expanded dogs inhibited sodium-potassium adenosine triphosphatase.[4] Finally, digoxin-like immunoreactive substance has been shown to have natriuretic activity.[5] This last finding prompted us to study whether concentrations of digoxin-like immunoreactive substance would be increased in a clinical setting such as congestive heart failure, in which natriuretic activity would be expected to be high.

Subjects, methods, and results

Plasma and urine were obtained from 15 patients with congestive heart failure (New York Heart Association class III or IV at time of study) who were not receiving digitalis or other drugs known to cross react with antidigoxin antibodies—for example, spironolactone. Twelve had ischaemic heart disease and three dilated cardiomyopathy. Plasma and urine samples were also obtained from 10 normal volunteers. Liver and renal function values were normal in all subjects.

Concentrations of digoxin-like immunoreactive substance were measured by a double antibody radioimmunoassay for digoxin (RIANEN, New England Nuclear, Billerica, MA, USA). The assay was slightly modified by including additional standards at the lower portion of the standard curve. The lower limit of detectability with 95% confidence limits was 0·06 nmol/l. In this assay there was no or insignificant cross reaction with hydrocortisone, deoxycorticosterone, 11-deoxycortisol, dehydroepiandrosterone, androstenedione, 17-hydroxyprogesterone, progesterone, aldosterone, or oestradiol. All samples were assayed in duplicate. In view of the observation of Valdes and Graves that the bulk of digoxin-like immunoreactive substance is protein bound and can be detected only after diluting and boiling serum,[1] we measured concentrations in native serum and in serum diluted to 1/4 in deionised water and boiled for 10 minutes. We also measured digoxin-like immunoreactive substance in untreated urine, and corrected for urine creatinine concentration.

In native serum of normal subjects no digoxin-like immunoreactive substance was detected. In native serum of the patients with congestive heart failure digoxin-like immunoreactive substance was detected in 11 cases with a mean concentration of 0·125 (SD 0·1) nmol/l (Student's t test, $p<0·001$) (table). The concentration of digoxin-like immunoreactive substance in diluted and boiled normal serum was 1·09 (0·15) nmol/l compared with 1·34 (0·29) nmol/l in congestive heart failure ($p<0·001$). Urinary concentrations of digoxin-like immunoreactive substance after correction for creatinine were significantly higher in patients with heart failure ($p<0·001$).

Digoxin-like immunoreactive substance in serum and urine

	Native serum (nmol/l)	Boiled serum (nmol/l)	Urine (nmol/l: creatinine, mmol/l)
Congestive heart failure:			
Mean (SD)	0·125 (0·10)	1·34 (0·29)	0·34 (0·08)
Range	(0-0·30)	(0·93-1·61)	(0·2-0·46)
Normal subjects:			
Mean (SD)	0	1·09 (0·15)	0·23 (0·08)
Range	—	(0·86-1·34)	(0·09-0·36)

Comment

Our results show that congestive heart failure must be added to the clinical states associated with increased concentrations of digoxin-like immunoreactive substance. Using the RIANEN assay for digoxin we found detectable concentrations of digoxin-like immunoreactive substance in 11 of 15 patients. In patients receiving digoxin digoxin-like immunoreactive substance is additive in the digoxin radioimmunoassay. Hence the presence of endogenous cross reacting material would falsely increase measured values, albeit only slightly. Impaired hepatic or renal function, which is often found in conjunction with heart failure, has been shown to increase the concentration of digoxin-like immunoreactive substance. The combined effects of congestive heart failure and hepatic or renal disease on digoxin-like immunoreactive substance may lead to more pronounced overestimation of true digoxin concentrations in patients receiving this drug.

Valdes and Graves found that diluting and boiling serum increase measurable concentrations of digoxin-like immunoreactive substance.[1] They suggested that these procedures liberate protein bound digoxin-like immunoreactive substance and allow determination of the total amount. We have shown that total digoxin-like immunoreactive substance is increased in the serum of patients with congestive heart failure and that the amount excreted in urine is also increased. These results suggest that the raised concentrations of digoxin-like immunoreactive substance found in congestive heart failure reflect increased synthesis of this material.

In view of the suggested physiological role of digoxin-like immunoreactive substance our results raise the intriguing possibility that concentrations of the substance are increased in patients with congestive heart failure as an adaptive phenomenon, analogous to similar alterations noted in concentrations of atrial natriuretic peptide in congestive heart failure.

