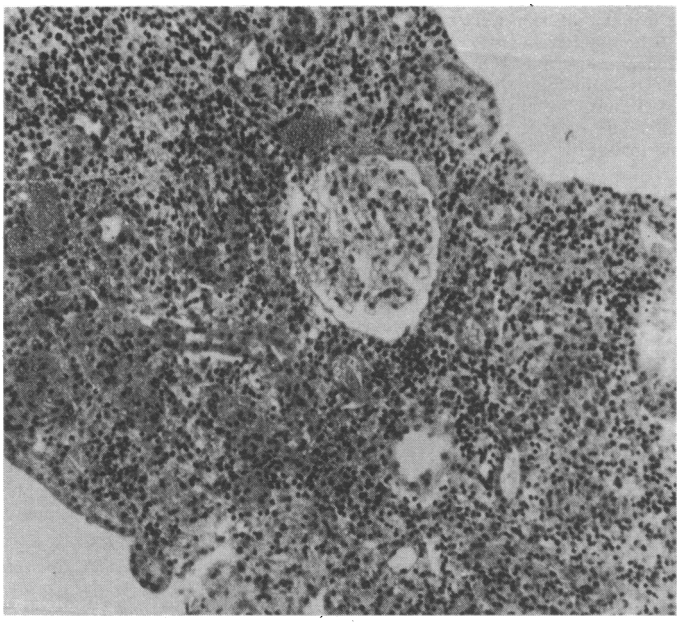

Pronounced diffuse interstitial inflammatory infiltrate with groups of histiocytes, some tubular degeneration, and normal glomerulus (H and E. × 28.)

He remained well until he was admitted in February 1978 with a one-week history of fever, myalgia, and productive cough. After persistent questioning he admitted taking co-trimoxazole. Investigations showed blood urea concentration 18·6 mmol/l (112 mg/100 ml); serum creatinine concentration 390 μmol/l (4·25 mg/100 ml); urine output 28 ml/h; urine osmolality 330 mosmol/kg. After biopsy peritoneal dialysis was started and methyl prednisolone 1 g given intravenously for two days and then 0·5 g for another two days. Recovery was rapid. Creatinine clearance was 70 ml/min on discharge. Two months later intravenous urography showed normal-sized kidneys and biopsy showed only a few foci of lymphocytes and mild patchy interstitial fibrosis. On each occasion immunoglobulins, complement, antistreptolysin O titre, DNA binding, and eosinophil count were normal.

Comment

Antibiotic-induced interstitial nephritis leading to acute reversible renal failure has been ascribed to sulphonamides,[2] penicillins,[3] and co-trimoxazole.[4] The characteristic histological changes of interstitial nephritis and their relation to acute renal failure after streptococcal and diptherial infection were first described in 1898.[5] The appearances are the same in drug hypersensitivity reactions. We believe our patient's acute attacks were due to co-trimoxazole and gentamicin, although the aetiological agent in the first attack is uncertain. Cases due to gentamicin have not, we believe, been reported. The absence of one or more of the classical features of fever, rash, eosinophilia, haematuria, and proteinuria should not, as our case shows, bar a diagnosis of antibiotic-induced acute interstitial nephritis. When suspicion exists early renal biopsy is advocated. From the results of treating this patient and others with high doses of corticosteroid we strongly recommend their use in these cases.

We thank the Director General of Medical Services (RAF) for permission to report this case, and Dr I Chorlton and the pathology department of IPTM PMRAF (H) Halton for assistance with the histology.

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Glycosylated haemoglobin in chronic renal failure

The observation that haemoglobin in the erythrocyte undergoes progressive glycosylation with the aging of the erythrocyte and that the rate of glycosylation is enhanced by hyperglycaemia has led to the concept that raised concentrations of glycosylated haemoglobin (HbA_1) indicate poor glycaemic control in diabetic patients.[1 2] Since information on other factors or pathological conditions which may alter HbA_1 concentrations is limited, the clinical application of this test has been confined to diabetic patients. We report here a study in which we measured HbA_1 concentrations in patients with chronic renal failure (CRF) and those with renal transplants.

