SHORT REPORTS

Hyponatraemia in congestive heart failure during treatment with captopril

The oral converting-enzyme inhibitor captopril shows promise in the treatment of cardiac failure. We used the drug in five patients with congestive heart failure that had proved unresponsive to conventional treatment and observed a clear-cut fall in plasma sodium concentration.

Methods and results

We studied five men aged 54-72 years with congestive heart failure (New York Heart Association functional class III or IV) secondary to coronary artery disease. All had previously received conventional medications, including vasodilators, without success. Throughout the seven-day study they received a constant dietary intake of sodium (33-48 mmol(mEq)/day) and potassium (73-100 mmol(mEq)/day); body posture was restricted to the supine and sitting positions in bed; and their regular doses of digoxin (62.5-250 µg/day) and frusemide (80-500 mg/day) were continued. All other drugs were stopped at least five days before the study. After a two-day run-in period captopril was administered by mouth in an eight-hourly incremental regimen (6.25-150 mg/dose), and blood was drawn one hour after each dose increase for measurement of plasma electrolyte and hormone concentrations.

Mean ($\pm$ SEM) plasma concentrations of sodium, angiotensin II, and aldosterone and body weight in five patients before and during treatment with captopril for cardiac failure.

Conversion: SI to traditional units—Sodium: 1 mmol/l = 1 mEq/l. Angiotensin II: 1 pmol/l $\approx$ 1 pg/ml. Aldosterone: 1 pmol/l $\approx$ 36 pg/100 ml.

Captopril induced a well-defined fall in plasma sodium concentration, which reached a nadir 7 mmol/l below baseline values on the third and fourth days of treatment (figure). Plasma concentrations of angiotensin II¹ and aldosterone² declined in parallel with those of sodium (figure), and for all data ($n=70$) significant relations between plasma concentrations of angiotensin II and sodium ($r=0.43$, $p<0.001$) and between concentrations of aldosterone and sodium ($r=0.37$, $p<0.001$) were observed. In contrast to the decline in plasma sodium, angiotensin II, and aldosterone concentrations, plasma renin activity increased appreciably. For all data ($n=70$) there was a significant reciprocal relation between plasma renin activity and concurrent plasma sodium concentrations ($r=-0.53$, $p<0.001$). Plasma potassium concentrations also rose, from a mean ($\pm$ SEM) of 3.55 ± 0.16 mmol/l before treatment to 4.40 ± 0.13 mmol/l on the fifth day of treatment.

Treatment with captopril did not alter cumulative sodium balance or body weight (figure). Haemodynamic improvement occurred in all patients during treatment, and no symptoms attributable to hyponatraemia were observed.

Comment

We found that plasma sodium concentration fell when captopril was used to treat resistant heart failure. A parallel decline in circulating concentrations of angiotensin II and aldosterone and reciprocal increments in plasma renin activity and plasma potassium concentrations were noted. It is tempting to relate the fall in plasma sodium and the rise in plasma potassium concentrations to the decrease in aldosterone concentrations, since similar though less pronounced electrolyte changes are seen during treatment with spironolactone in congestive heart failure.³ Interestingly, frank hyponatraemia is not often observed in the syndrome of hyporeninaemic hypoaldosteronism unless there is coincidental sodium restriction or volume depletion.⁴ Since angiotensin II can stimulate thirst, release of antidiuretic hormone, and water retention by the kidneys,⁵ a fall in angiotensin II taken alone might be expected to result in a rise rather than a fall in plasma sodium concentration. Whatever the mechanisms entailed, plasma sodium as well as potassium concentrations should be monitored during captopril treatment in cardiac failure.

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Diagnosis and cure of recurrent urinary infection with microaerophilic and anaerobic bacteria

There has recently been considerable speculation whether microaerophilic¹ and anaerobic bacteria² cause urinary tract infections. We describe a patient who repeatedly had "sterile pyuria" whom we found to be suffering from repeated infections caused by microaerophilic and anaerobic organisms.

Case report

A 76-year-old fit-looking and active woman with a 13-year history of urinary tract infection caused by *Escherichia coli* and *Proteus spp* first attended our clinic in October 1978. An ileocystostomy had been carried out in May 1966 to increase her bladder capacity. Her non-functioning right kidney (extensively calcified and containing a large staghorn calculus) had been removed in January 1972. We found raised serum urea (15.7 mmol/l

(95.6 mg/100 ml)) and creatinine (170 μ mol/l (1.9 mg/100 ml)) concentrations, but electrolyte, liver function, and haematological values were normal. An excretory pyelogram performed in May 1980 showed no abnormalities.

Two mid-stream specimens of urine (MSU) showed gross pyuria (up to 30×10^9 /l white blood cells) but no significant bacterial growth aerobically. The result of culture for *Mycobacterium tuberculosis* was negative. Subsequent MSUs were cultured both anaerobically and aerobically using a dilution technique,³ and the findings are shown in the table. A microaerophilic species, *Streptococcus milleri* (10^7 /ml), and four species of strict anaerobes were present in two successive specimens, with gross pyuria, but few aerobic organisms were isolated ($<10^3$ /ml).

Serial results of MSU culture and white cell counts and treatment given.

