVESTIGATIONS

Capillary blood was analysed immediately for pH, carbon dixoide pressure (P_{CO_2}), and standard bicarbonate by the conventional Astrup technique.[3] The normal range for pH is 7·36-7·42, for standard bicarbonate 22·4-25·8 mmol (mEq)/l, and for P_{CO_2} 4·3-5·9 kPa (32-44 mm Hg).

Venous blood was taken just before and on completion of the infusion but without tourniquet and between uterine contractions to avoid spurious increases in blood lactate. Enzymatic methods were used to measure lactate[4] and pyruvate,[5] with a fluorimetric method[6] for acetoacetate and 3-hydroxybutyrate. The normal ranges established in this laboratory are: serum acetoacetate 0·01-0·1 mmol/l (0·1-1·0 mg/100 ml), serum 3-hydroxybutyrate 0·02-0·6 mmol/l (0·21-6·2 mg/100 ml), blood lactate 0·7-2·0 mmol/l (6·3-18 mg/100 ml), and blood pyruvate 0·04-0·08 mmol/l (0·35-71 mg/100 ml).

Serum osmolality was measured with an Advanced Instruments osmometer, the normal range being 275-295 mmol (mosmol)/l, while blood glucose was estimated by a conventional glucose oxidase method with the normal range 3·6-5·6 mmol/l (65-101 mg/100 ml).

LACTIC ACIDOSIS

No universally acceptable definition of the term lactic acidosis exists. A leading article in the *British Medical Journal*[8] defined it as a "raised lactate level together with a reduced arterial pH," while Oliva[9] defined it as "a blood lactate concentration greater than 2·0 mEq/l (2 mmol/l) with an arterial pH below 7·37 in the absence of other causes of acidosis." An alternative definition[10] is that it is a state in which lactate accumulation contributes substantially to the pathogenesis of a metabolic acidosis, irrespective of other acids that accumulate, but which seldom occurs with a blood lactate below 5 mmol/l (45 mg/100 ml).

We used the term hyperlactataemia when the blood lactate was greater than normal, irrespective of blood pH. We confined the term lactic acidosis to those cases in which the blood lactate was greater than 5 mmol/l (45 mg/100 ml), the pH lower than 7·36, and the standard bicarbonate reduced below 22 mmol/l.

INTRAVENOUS INFUSION

The rate of infusion of 30% dextrose, 30% sorbitol, and 20% fructose was adjusted to administer 0·75 g of substrate kg body weight^{-1} hour^{-1} for three hours, while the control group were given 500 ml of normal saline.

In parenteral nutrition regimens the recommended infusion rate to cover the average daily calorie requirements of an adult is 0·5 g kg body weight^{-1} hour^{-1}. The relatively high infusion rate we used was chosen to provide maximum stimulus to the biochemical processes that reduce ketonaemia and, at the same time, to adequately "stress" the metabolic pathway responsible for the production of lactic acid.

The solution of the substrates infused were hypertonic. The osmolality of 30% glucose is 1665 mmol/l, 30% sorbitol 1647 mmol/l, and 20% fructose 1110 mmol/l.

Results

SERUM ACETOACETATE AND 3-HYDROXYBUTYRATE

The mean preinfusion serum acetoacetate was raised in the control and test groups (table I). There was an increased mean serum 3-hydroxybutyrate concentration in all but those who received glucose, in whom it was at the upper limit of normal. The highest individual acetoacetate was 1·08 mmol/l (11 mg/100 ml), a tenfold increase above normal, and the highest 3-hydroxybutyrate 4·0 mmol/l (41 mg/100 ml), a sevenfold increase above normal.

In the control group there was a considerable increase in both metabolites after infusion. In contrast, glucose, fructose, and sorbitol had a strong antiketogenic effect and application of the F test showed that there was a significant difference between the substrate and control groups ($P = 0·05$-$0·01$) for serum acetoacetate and 3-hydroxybutyrate. The antiketogenic effect of the substrates was similar and the F test confirmed that there was no significant statistical difference between them.

BLOOD LACTATE AND PYRUVATE

The preinfusion blood lactate was increased in 29 and the pyruvate in 24 patients. The mean preinfusion lactate and pyruvate levels were raised above normal in the test groups, but in the control group only the lactate was raised.

After infusion in the control group the mean blood lactate fell to just above normal, but after glucose, fructose, and sorbitol 31 women were found to have a raised blood lactate, and in 28 it was higher than the preinfusion concentrations. In 10 patients the postinfusion lactate was 3-4 mmol/l (27-36 mg/100 ml), in five patients 4-5 mmol/l (36-45 mg/100 ml), in two patients 5-6 mmol/l (45-54 mg/100 ml), and in seven patients 6-7 mmol/l (54-63 mg/100 ml).