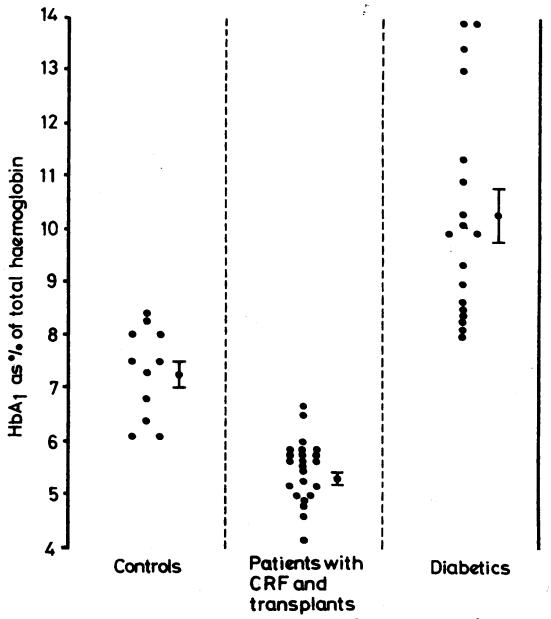
Patients, methods, and results

Seventeen patients with CRF (age range 10-53 years, mean 34 years) on long-term haemodialysis of variable duration (two months to five years) and from different causes were studied. Five patients who had had renal transplants (creatinine clearance range 10-53 ml/min) for less than three months were also studied. None of these patients had fasting or postprandial hyperglycaemia, glycosuria, or hypoglycaemia. Blood samples were collected in heparin and were stored in a refrigerator at 4°C before HbA_1 measurement. All estimations were carried out within three days of collection of the sample. HbA_1 was measured by a kit (Isolab Laboratories) which used chromatographic separation of HbA_1 from HbA on a biorex microcolumn. This microcolumn method has recently been shown to produce results similar to those obtained with the macrocolumn method[3] of Trivelli *et al.*[4] All HbA_1 results were expressed as percentage of total haemoglobin and not as absolute concentrations. To demonstrate that uraemic plasma did not interfere with the mobility of HbA_1, estimations of HbA_1 in the normal blood diluted with normal and uraemic plasma were carried out.

All but one of the patients with CRF or a renal transplant had low HbA_1 concentrations (see figure). The remaining patient had been transfused with four units of blood two days before the collection of his blood sample. All patients with renal transplants had HbA_1 concentrations similar to those observed in patients with CRF (see figure). There was a direct correlation between HbA_1 and total haemoglobin concentrations ($r=0·6$, $P=0·001$). Dilution of normal blood with normal and uraemic plasma did not alter HbA_1 concentrations.

Comment

This is the first demonstration of low HbA_1 concentrations in CRF. Since there was no obvious abnormality in the glucose homoeostasis in any of these patients, the low concentration of HbA_1 was probably related to the shortened life span of erythrocytes known to



HbA_1 concentrations in patients with CRF and renal transplants compared with those in controls and diabetic patients (with blood glucose concentrations >7·1 mmol/l). Means ± SE of means are shown. CRF *v* controls: $P<0·001$; diabetics *v* controls: $P<0·001$.

occur in patients with CRF. A shortened life span of red blood cells would ensure that the erythrocytes in circulation were relatively young and that they had a relatively short time to glycosylate haemoglobin. We ruled out the possibility that HbA_1 measurement might have been interfered with by factors in the plasma of uraemic patients. Our observations disagree with those reported in a study on patients on haemodialysis in which raised HbA_1c levels were found.[5] Most patients in that study, however, had blood glucose concentrations greater than 7 mmol/l (126 mg/100 ml).

Clinically it is important to appreciate that CRF is associated with subnormal HbA_1 concentrations since HbA_1 values would have to be interpreted with caution before and after transplantation in patients with diabetic nephropathy. This is especially relevant if HbA_1 is to be used as a marker of diabetic control in studies relating the quality of long-term glycaemic control to the development of diabetic complications.

We were surprised to find a direct correlation between HbA_1 and total haemoglobin concentration in patients with CRF since the anaemia in this condition is thought to be mainly due to marrow suppression.

In conclusion, the primary effect of CRF on HbA_1 is that of a reduction due to shortened red blood cell survival. The superimposition of hyperglycaemia on CRF could lead to a normal or raised HbA_1. The significant linear correlation between HbA_1 and haemoglobin concentrations in a condition with an anaemia due to multiple factors would suggest that HbA_1 has the potential for being developed into a rapid and cheap quantitative test for haemolysis.

