ADDENDUM—In view of the long term benefit apparently due to chiropractic we initiated a three year follow up, sending multiple reminders to those initially not responding. By mid April 1990—beyond the closing date for the earlier results—data were available for 113 patients, representing a 79% response. At three years the mean fall in Oswestry score for those treated by chiropractic was 9·6% points more than for those treated in hospital (p=0·01). The fall was greater (13·8% p=0·003) among those presenting with current episodes of more than a month's duration than for those presenting with episodes of less than a month (5·3%, NS). Among those with a previous history of back pain, the improvement in Oswestry score at three years was 9·7% points greater in patients treated by chiropractic than those treated in hospital (p=0·02). A similar difference between the two forms of treatment (9·4%) was found among those with no previous history of back pain, but numbers in this group were smaller and the difference was not significant.

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Low molecular weight heparins and hypoaldosteronism

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Treatment with heparin can impair production of aldosterone,[1,2] though this is usually not clinically important. We diagnosed hyperkalaemia related to hypoaldosteronism in a 79 year old woman who was being treated with low molecular weight heparin; the condition resolved when the treatment was withdrawn. This prompted a prospective, randomised systematic study of the effects of the low molecular weight heparins on adrenal function.

Patients, methods, and results

Twenty seven patients in hospital who were confined to bed were given low molecular weight heparin, either Fraxiparine (3300 anti-factor X a units daily) or enoxaparin (2100 units daily), to prevent thromboembolic complications. The treatment was stopped when the patients could get up. The doses were available prepackaged in subcutaneous injection syringes and designed to prevent venous thrombosis. Patients who had diabetes mellitus or renal insufficiency, or were taking drugs known to interfere with aldosterone metabolism (converting enzyme inhibitors or antialdosterone drugs) were not included. Two patients continued taking frusemide (20 mg/day) during the study; none of the other patients took diuretics. All patients received the standard hospital diet (normal salt intake) throughout the study.

Blood samples were taken before treatment, after four days of treatment, and three days after treatment had been stopped. Blood was taken in the morning after at least 12 hours' supine rest. It was analysed for serum sodium and potassium concentrations with an automatic analyser (Technicon, Dublin, Ireland), and plasma aldosterone and cortisol concentrations and renin activity with a radioimmunoassay. (The plasma samples were kept at −20°C until the end of the analysis, and each patient's plasma was assayed for all three periods simultaneously to eliminate interassay variations.)

Results

Twelve patients received enoxaparin (seven women, five men; mean (SD) age 68·3 (11·7) years (range 37-79)), and 15 received Fraxiparine (11 women, four men; mean age 70·3 (13·0) years (range 34-85)). The plasma aldosterone concentration had decreased after four days of treatment by a mean of 43·9 (4·11)% (p<0·001). Three days after the treatment was stopped the concentration had almost returned to initial values (table). No difference was found between patients receiving enoxaparin and Fraxiparine. The two patients taking frusemide, who initially had high plasma aldosterone concentrations also had decreased plasma aldosterone concentrations during treatment with low molecular weight heparin. In four patients (three taking enoxaparin, one Fraxiparine) plasma aldosterone was not detectable during treatment.

The mean serum potassium concentration increased significantly (p<0·001) during treatment with both drugs and decreased after treatment was stopped. The other variables measured did not change significantly.

Comment

We found that low molecular weight heparin inhibited the production of aldosterone, as does standard heparin. The mechanism whereby heparin inhibits aldosterone biosynthesis is not proved. Several

Mean (SD) values of biochemical variables measured in elderly patients before, during (after four days' treatment), and (three days) after treatment with low molecular weight heparins

	Fraxiparine			Enoxaparin		
	Before	During	After	Before	During	After
Plasma aldosterone (pmol/l)	332·6 (204·6)	184·7 (109·2)**	266·6 (150·4)*†	285·4 (105·8)	174·2 (113·7)**	220·4 (97·8)*†
Plasma renin activity (nmol/l/h)	33·4 (24·6)	31·4 (14·9)	30·3 (26·0)	23·1 (14·2)	25·5 (10·0)	22·2 (7·7)
Cortisol (nmol/l)	511·1 (114·3)	516·1 (156·2)	496·8 (149·1)	527·3 (101·9)	489·4 (150·2)	664·5 (133)
Serum sodium (mmol/l)	141 (2·5)	139·7 (2·2)	139·6 (1·8)	139·6 (2·6)	138·6 (3·4)	138·5 (2·9)
Serum potassium (mmol/l)	4·0 (0·3)	4·4 (0·4)**	4·2 (0·4)	4·1 (0·3)	4·5 (0·4)**	4·3 (0·4)

*p<0·05, **p<0·001 Compared with value before treatment by paired *t* test.
†p<0·05 Compared with value during treatment by paired *t* test

investigators have suggested that heparin inhibits 18-hydroxylase, but other mechanisms are possible—for example, a non-specific toxic effect on granulosa cells, a modification of the production of adrenocorticotrophic hormone, or inhibition by the preservative chlorbutol.[3-5] We found no change in plasma cortisol concentrations, which probably excludes an effect on adrenocorticotrophic hormone, and decreased aldosterone concentrations without any change in plasma renin activity, which could suggest a direct effect on the glomerular zone of the adrenal gland. Neither drug contained chlorbutol.

