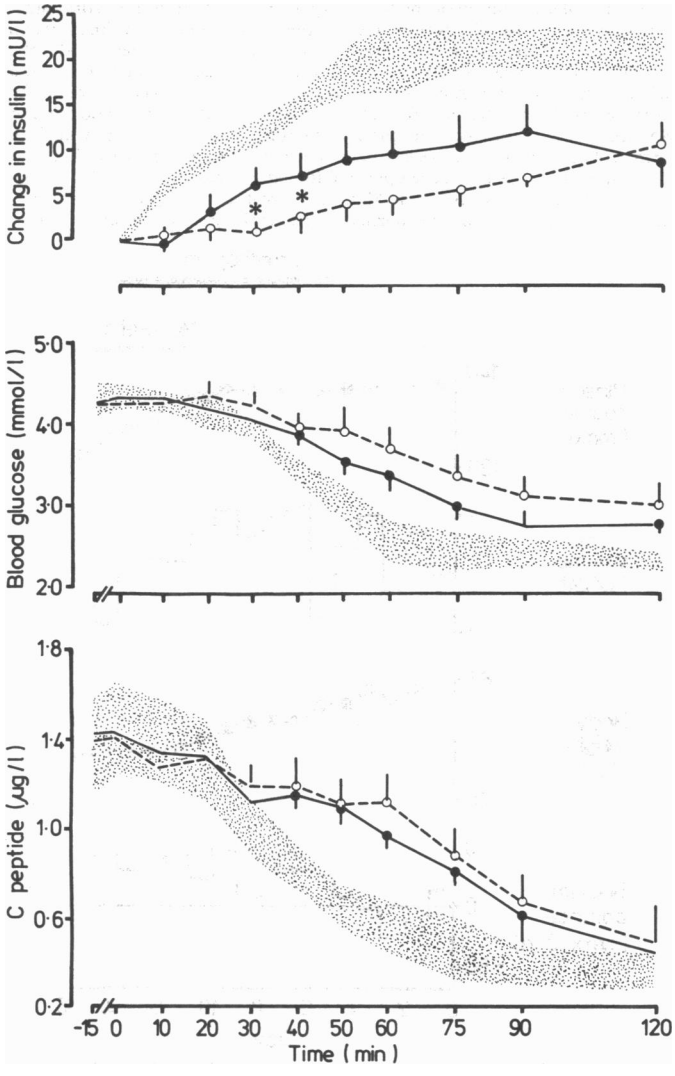

Effect on circulating concentrations of insulin, glucose, and C peptide of subcutaneous injection of 10 U Actrapid HM and 16 U Ultratard HM into thighs of eight non-diabetic men.

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 ≈ 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.

1 Anonymous. Type 1 diabetes . . . regimens, targets, and caveats [Editorial]. *Diabetes Care* 1982;5:547-52.
2 Reeves ML, Seigler DE, Ryan EA, Skyler JS. Glycemic control in insulin-dependent diabetes mellitus. Comparison of outpatient intensified conventional therapy with continuous subcutaneous insulin infusion. *Am J Med* 1982;72: 673-80.
3 Holman RR, Steemson J, Darling P, Reeves WG, Turner RC. Human ultralente insulin. *Br Med J* 1984;288:665-8.
4 Kemmer FW, Berchtold P, Berger M, *et al.* Exercise induced fall of blood glucose unrelated to alteration of insulin mobilisation. *Diabetes* 1980;28:1131-7.
5 Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care* 1982;5:77-91.

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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		

Comment

Opinion on safe limits of consumption of alcohol for men and women varies considerably. This may be related to several factors. Firstly, there is a paucity of experimental data on the effects on health of different levels of alcohol consumption, particularly from long follow up studies, and the quality of data that are available varies. Secondly, in formulating opinions on safe limits people may select from existing data, with some possibly considering only the results of studies carried out in their own particular research interest rather than the data from a greater range of studies. Finally, the variation in opinion may originate from different interpretations of "healthy," with some restricting their interpretation to include only physical illness such as cirrhosis and others including broader social factors such as the disruption of family relationships or interference with work.

There is clearly a lack of consensus on reasonable guidelines for safe drinking. We believe that a comprehensive review of the existing data should be carried out and that properly designed long term prospective studies on the effects of different levels of alcohol consumption on health should be undertaken.

1 Advisory Committee on Alcoholism. *The pattern and range of services for problem drinkers*. London: DHSS, 1978.
2 Royal College of Psychiatrists. *Alcohol and alcoholism*. London: Tavistock, 1979.
3 Anonymous. *That's the limit*. London: Health Education Council, 1983.
4 Pattison CJ, ed. *Register of United Kingdom alcohol research (1982-3)*. Edinburgh: Alcohol Research Group, Department of Psychiatry, University of Edinburgh, 1983.