Three separate courses of antibiotic treatment, first with cephadrine (1 g 12-hourly) then twice with amoxycillin (500 mg 8-hourly), all produced a similar clinical response: the bacteriuria was initially eradicated and pyuria greatly reduced, but relapse occurred each time, *Str milleri* returning in large numbers ($>10^7$ /ml). *Peptococcus* sp was also present (10^7 /ml) on one occasion. Bacteriological relapse was associated with an increase in white cell excretion. Eventually *Str milleri* disappeared spontaneously, but an aerobic streptococcus (10^6 /ml) was then found. Combined treatment with nitrofurantoin (50 mg 12-hourly) and sulphadiazine (150 mg 12-hourly) cleared the streptococci, but the urine then contained large numbers of anaerobic species (predominantly *Bacteroides* spp, 10^9 /ml). The patient remained symptom-free at all times. In view of the recurrent nature of relapses and reinfections, and the fact that the patient was well, no further antibiotic treatment was given, and the infection cleared spontaneously. Four months later *Str milleri* (10^6 /ml) was again found; phenoxymethylpenicillin (250 mg 8-hourly) cleared this infection, and since March 1980 the urine has remained free of anaerobes and microaerophilic bacteria.

Comment

Anaerobes and microaerophilic bacteria may be isolated in large numbers ($>10^5$ /ml) in mid-stream urine specimens from patients without signs of infection³ and from normal subjects (unpublished work). Nevertheless, we are convinced, after repeated cultures and temporary eradication of bacteriuria together with concomitant reductions of pyuria after treatment, that genuine infective processes were occurring in this patient. Our findings lend weight to the theory that growth conditions for strict anaerobes and microaerophilic organisms are favourable in the urinary tract⁴ and that such species can cause true infections.⁵

In this case *Str milleri* was usually the predominant species, often accompanied by several species of strict anaerobes in large numbers ($>10^5$ /ml) always including *B melaninogenicus*. Metronidazole was not given because it is inactive against *Str milleri*.

Our findings highlight the difficulty of treating infections of this nature, which can be associated with urological abnormalities. Thus when persistent "sterile pyuria" is reported the clinician should look for microaerophilic and anaerobic bacteria as well as excluding infection by *M tuberculosis*. In this patient the use of appropriate culture techniques enabled us to diagnose the microaerophilic and anaerobic infection and eventually to eradicate it.

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Osteomalacia developing during treatment of osteoporosis with sodium fluoride and vitamin D

Combined treatment with sodium fluoride, calcium, and vitamin D is claimed to be beneficial in some patients with osteoporosis.^{1,2} Fluoride alone leads to accumulation of unmineralised bone, producing the histological picture of osteomalacia.³ The addition of calcium or vitamin D, or both, is believed to prevent this complication.^{1,2} We report a case where osteomalacia developed during sodium fluoride treatment despite large doses of vitamin D and associated high plasma 25-hydroxyvitamin D (25-OHD) concentrations.

Case report

A 61-year-old woman presented in 1978 with a 15-year history of lower back pain which had rapidly increased over the previous nine months. Plasma concentrations were: calcium 2.50 mmol/l (10 mg/100 ml), phosphate 1.1 mmol/l (3.4 mg/100 ml), and plasma alkaline phosphatase 9 KA U/100 ml. Radiographs showed severe osteoporosis with vertebral compression fractures of T 7, 8, and 11 and L 1, 3, and 5. Iliac bone tissue was normal on biopsy (table). Sodium fluoride 50 mg daily, vitamin D₂ 50 000 U weekly,

Quantitative bone histology before and after sodium fluoride and vitamin D treatment. The mineralisation rate was not measured in the first biopsy

	Before treatment (May 1978)	After treatment (March 1980)	Normal (mean $\pm$ SD)
Cancellous bone volume (% total cancellous area)	21.5	25.6	23.7 $\pm$ 4.9
Osteoid volume (% total cancellous volume)	3.9	18.5	3.9 $\pm$ 1.9
Total resorption surface (% total cancellous surface)	7.3	77.7	3.0 $\pm$ 1.2
Calcification fronts (% total osteoid surface)	60.0	33.3	76.4 $\pm$ 7.8
Mineralisation rate (μ /day)		<0.1	0.64 $\pm$ 0.06

and calcium gluconate 600 mg twice daily were given by mouth. Calcium supplements were discontinued after two months because the patient was unable to tolerate them. Dietary calcium intake was assessed at 851 mg/day. Renal function was normal. The plasma 25-OHD concentration was measured by competitive protein-binding assay⁴ and plasma 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) by radioimmunoassay.⁵ Undecalcified sections (8 μ m) of transiliac bone tissue were quantitatively assessed. Control values were obtained from six healthy women aged 51-69 years (mean 58). The mineralisation rate was measured by double labelling with demethylchlorotetracycline.

During treatment bone pain increased and three further vertebral compression fractures occurred. Plasma calcium, phosphate, and alkaline phosphatase concentrations remained normal throughout treatment and in March 1980 were 2.49 mmol/l (10 mg/100 ml), 0.9 mmol/l (2.86 mg/100 ml), and 11 KA U/100 ml respectively. At this time the plasma 25-OHD concentration was 125 nmol/l (50 ng/ml) and the plasma 1,25-(OH)₂D₃ was 19 pg/ml. Bone biopsy in March 1980 showed moderately severe osteomalacia and secondary hyperparathyroidism. Most of the bone and osteoid showed a normal lamellar pattern under polarised light.