The mean lactate after infusion of each substrate (table I) was considerably raised, and when compared with the control group using the F test there was a statistically significant difference ($P = 0·05$-$0·01$). No statistically significant difference was found between the three substrates, which were equally effective in stimulating the production of excess lactate.

The changes in blood pyruvate after infusion were less definite and there was no significant difference in the pyruvate response of the glucose, fructose, and sorbitol groups.

ACID BASE BALANCE

Though the mean preinfusion values for pH, P_{CO_2} and standard bicarbonate (table I) were within the normal range 12 patients had a pH of less than 7·36 and 11 a standard bicarbonate of less than 22 mmol/l. Eight patients had a mild metabolic acidosis with a raised blood acetoacetate and 3-hydroxybutyrate. The blood lactate was also increased in six of these patients, who therefore had mixed metabolic acidosis rather than simple ketoacidosis.

After substrate infusions the number of patients with abnormal acid-base results increased, but with no significant alteration in the mean values. Eighteen had a pH of less than 7·36 and 16 a standard bicarbonate of less than 22 mmol/l. The number of women with a

TABLE I—*Mean values (± SD) for acid base status, blood aceto acetate, 3-hydroxybutyrate, lactate, and pyruvate before and after infusion of glucose, fructose, and sorbitol (0·75 g/kg body weight^{-1} hour^{-1}) during labour*

	pH		P_{CO_2} (kPa)		Standard HCO_3 (mmol/l)		Acetoacetate (mmol/l)		3-Hydroxybutyrate (mmol/l)		Lactate (mmol/l)		Pyruvate (mmol/l)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Saline	7·42 ± 0·04	7·41 ± 0·03	5·12 ± 0·87	4·8 ± 0·59	25 ± 3·4	23·8 ± 2·1	0·18 ± 0·15	0·45 ± 0·32	0·69 ± 0·60	1·12 ± 0·80	2·27 ± 1·40	2·08 ± 0·73	0·07 ± 0·03	0·08 ± 0·07
Glucose	7·39 ± 0·05	7·39 ± 0·05	4·9 ± 0·89	4·5 ± 0·83	22·7 ± 3·9	22·1 ± 4·4	0·24 ± 0·3	0·11 ± 0·09*	0·52 ± 0·62	0·28 ± 0·23*	2·87 ± 1·37	4·21 ± 1·5*	0·11 ± 0·07	0·15 ± 0·10
Sorbitol	7·40 ± 0·05	7·39 ± 0·06	4·9 ± 0·93	4·4 ± 0·85	24·2 ± 4·8	22 ± 4·1	0·18 ± 0·10	0·10 ± 0·15*	0·62 ± 1·16	0·29 ± 0·38*	2·37 ± 1·01	3·3 ± 1·53*	0·19 ± 0·25	0·23 ± 0·28
Fructose	7·36 ± 0·04	7·36 ± 0·04	4·7 ± 0·69	4·5 ± 0·65	21·3 ± 3·3	20·1 ± 2·7	0·24 ± 0·19	0·19 ± 0·12*	0·82 ± 0·45	0·50 ± 0·27*	2·95 ± 1·13	3·88 ± 1·8*	0·20 ± 0·19	0·18 ± 0·08

*Significant difference compared to saline control (F test; $P = 0·05$-$0·01$).

Conversion: SI to traditional units—P_{CO_2}: 1 kPa ≈ 7·5 mm Hg. HCO_3: 1 mmol/l = 1 mEq/l. Acetoacetate: 1 mmol/l ≈ 10 mg/100 ml. 3-Hydroxybutyrate: 1 mmol/l ≈ 10·3 mg/100 ml. Lactate: 1 mmol/l ≈ 9 mg/100 ml. Pyruvate: 1 mmol/l ≈ 8·8 mg/100 ml.

metabolic acidosis increased to 14, who were distributed evenly among the substrate groups. This can be explained by the large increase in blood lactate in spite of a reduction of acetoacetate and 3-hydroxybutyrate in all but two cases. Of the 14 patients with a postinfusion metabolic acidosis nine had a true lactic acidosis with the blood lactate in excess of 5 mmol/l (45 mg/100 ml). Five were induced by glucose, three by fructose, and one by sorbitol. In many patients the hyperlactataemia caused by the "lactatogenic" effect of these substrates replaced the original ketonaemia.