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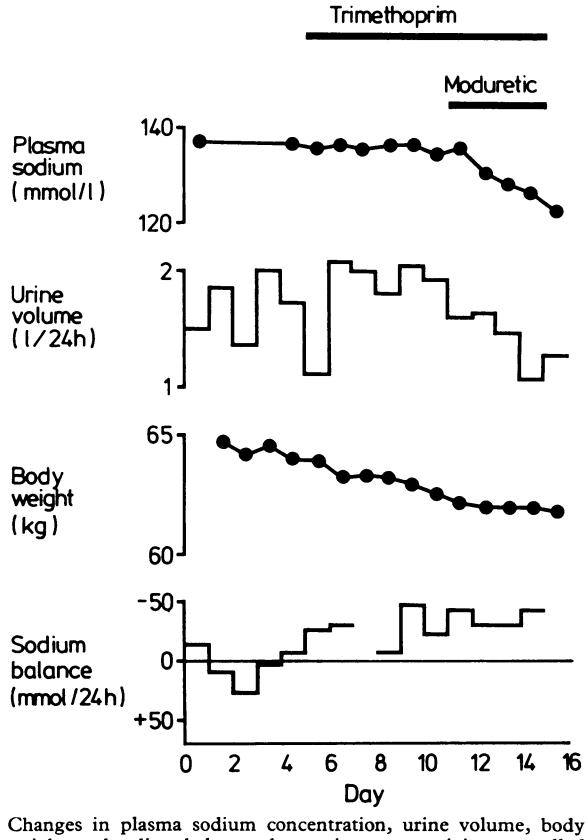
Hyponatraemia associated with trimethoprim and a diuretic

Co-trimoxazole may produce natriuresis but has not previously been reported as reducing plasma sodium concentrations. We report on a patient who developed symptomatic hyponatraemia when treated with trimethoprim, which recurred on rechallenge with the drug.

Case report

A 75 year old woman had a recurrent urinary tract infection, which was initially treated with nalidixic acid. Plasma sodium concentration was normal at 136 mmol(mEq)/l. Infection persisted so treatment was changed to trimethoprim 200 mg twice daily. Four days later she developed nausea and anorexia and was found to have hyponatraemia with a plasma sodium concentration of 107 mmol/l. She also had a history of seropositive rheumatoid arthritis, pulmonary fibrosis, cor pulmonale, hypertension, and hypothyroidism for which she was taking amiloride 10 mg, hydrochlorothiazide 100 mg (as Moduretic two tablets daily), methyldopa 500 mg, and thyroxine sodium 150 μg daily. Additional biochemical tests showed that plasma potassium concentration was 4·3 mmol(mEq)/l, urea 6·5 mmol/l (39 mg/100 ml), and osmolality 225 mmol(mOsm)/kg. Urinary sodium concentration was 31 mmol/l, potassium 75 mmol/l, and osmolality 523 mmol/kg. A short Synacthen test showed a normal cortisol response. Creatinine clearance was 50 ml/min. Trimethoprim and Moduretic were stopped and fluid intake restricted to 500 ml/day. Over the next 11 days the plasma sodium concentration rose gradually to 135 mmol/l. She was discharged from hospital taking methyldopa, thyroxine, and Moduretic.

She was well on review four months later and gave informed consent for rechallenge with trimethoprim. Moduretic was stopped, and six weeks later she was admitted for a sodium balance study. At this time she had some leg oedema and body sodium content increased (exchangeable sodium 2510 mmol compared with 2060 mmol expected). Plasma and urinary sodium concentrations, urinary volume, and body weight were measured daily (figure). Dietary intake of sodium (70 mmol/24 h) and fluid (1·8 l/24 h) were controlled. The ankle oedema largely resolved after her admission, which accounted for the weight loss in the control period. Trimethoprim 200 mg twice daily did not produce hyponatraemia, but when Moduretic one tablet daily was added urinary volume fell and hyponatraemia and malaise developed. On the final day urinary osmolality was 481 mmol/kg compared with the plasma value of 252 mmol/kg. After trimethoprim and Moduretic were stopped the plasma sodium concentration returned to normal. On review five weeks later plasma sodium concentration was 141 mmol/l but she had developed ankle oedema again and so Moduretic two tablets daily was restarted. With this treatment plasma sodium concentration remained within the normal range for the subsequent nine months.



Changes in plasma sodium concentration, urine volume, body weight, and sodium balance when patient was receiving controlled sodium and fluid intakes, and during periods of administration of trimethoprim 200 mg twice daily and Moduretic one tablet daily.
Conversion: SI to traditional units—Sodium: 1 mmol=1 mEq.

Comment

Hyponatraemia developing within a few days of the start of treatment with amiloride and hydrochlorothiazide occurs rarely,[2] and in our patient this combination alone did not produce such an effect. When the patient was also taking trimethoprim, however, hyponatraemia developed rapidly. Changes of renal function including effects on renal tubular secretion and sodium handling have been recorded as associated with treatment with co-trimoxazole and trimethoprim.[1 3 4] In our patient urine osmolality was inappropriately high in relation to the low plasma osmolality that developed during the combined treatment. Trimethoprim seems therefore to have an additional renal action in sometimes causing impairment of free water clearance. This effect may be similar to that of chlorpropamide.[5] We have seen several other patients who have developed hyponatraemia while taking trimethoprim or co-trimoxazole. All were elderly (age range 62-84) and taking several drugs, including diuretics in all but one. The interval between the start of treatment and the development of hyponatraemia was four to 12 days. We have reported this side effect to the Committee on Safety of Medicines.

The possibility of hyponatraemia should always be considered when an elderly patient develops anorexia and nausea after starting treatment with trimethoprim or co-trimoxazole.

1 Shouval D, Ligumsky M, Ben-Ishay D. Effect of co-trimoxazole on normal creatinine clearance. *Lancet* 1978;i:244-5.
2 Strykers PH, Stern RS, Morse BM. Hyponatremia induced by a combination of amiloride and hydrochlorothiazide. *JAMA* 1984;**252**:389.
3 Berglund F, Kellander J, Pompeius R. Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. *J Urol* 1975;**114**:802-8.
4 Kalowski S, Nanra RS, Mathew TH, Kincaird-Smith P. Deterioration in renal function in association with co-trimoxazole therapy. *Lancet* 1973;i:394-7.