SHORT REPORTS

Postmortem diagnosis of familial hypercholesterolaemia

Despite the growth in the availability and complexity of biochemical tests in recent years, they have been used largely to establish a diagnosis in living patients. We report a case in which a biochemical test performed on blood collected post mortem not only helped to establish a diagnosis in the index case but also had profound implications for surviving family members.

Case report

A 26 year old lean, muscular man collapsed while jogging and died despite attempts at resuscitation. He had jogged and played squash regularly and had not suffered any recent illnesses. He had consulted his general practitioner a year before his death complaining of chest pain, which was attributed to bruised ribs.

A postmortem examination was performed. External appearances were normal, and arcus senilis and tendon xanthomas were absent. Internal examination showed extensive atheromatous plaques throughout the aorta and its major branches and atheromatous occlusion of more than 75% of the lumina of the proximal left anterior descending and circumflex coronary arteries. The right coronary artery showed evidence of recanalisation of previous thrombosis. There was no evidence of recent coronary artery thrombosis or acute myocardial infarction, but the left ventricle showed extensive subendocardial fibrous scarring. In view of the severity of the atheroma and the patient's age a diagnosis of familial hypercholesterolaemia was considered.

Serum cholesterol concentrations were measured in cardiac blood obtained 40 hours post mortem using a cholesterol oxidase method (Technicon diagnostics kit No TO1-1305-01) and a Technicon RA1000 random access analyser. Cholesterol concentrations remain fairly stable for up to 60 hours post mortem,^{1,2} and provided that a suitable blank is performed haemolysis of up to 2.7 g haemoglobin/dl does not interfere with the cholesterol estimation (DS, unpublished observations). Serum cholesterol

Serum cholesterol concentrations in family members and index case

	Age (years)	Cholesterol (mmol/l)
Father	56	6.5
Mother	51	15.6
Index case	26	21.6
Brother	25	6.8
Brother	23	4.5
Sister	21	12.4
Brother	20	6.4
Brother	19	9.7
Sister	18	5.8

Conversion: SI to traditional units—
Cholesterol: 1 mmol/l $\approx$ 38.7 mg/100 ml.

concentration was considerably raised at 21.6 mmol/l (835 mg/100 ml), which prompted a survey of cholesterol concentrations in family members; this showed increased concentrations in one parent and two of six siblings of the index patient (table).

Comment

Our patient was probably suffering from heterozygous familial hypercholesterolaemia. This is perhaps the most common single gene disorder affecting man, with a heterozygote prevalence of about one in 500.³ It is inherited in an autosomal dominant fashion, and its principal features are premature ischaemic heart disease and considerable hypercholesterolaemia. Recent evidence suggests that energetic methods of reducing blood cholesterol concentrations result in a reduced risk of coronary heart disease, but efforts to screen close relatives of patients with hypercholesterolaemia are currently neglected.⁴ The importance of identifying subjects at risk from coronary heart disease is emphasised by the growing number of reports of sudden death during exercise.⁵

Cholesterol concentrations in blood collected post mortem are a valid reflection of antemortem concentrations, and their measurement is indicated in cases of premature, sudden death from coronary heart disease, which is often associated with exercise. If hyper-

cholesterolaemia is found post mortem surviving family members should be investigated because advice and treatment may have important consequences.

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Miscibility of human and bovine ultralente insulin with soluble insulin

Adjustable mixtures of short and either intermediate or long acting insulins have become routine treatment for young patients with type 1 diabetes.^{1,2} Recently, a new human ultralente insulin preparation Ultratard HM (Novo, Copenhagen) has been introduced as a substitute for the bovine ultralente insulin Ultratard MC (Novo).³ When short and long acting insulins are mixed in one syringe before administration it is of crucial importance that the initial rapid absorption of the regular component is preserved.

In the present study we investigated absorption kinetics and bioavailability of subcutaneously injected regular insulin mixed with Ultratard HM or Ultratard MC.

Subjects, methods, and results

Sixteen men of normal weight were assigned to receive either human or bovine ultralente insulin. Each proband was subjected to three different tests carried out in randomised order after an overnight fast of 14 hours: (1) 10 U Actrapid HM and 16 U Ultratard HM, or 10 U Actrapid MC and 16 U Ultratard MC, were injected simultaneously into contralateral thighs; (2) the same insulins in identical ratios were injected immediately after mixing in one syringe; and (3) the same insulins in identical ratios were injected five minutes after mixing. Throughout the tests the probands rested supine and abstained from food and drink. At the time points indicated in the figure venous blood was taken for determination of plasma glucose, serum insulin, and plasma C peptide concentrations using methods described previously.⁴ Serum insulin concentrations were measured only in the study of human ultralente insulin. Data are given as means (SEM). Insulin values are expressed as the increase above basal concentrations. Student's *t* test for paired comparisons was used to evaluate the significance of the differences between the results of the tests in the same subjects; *p* < 0.05 indicated significance.

