phylaxis, and there is also preliminary evidence for improvement in organ function in patients treated in this way.[13] Thus where possible affected children should presumably be treated with desferrioxamine using the subcutaneous infusion approach or, if this is not practicable, by administering the drug intramuscularly at the dose of at least the 15-28 mg/kg/day achieved at the beginning of the study by Barry *et al.*[3] Also the progress of the children treated in this way should be monitored with respect to age at onset of puberty, liver iron loading and function,[9] endocrine and cardiac function,[14 15] growth rate, and overall wellbeing. If really large effects on survival are produced by these more aggressive forms of chelation treatment they may hopefully be shown convincingly by simple comparison of future mortality with the data we report here. More moderate effects, however, might fail to be clearly recognised in such a non-random historical comparison and, of course, any general improvements in ancillary management may yield improved survival which is mistakenly attributed to infusions of desferrioxamine. Perhaps, however, these difficulties of interpretation will eventually be bypassed by introducing less troublesome methods of avoiding iron overload.

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The data and statistical appendices may be obtained on request from DJW.

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SHORT REPORTS

Importance of short-term changes in glycosylated haemoglobin

Formation of glycosylated haemoglobin (haemoglobin A_1) has been considered to occur slowly within the erythrocyte at a rate dependent on the ambient blood glucose concentration. The amount formed has therefore been thought to reflect the average blood glucose concentration over the previous two to three months. Recent reports have shown, however, that acute reversible changes in glycosylation may occur and are related to short-term fluctuations in blood glucose concentration.[1-3] These reports raise important questions concerning the validity of measurements of haemoglobin A_1 as indicators of long-term diabetic control.

We examined the magnitude of these reversible changes, and their relation with the total proportion of haemoglobin A_1 and blood glucose concentration, in an attempt to assess their importance in clinical practice.

Patients, methods, and results

The method for measuring the reversible, or labile, fraction (difference in percentage) of haemoglobin A_1 was established by comparing the time course of changes in the percentage of haemoglobin A_1 due to dissociation of this fraction during incubation for 24 hours in glucose-free medium (0·9% saline) at 4°C, 22°C, and 37°C. Blood was drawn from six diabetic inpatients and two normal subjects and was placed into EDTA. The proportion of haemoglobin A_1 was assayed by a microcolumn method modified from that of Kynoch and Lehmann.[4] At 37°C dissociation of the labile fraction appeared complete at 18 hours. At 22°C the fall in the percentage of haemoglobin A_1 at 18 and at 24 hours did not differ appreciably from the fall at 37°C, whereas at 4°C no appreciable dissociation was seen.

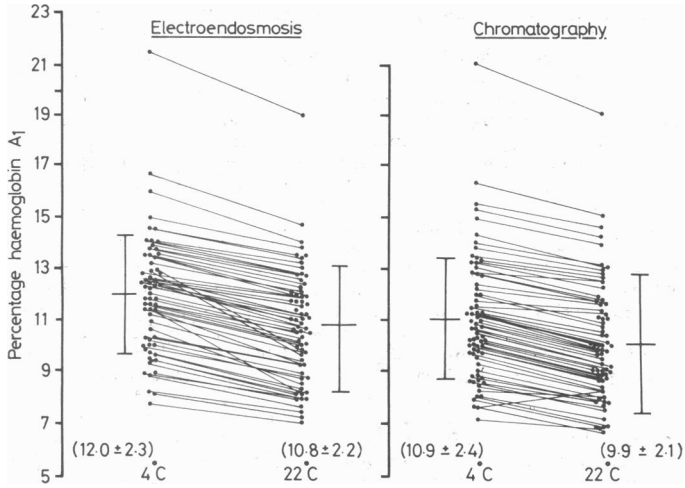
In a larger study of 65 diabetic outpatients we took the magnitude of the difference in the percentage of haemoglobin A_1 as the difference between the percentage of haemoglobin A_1 measured after 18 hours' incubation in saline at 4°C and 22°C. Blood was obtained by fingerprick, and two 50 μl aliquots were added immediately to 1 ml of 0·8% saline for subsequent measurement of percentage of haemoglobin A_1. A further aliquot was used for immediate estimation of blood glucose concentration. Percentage of haemoglobin A_1 was measured using both the microcolumn method and electroendosmosis (Corning Medical Ltd). Good agreement between these two methods has been shown in this laboratory.[5]

The figure shows the results of this study. Good agreement between the two methods was again seen. The difference in the percentage of haemoglobin A_1 was relatively small (1·2 ± SD 0·9%, range −0·5 to 3·7; and 1·0 ± 0·7%, range −0·23 to 2·02 for the two methods respectively).

Comment

Our results confirm the presence of a reversibly bound labile component in the glycosylated haemoglobin fraction which can be removed by incubation in glucose-free medium for 18 hours at 22°C. In the group of patients studied removal of this labile fraction produced a fall of approximately 1%, determined by both methods of measurement, in the percentage of haemoglobin A_1, though just occasionally the difference was greater. This suggests that removal of the labile fraction does not appreciably improve the clinical value of the results and does not justify the time and cost incurred in the additional manipulation of samples.