To our knowledge this is the first time that reductions in aldosterone concentrations have been reported in patients receiving low molecular weight heparin. The changes in aldosterone concentrations could have been increased by the age of our patients. Whatever its exact cause the effect of both standard and low molecular weight heparin could be clinically important for patients whose renin-angiotensin-aldosterone axis is inhibited by a drug, a disease, or age. As the use of low molecular weight heparin has increased rapidly, mainly because of its ease of use and low haemorrhagic risk, we think that doctors should be aware of the potential risk incurred by their patients and should be especially cautious when patients are already at risk of decreased aldosterone function or of hyperkalaemia. This is important because some or most of the patients at risk are likely to need heparin or preventive anticoagulation. The serum potassium concentration of such patients should be monitored when any type of heparin is given.

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Renographic monitoring of renal function in patients with Crohn's disease treated with low dose cyclosporin: a controlled study

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Nephrotoxicity is the main obstacle to the clinical use of cyclosporin, a potent T cell specific immunosuppressant.[1] Its increasing use in non-fatal immune diseases emphasises the need for additional simple ways of monitoring cyclosporin nephrotoxicity.

Hippuran renography is a sensitive method of measuring effective renal plasma flow and renal tubular function.[2] Following an injection of ^{131}I hippuran two values are measured; firstly, the time taken to achieve maximal activity, and, secondly, the residual activity 20 minutes after the injection (T_{20}). A correlation has been found between the T_{20} and the degree of interstitial fibrosis seen in renal biopsies obtained from five patients with diabetes of recent onset who were being treated with cyclosporin (unpublished data). This correlation led us to perform renography on patients entering our placebo controlled, double blind, multicentre trial of low dose cyclosporin treatment in Crohn's disease.[3]

Patients, methods, and results

Thirty eight Danish patients (aged 16-60 years (median 30)) with chronically active Crohn's disease took part in the study. Patients with renal disease, urinary tract disease, or both, were excluded, as were patients receiving nephrotoxic drugs. All had ^{131}I hippuran renography and ^{51}Cr-EDTA clearance performed.[3] Cyclosporin was given in an initial dose of 5·0-7·5 mg/kg/day.[3] Renal function was measured three times: at initial examination, before treatment was started; at a final examination, performed after a median of three months; and at a follow up examination, performed a median of four to six months after stopping the cyclosporin.

The median final T_{20} was significantly greater in both kidneys in patients who had received cyclosporin than in those who had received a placebo (table). Ten (48%) of the patients treated with cyclosporin and three (18%) of the patients given a placebo had a final T_{20} in both kidneys that was above the normal range ($p=0·11$), whereas only a fifth of all the patients in the two groups had an initial T_{20} that was above the normal range. No differences in T_{20} were seen between the two groups at follow up. The median ^{51}Cr-EDTA clearance was lower in the 10 patients receiving cyclosporin who had an increased T_{20} (80 ml/min/1·73 m^2 (range 33-90)) compared with the 11 patients with normal values of T_{20} (95 ml/min/1·73 m^2 (range 61-116)) ($p=0·011$). The median plasma creatinine concentration in those with a raised T_{20} taking cyclosporin was higher (99 μmol/l (range 70-150)) than in those with a normal T_{20}

Results of renal function tests in patients with Crohn's disease treated with low dose cyclosporin or placebo. Values are medians (range)

Group and examination	Time (months)	No	^{51}Cr EDTA clearance (ml/min/1·73 m^2)	^{131}I Hippuran renography: Time to maximal activity (peak)* Left kidney (min)	Time to maximal activity (peak)* Right kidney (min)	Residual activity at 20 min (T_{20})** Left kidney (%)	Residual activity at 20 min (T_{20})** Right kidney (%)	Plasma creatinine concentration (μmol/l)
Cyclosporin								
Initial	0	11	99 (56-139)	3·3 (2·1-5·3)	2·6 (0·0-3·4)	12 (6-91)	11 (0-34)	83 (50-121)
Final	3 (1-5)	21	88 (33-116)	3·0 (2·0-6·3)	3·0 (2·0-7·7)	22 (11-86)	23 (12-76)	89 (69-150)
p Value (*v* placebo)***			0·063 (NS)	NS	NS	0·022	0·005	0·025
p Value (*v* initial)****			NS	NS	NS	NS	0·019	0·074 (NS)
Follow up	9 (5-9)	9	105 (87-136)	3·0 (1·7-3·6)	3·0 (2·0-4·1)	13 (4-18)	17 (9-29)	76 (60-106)
Placebo								
Initial	0	9	93 (84-103)	4·0 (2·1-5·6)	3·0 (2·2-6·1)	23 (9-41)	15 (8-52)	84 (74-110)
Final	3 (2-6)	17	98 (61-131)	3·3 (1·6-6·3)	3·5 (0·0-6·6)	16 (8-47)	16 (0-41)	80 (51-111)
Follow up	7 (4-12)	8	65 (65-134)	3·5 (2·7-7·4)	3·0 (0·0-4·7)	19 (8-55)	14 (0-100)	80 (69-140)

*Peak normally <3·5 min.[4]
**T_{20} normally <22%. Defined as count rate at 20 min divided by count rate at time of maximal activity with a diuresis >2 ml/min (fulfilled by all patients studied).[4]
***Mann Whitney test for unpaired data.
****Pratt's test for paired data: cyclosporin n=11, placebo n=9.