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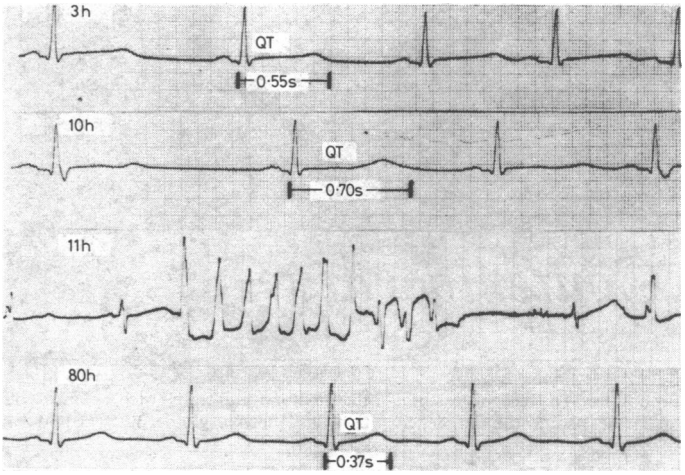
Sotalol intoxication with prolonged Q-T interval and severe tachyarrhythmias

The main clinical features after massive doses of beta-blocking agents include bradycardia, hypotension, low-output cardiac failure, and cardiogenic shock. Whether the features are influenced by the various pharmacological properties of different beta-blockers is unknown.[1] Sotalol hydrochloride is a non-selective beta-blocking drug devoid of intrinsic sympathomimetic and membrane-stabilising activity. Interestingly, sotalol has been classified as a group 3 antiarrhythmic drug,[2] and in contrast to other beta-blockers high concentrations prolong the duration of action potential in canine ventricular muscle and Purkinje fibres.[3]

We report what we believe to be the first two cases of severe sotalol poisoning. Each was characterised by a concentration-dependent prolongation of the Q-T interval and a pronounced susceptibility to severe tachyarrhythmias.

Case reports

Case 1—A 39-year-old man taking 160 mg sotalol daily for mild hypertension was admitted to the emergency room two hours after ingesting 2·4 g sotalol (30 80-mg tablets) with small amounts of diazepam and chlordiazepoxide and some alcohol. He was drowsy but orientated, with a blood pressure of 130/80 mm Hg and heart rate 50/min. Gastric lavage yielded a tablet mass. Four hours after ingestion blood pressure could be maintained at 80/50 mm Hg only with a dopamine infusion (0·5 mg/min), and heart rate by intracardiac pacing with a bipolar electrode. Nine hours after ingestion two episodes of ventricular fibrillation occurred with transient loss of consciousness: the first episode ceased spontaneously, and the second disappeared with pacing. Subsequent numerous multifocal ventricular extrasystoles disappeared with lignocaine and pacing at 140/min. Pacing and dopamine infusion were needed for up to 40 hours and lignocaine for up to 70 hours after ingestion. Thirteen hours after ingestion the serum sotalol concentration was 16 mg/l (therapeutic concentration about 1-2 mg/l). The electrocardiogram showed a maximum Q-T interval of 0·68 s (at a heart rate of 70/min normal Q-T interval is 0·37 s). The serum half life of sotalol was 13 hours, the decline in concentration correlating closely with return to normal of the Q-T interval.



Case 2. Electrocardiograms 3, 10, 11, and 80 hours after ingestion of 8 g sotalol. Tracings at 3, 10, and 80 hours recorded with lead I at 50 mm/s; tracing at 11 hours recorded from monitor at 25 mm/s.

Case 2—A 59-year-old man was admitted three hours after ingesting 8 g sotalol (100 tablets). Blood pressure was 85/55 mm Hg and heart rate 60/min. Gastric lavage was performed and 50 g activated charcoal given. He was infused with isoprenaline and the blood pressure rose to 100/70 mm Hg. Six hours after ingestion multifocal ventricular extrasystoles (up to 24/min), some clearly aberrantly conducted beats, and short episodes of ventricular tachycardia were observed. Twenty-two hours after ingestion the serum sotalol concentration was 7·5 mg/l, the half life being 15 hours. A maximum Q-T interval of 0·70 s at a heart rate of 45/min was recorded 10 hours after ingestion (see figure) (normal Q-T interval at this heart rate 0·45 s). The Q-T interval decreased with an apparent half life of 14 hours, being normal three days after ingestion.

Comment

The most important findings in these two patients were hypotension, bradycardia, a prolonged Q-T interval, ventricular extrasystoles, ventricular tachycardia, and, in case 1, ventricular fibrillation. A prolonged Q-T interval predisposes to ventricular tachyarrhythmias but the exact mechanism is obscure. In contrast to propranolol and alprenolol, sotalol at concentrations of 10-100 μmol/l (about 3-30 mg/l) has been shown in vitro to delay repolarisation and lengthen the effective refractory period and duration of the action potential in Purkinje fibres as well as in atrial and ventricular muscle.[3] These effects occurred in our patients as a prolonged Q-T interval with a susceptibility to tachyarrhythmias. These phenomena are not typical after poisoning with other beta-blocking agents.[1]

The close correlation observed between the serum sotalol concentration and the Q-T interval suggests that the Q-T interval could be used as an index of the severity of sotalol intoxication.

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