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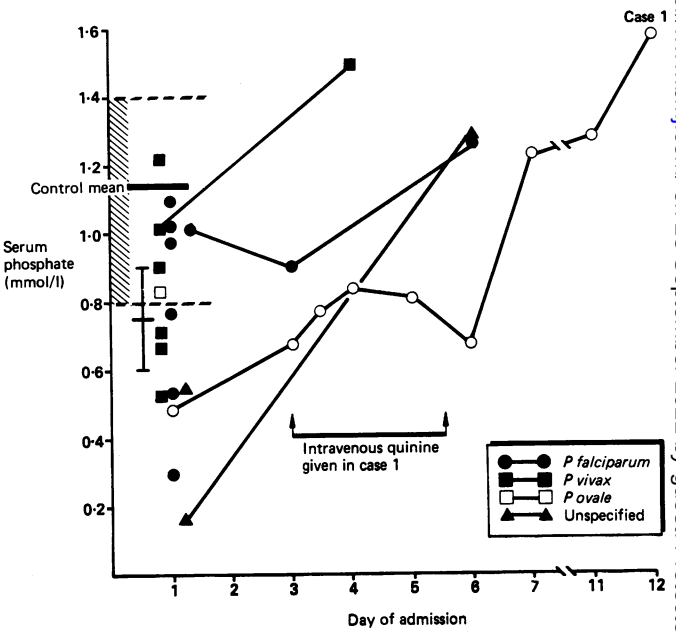
Hypophosphataemia: a feature of malaria?

Many patients with malaria admitted to this hospital have unexplained low serum phosphate concentrations. I report on 17 such patients; in one the phosphate concentration seemed to be related to treatment.

Patients and findings

Case 1—A 36 year old Welshman was admitted after returning from Kenya with a history of fever and headache. On examination his fever was confirmed and he was unwell but alert. A blood film showed a 10% parasitaemia with *Plasmodium falciparum*. His condition initially improved with oral quinine and the parasite count fell, but his blood film remained positive until day 5. On day 3 his condition deteriorated and he developed headache and drowsiness. He was given quinine 3 g in saline intravenously, as is recommended for patients with this degree of parasitaemia,[1] and sulfadoxine 3 g and pyrimethamine 150 mg (Fansidar) orally over days 3-5. Capillary glucose concentrations were estimated every three hours and ranged between 4·5 and 6·5 mmol/l. On day 5 he was alert and free from headache, and his condition then improved steadily.

Of 28 patients with malaria admitted between January 1984 and December



Serum phosphate concentrations in patients with malaria by plasmodial species. Vertical bar indicates mean concentration with 95% confidence interval in patients with malaria; solid horizontal bar indicates control mean; hatched area indicates normal range for the laboratory.

1986, 22 had their serum phosphate concentrations measured before any treatment was started. Four children aged 2-10 years and a pregnant woman were excluded from further analysis, which left 17 patients (11 men, six women; mean age 32 years, range 17-64).

The figure shows the serum phosphate concentration according to plasmodial species and day of admission. A total of 8885 consecutive measurements of phosphate concentration obtained with the same autoanalyser during March 1987 served as control values (mean 1·14 mmol/l); this control mean was significantly different from the mean in the patients with malaria on admission (0·75 mmol/l) (one sample, two tailed Student's t test: $t=-5{\cdot}57$, $p<0{\cdot}001$). Serum phosphate concentrations increased in all patients for whom subsequent values were available. In case 1 the phosphate concentration initially rose but then fell over days 4-6 coincident with the administration of intravenous quinine during his relapse (he received no other intravenous fluids during this time). It then rose sharply (figure).

There was no obvious cause for the low serum phosphate concentrations; six patients vomited, but in only case 1 was vomiting severe. Only one patient (case 1) was particularly unwell, and there was no correlation between the duration of the patients' symptoms and the serum phosphate concentration observed.

The mean serum calcium concentration in the patients with malaria on admission was 2·30 mmol/l uncorrected, and 2·25 mmol/l when corrected to an albumin concentration of 40 g/l; simple regression analysis showed a weak correlation with serum phosphate concentration, which was not significant ($r=0{\cdot}39$, $p=0{\cdot}13$). The mean albumin concentration was 38·4 g/l.

Comment

Acute severe hypophosphataemia (less than 0·32 mmol/l) in the absence of total body phosphate depletion results in cellular anoxia through depletion of intracellular adenosine triphosphate and may cause respiratory failure, encephalopathy, cardiac depression,[2] and haemolysis (by impaired red cell deformability).[3] Hypophosphataemia is associated with fever, persistent vomiting, and diarrhoea[2] but has not been reported with malaria. Giving carbohydrate or insulin may cause profound hypophosphataemia because of the intracellular shift of phosphate essential for glycolysis, glycogenolysis, glycogenesis, and other anabolic processes.[2] Intravenous quinine releases endogenous insulin[4] (which might account for the fall in serum phosphate concentration in case 1), but hypoglycaemia may occur before quinine is given. Furthermore, White *et al* reported hypoglycaemia in African children with malaria without hyperinsulinaemia and suggested that impaired gluconeogenesis and glycogenolysis were responsible.[5]

It is therefore not surprising that hypophosphataemia occurs in malaria—especially if quinine is administered—and theoretically it could aggravate the pathophysiological effects of the parasite. If these results are confirmed then serum phosphate concentration should be measured in all patients with malaria, especially those receiving intravenous quinine or carbohydrate, and hypophosphataemia should be rapidly corrected.