Measurement of the percentage of haemoglobin A_1 is at its most useful in the diabetic clinic, when the result is available at the time that the patient is seen. Time spent in removing the labile fraction would preclude the availability of the result at the time of consultation, and the benefits obtained would not, in our opinion, justify the extra cost and effort. This immediate availability of results is possible only



Changes in percentage of haemoglobin A_1 after incubation in 0·9% saline for 18 hours. Mean difference in percentage of haemoglobin A_1 was 1·2 ± SD 0·9 and 1·0 ± 0·7 (n = 65) for electroendosmosis and chromatography respectively.

with reorganisation of the average diabetic clinic to permit at least one hour between blood sampling and consultation. This places further strain on both patients and clinic organisers but in our experience is worth while for both patient and physician.[5]

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Department of Medicine, St Thomas's Hospital Medical School, London SE1 7EH
F S SHENOUDA, MB, MSC, research fellow
C S COCKRAM, BSC, MRCP, lecturer in medicine
M D BARON, MA, research assistant
A TSATSOULIS, MB, visiting research fellow
LIN WEN HAN, MB, visiting research fellow
P H SÖNKSEN, MD, FRCP, professor of endocrinology

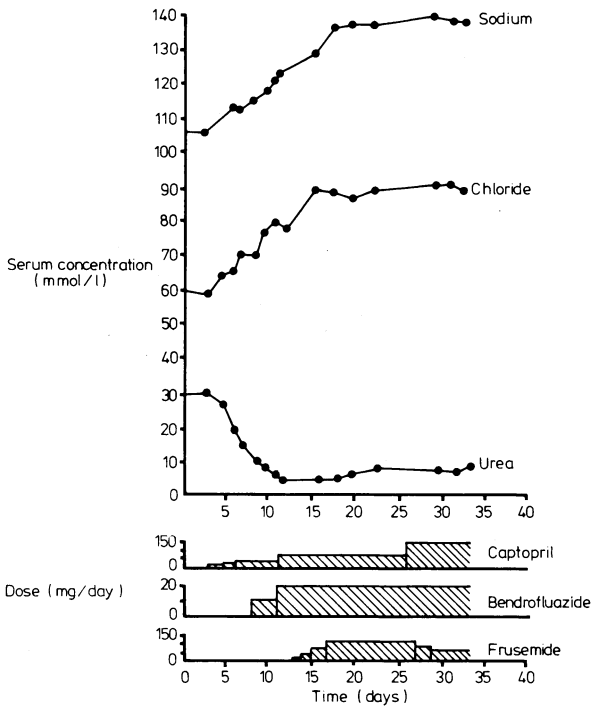
Severe hyponatraemia and cardiac failure successfully treated with captopril

Captopril, an orally active inhibitor of converting enzyme, has for some time been used to treat congestive cardiac failure and hypertension, particularly renovascular hypertension.[1-3] We report on a patient with inoperable congenital heart disease and severe cardiac failure, resistant to conventional treatment, who developed profound hyponatraemia that responded to treatment with captopril.

Case report

A 29-year-old man with inoperable congenital cyanotic heart disease (transposition of the great vessels, high stenosis of the outflow of the right ventricle, and ventricular septal defect) was admitted on 18 April 1981 with severe ventricular failure and hyponatraemia (sodium concentration 125 mmol(mEq)/l, potassium 4·6 mmol(mEq)/l, chloride 71 mmol(mEq)/l, urea 26·8 mmol/l (161 mg/100 ml), and creatinine 100 μmol/l (1·13 mg/100 ml)). A Pott's anastomosis had been carried out when he was 4 years old, and he had subsequently remained cyanosed with pulmonary hypertension and atrial fibrillation controlled by digoxin. In the nine years before admission his congestive cardiac failure had become increasingly difficult to control. Initially his progressive cardiac failure was treated with digoxin, high doses of diuretics (bumetanide 5 mg twice daily, chlorthalidone 100 mg, and spironolactone 100 mg daily) and vasodilator drugs (hydralazine 50 mg twice daily, which he could not tolerate, and isosorbide dinitrate 20 mg thrice daily, which was ineffective). His cardiac failure did not improve and by 1 June he was listless, drowsy, and confused. Serum electrolyte concentrations were: sodium 106 mmol/l, potassium 3·9 mmol/l, and chloride 59 mmol/l; urea concentration 30·8 mmol/l (185 mg/100 ml), creatinine 74 μmol/l (837 μg/100 ml). Haemoglobin was 18·3 g/dl, and packed cell volume 0·556 (55·6%).

Because of the gross hyponatraemia and prerenal uraemia all drugs were stopped and captopril 25 mg thrice daily was introduced. There was a rapid and large diuresis and a striking improvement in the clinical and biochemical state (figure). Nine days later diuretics were added in doses smaller than



Electrolyte changes after introduction of captopril.
Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l. Chloride: 1 mmol/l = 1 mEq/l. Urea: 1 mmol/l ≈ 6 mg/100 ml.

previously needed and captopril was increased to 50 mg thrice daily. Serum biochemical concentrations returned to near normal (sodium 136 mmol/l, potassium 4·2 mmol/l, chloride 89 mmol/l, urea 6·6 mmol/l (40 mg/100 ml), and creatinine 54 μmol/l (611 μg/100 ml)), and he was discharged home on 24 July taking captopril 50 mg thrice daily, bendrofluazide 10 mg twice daily, frusemide 80 mg daily, digoxin 0·25 mg daily, and warfarin. He remained well.

Comment

This patient with inoperable cyanotic congenital heart disease had not only congestive cardiac failure resistant to conventional treatment but also profound hyponatraemia. Previous work[4] has shown that severe cardiac failure can cause constriction of the proximal glomerular capillaries, thus slowing the perfusion of the vasa recta loop with consequent retention of urea and hyponatraemia. Captopril could well correct these various postulated effects because in normal subjects and patients with essential hypertension it increases renal plasma flow and lowers renal vascular resistance, thus increasing glomerular filtration rate and creatinine clearance.[1]

This effect, combined with captopril's other effects of improving cardiac output and decreasing systemic vascular resistance and ventricular filling pressure,[3] might explain our patient's rapid and