In the study of Ultratard HM basal insulin concentrations (mean of two measurements) were 10.9 (1.5) mU/l (test 1), 7.3 (1.0) mU/l (test 2), and 6.9 (1.0) mU/l (test 3). The increase in serum insulin concentration was significantly higher in test 1 than in tests 2 and 3 throughout the study and significantly higher in test 2 than test 3 at 30 and 40 minutes (figure). These differences in the behaviour of serum insulin concentrations were inversely reflected in blood glucose and C peptide concentrations (C peptide concentrations indicating suppression of endogenous insulin).

In the study of Ultratard MC we did not observe any difference in the behaviour of blood glucose and C peptide concentrations between tests 1 and 2, but blood glucose concentrations remained significantly higher in test 3 than in test 1. Accordingly, C peptide concentrations were significantly higher in test 3 than in test 1 between 30 and 50 minutes after injection.

Effect on circulating concentrations of insulin, glucose, and C peptide of subcutaneous injection of 10 U Actrapid HM and 16 U Ultratard HM into thighs of eight non-diabetic men.

Shaded area represents mean (SEM) of control tests (separate injection of the two insulins); solid line represents injection of both insulins immediately after mixing in one syringe (test 2); and broken line represents injection of both insulins five minutes after mixing (test 3). Circled points indicate significant differences from control values ($p < 0.05$); asterisks indicate significant differences between tests 2 and 3.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

Comment

The results of this study show that if the new human ultralente insulin Ultratard HM is mixed with Actrapid HM in a ratio of 16:10 in one syringe the steep initial rise in insulin concentration, and hence the rapid hypoglycaemic effect of the soluble insulin component, is lost, even when the mixture is injected immediately after mixing. Furthermore, these data confirm clinical experience of the miscibility of Ultratard MC with Actrapid MC provided that the insulins are injected immediately after mixing^{1,2}; but a time lag of five minutes between mixing and injection resulted in a significant loss of the initial rapid hypoglycaemic effect.

In the tests of bovine ultralente insulin circulating concentrations of exogenous insulin were not measured as two heterologous insulins were used. As in previous studies the differences in serum insulin concentrations between the various tests of human ultralente insulin were inversely reflected by the behaviour of blood glucose and C peptide concentrations.⁵ It thus appears reasonable to assume that in the study of bovine ultralente insulin the behaviour of blood glucose and C peptide concentrations reflected circulating insulin concentrations. The causes for the differences in miscibility between Ultratard HM and Ultratard MC must remain speculative; differences in zinc content might be one explanation.

In conclusion, our results indicate that Ultratard HM and Actrapid

HM must not be mixed but should be injected separately to preserve the rapid hypoglycaemic effect of the regular insulin component.

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What are safe levels of alcohol consumption?

Primary health care workers have an important part to play in preventing alcohol related problems by giving advice on safe limits of alcohol consumption.¹ It is by no means clear, however, up to what point alcohol consumption should be regarded as safe, and current advice varies considerably. A working party of the Royal College of Psychiatrists recommended an upper limit of 56 units of alcohol a week (one unit is equivalent to half a pint of beer, one measure of spirits, or a glass of wine or sherry) but made no comment about different consumptions for men and women.² This contrasts sharply with the recent campaign of the Health Education Council advising consumption of under 21 units a week for men and 14 for women, implying that consumption beyond this was harmful.³ In the light of such variation we carried out a survey of opinion within a group of 70 people currently engaged in alcohol research in Britain.

Methods and results

We selected 70 people from a register of alcohol research in the United Kingdom (1982-3).⁴ Everyone taking part in research into the epidemiology, clinical aspects, and management of alcohol problems was included except for those carrying out animal or in vitro experiments. From these we took a random sample of 60 people weighted for number of research projects. We added to the group 10 other people known to be engaged in work of particular importance.

We asked the following two questions. (1) In your opinion, for a healthy man what would constitute a reasonable guideline in health education for a safe upper limit of drinking? (2) In your opinion, for a healthy woman who is not pregnant or trying to become pregnant what would constitute a reasonable guideline in health education for a safe upper limit of drinking?

We received 56 replies. Of the respondents, 46 volunteered an opinion on a safe consumption for men, and 45 for women. The respondents who did not give an opinion either said that they did not feel qualified to do so or questioned the appropriateness of recommending a single safe limit of weekly alcohol consumption. The distribution of opinion among the remaining respondents (table) did not differ appreciably between the initial group of 60 and the additional group of 10, or between those working in the north of the United Kingdom and those working in the south. In addition, there were no major differences in response between people whose main research interest was the epidemiology, clinical aspects, or management of alcohol problems.

Number of units of alcohol per week recommended as upper limit of "safe" drinking (figures are numbers of respondents)

	No of units of alcohol/week									
	0-6	7-13	14-20	21-27	28-34	35-41	42-48	49-55	56-62	63-69
Men		7	10	3	10	3	4	4	5	
Women	3	13	13	4	7	3	1	1		