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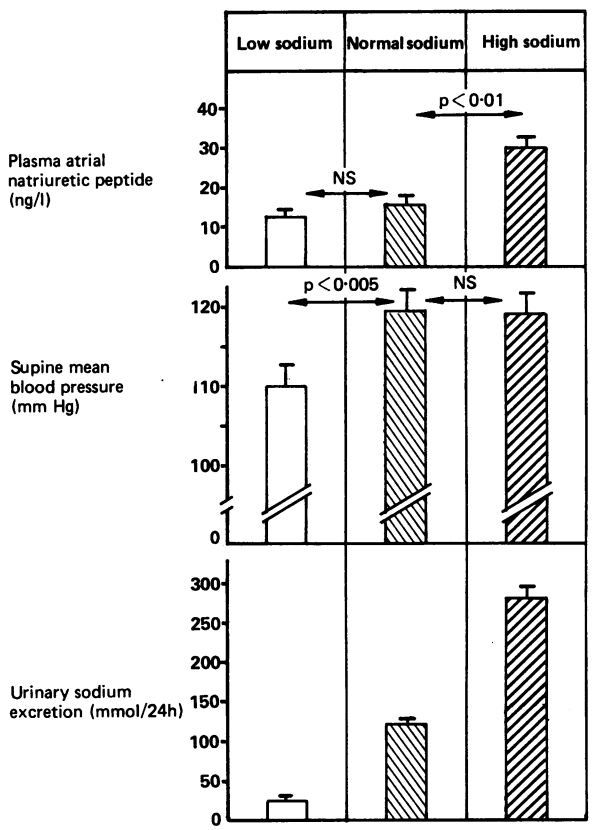
Plasma atrial natriuretic peptide in essential hypertension: effects of changes in dietary sodium

Plasma concentrations of atrial natriuretic peptides are raised in a substantial proportion of patients with essential hypertension,[1] but the relevance of these raised values, particularly in relation to changes in sodium intake and blood pressure, is not known. We have therefore studied the effect of changes in dietary sodium intake on plasma atrial peptides and on blood pressure in patients with untreated essential hypertension.

Patients, methods, and results

Twelve patients (seven men, five women; two black, 10 white) aged 39-68 years with uncomplicated essential hypertension and not receiving treatment were studied as outpatients. Plasma atrial peptide concentration, renin activity, and aldosterone and electrolyte concentrations, blood pressure, and 24 hour urinary sodium excretion (mean of two estimations) were measured with the patients having their usual sodium intake, on the fifth day of a low sodium diet (10 mmol/day), and on the fifth day of a high sodium diet (350 mmol/day), the sequence of low and high sodium intakes being allocated at random.[2]

Mean (SEM) plasma atrial peptide concentration when patients were having their normal sodium intake was 15·9 (3·0) ng/l, with a 24 hour urinary sodium excretion of 123·4 (8·2) mmol and an average supine blood pressure of 161 (6)/98 (2) mm Hg. Plasma atrial natriuretic peptide concentration increased to 30·1 (3·1) ng/l on the fifth day of the high sodium intake, but there was no overall significant change in values between the normal and fifth day of the low sodium intake (figure). Mean blood pressure was reduced from 119 (3) mm Hg during normal sodium intake to 110 (3) mm Hg on the fifth day of the low sodium intake, but there was no difference in blood pressure between the period of normal sodium intake and the fifth day of the high sodium intake (figure). Plasma renin activity and aldosterone concentration increased with the reduction in sodium intake and were suppressed on the fifth day of the high sodium intake; throughout the study there were no significant changes in plasma sodium or potassium concentration or urinary potassium or creatinine excretion and volume (results not shown).



Plasma immunoreactive atrial peptide concentrations, supine mean blood pressure, and urinary sodium excretion in 12 patients with untreated essential hypertension on a normal and fifth day of a low or high sodium intake. Values are means and SEM (bars). Significance of differences assessed by Student's paired t test (two tailed).

Comment

These findings show that the plasma concentration of atrial peptides in patients with essential hypertension may be influenced by changes in dietary sodium, as occurs in normotensive subjects.[2] In patients with essential hypertension, however, the main change in plasma atrial peptide values occurred when transferring from the normal to the high sodium diet, and there was little change when sodium intake was restricted. We and others[3] have previously recorded in hypertensive patients a blunted response of the renin system to a reduction in sodium intake and shown that, at least in part, the fall in pressure with sodium restriction was due to the relative lack of rise in plasma renin activity with sodium restriction. The mechanism for this blunted renin response, however, is unresolved, but in view of the renin inhibitory action of the atrial peptides[4] the absence of a fall in circulating