NEONATAL ASSESSMENT

It was difficult to correlate neonatal Apgar scores with the maternal acid-base balance and lactate concentrations, as the births occurred at varying intervals after infusion. Fifteen babies born to mothers with hyperlactataemia had Apgar scores of 8 or 9, three had scores of 7, and one with a score of 6 had congenital heart disease from which it died soon after birth. Of the nine babies born to the mothers who had lactic acidosis one, who required a caesarean section for a failed forceps delivery, had a score of 4; three had scores of 6 (one with fetal distress); three had scores of 7, and two had scores of 9.

BLOOD GLUCOSE

After the infusion of sorbitol and fructose the mean blood glucose increased slightly to 8·1 and 7·3 mmol/l (146 and 132 mg/100 ml) respectively (table II). In complete contrast was the rise after glucose, when the mean level rose to 17·9 mmol/l (320 mg/100 ml). The smaller rise of blood glucose after fructose and sorbitol might be explained by the presence of a rate-limiting step in the incorporation of these substrates into the Embden-Meyerhof glycolytic pathway.

TABLE II—*Mean (±SD) serum osmolality and blood glucose after infusion of glucose, fructose, and sorbitol (0·75 g/kg body weight^{-1} h^{-1})*

	Osmolality (mmol/kg)		Glucose (mmol/l)	
	Before	After	Before	After
Saline (controls) ..	275 ± 8·9	278 ± 9·4	4·9 ± 1·8	3·5 ± 0·8
Glucose	281 ± 10·2	283 ± 11·6	6·4 ± 1·3	17·9 ± 7·9
Sorbitol	287 ± 15·1	281 ± 10·8	7·1 ± 2·3	8·1 ± 2·7
Fructose	279 ± 8·2	279 ± 8·8	5·8 ± 1·2	7·3 ± 1·2

Conversion: SI to traditional units
Osmolality: 1 mmol/kg = 1 mosmol/kg.
Glucose: 1 mmol/l ≈ 18 mg/100 ml.

SERUM OSMOLALITY

The alterations in serum osmolality after infusion of the hypertonic solutions were small and remained within the normal range (table II). It was unlikely that any significant change would have been observed with such short infusions.

Discussion

Prompt treatment of ketonaemia may prevent the development of ketoacidosis, while the treatment of established ketoacidosis will not only improve the maternal condition but also protect the fetus from the deleterious effects of a prolonged maternal metabolic acidosis. This investigation has shown the value of intravenous glucose, fructose, and sorbitol for treating ketonaemia; they produced a rapid and significant reduction in serum acetoacetate and 3-hydroxybutyrate. This was achieved with a comparatively high rate of infusion (0·75 g of substrate kg body weight^{-1} hour^{-1}), which clearly showed the "lactatogenic" potential of all three substrates. They produced hyperlactataemia in 28 patients, 14 of whom developed a metabolic acidosis, which was a lactic acidosis in nine patients. In many cases the increased production of lactate was additional to the small increase of blood lactate present before infusion, which is thought to be due mainly to muscular activity during labour.[11 12]

As maternal blood lactate increases so does the fetal blood concentration, and this can be superimposed on any increase in fetal lactate that occurs during periods of intrauterine anoxia,[13] which may even exceed the maternal level. The accumulation of lactate may cause or exacerbate a pre-existing fetal acidosis and precipitate fetal distress.

Treatment of ketosis of labour with intravenous fructose[2] causes an increase in maternal lactate and fetal base deficit, and when used in the parenteral nutrition of shocked patients with poor tissue perfusion and in infants treatment may be complicated, in some cases, by lactic acidosis.[14] Our findings have confirmed that not only fructose but also sorbitol and glucose carry a similar risk when given to women in labour.

Although scalp vein sampling was not possible in this investigation, the Apgar scores indicated that those mothers with lactic acidosis tended to have a slightly higher proportion of babies with lower scores than the others, but the numbers involved were too small for reliable statistical evaluation. The high infusion rate may have exaggerated the increase in maternal lactate, but fructose, even at the slower rate of 0·5 g kg body weight^{-1} hour^{-1}, causes hyperlactataemia and depresses the plasma bicarbonate in adults.[15]

Ketonuria in labour is not always associated with ketoacidosis, and treatment with hypertonic carbohydrate solutions should therefore be judicious and in selected cases. The amount of substrate infused should be sufficient to control the ketonaemia but not so excessive as to induce a potentially dangerous lactic acidosis. In practice the maternal blood lactate usually returns to basal levels three hours after completion of the infusion, and hyperlactataemia and lactic acidosis may be prevented if the solutions are given intermittently and in conjunction with the occasional measurement of blood lactate.

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