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.

- 1 O'Kelly R, Magee F, McKenna J. Routine heparin therapy inhibits adrenal aldosterone production. *J Clin Endocrinol Metab* 1983;56:108-12.
- 2 Ponce SP, Jennings AE, Madias NE, Harrington JT. Drug-induced hyperkalemia. *Medicine (Baltimore)* 1985;64:357-70.
- 3 Abbott CE, Monkhouse FC, Steiner JW, Laidlaw JC. Effect of a sulphated mucopolysaccharide (RO1-8307) on zona glomerulosa of the rat adrenal gland. *Endocrinology* 1966;78:651-6.
- 4 Conn JW, Rovner OE, Cohen EL, Anderson JE. Inhibition by heparinoid of aldosterone biosynthesis in man. *J Clin Endocrinol Metab* 1966;26:527-32.
- 5 Sequeira SJ, McKenna J. Chlorbutol, a new inhibitor of aldosterone biosynthesis identified during examination of heparin effect on aldosterone production. *J Clin Endocrinol Metab* 1986;63:780-4.

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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 ¹³¹I hippuran two values are measured; firstly, the time taken to achieve maximal activity, and, secondly, the residual activity 20 minutes after the injection (T₂₀). A correlation has been found between the T₂₀ 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 ¹³¹I hippuran renography and ⁵¹Cr-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 T₂₀ 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 T₂₀ 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 T₂₀ that was above the normal range. No differences in T₂₀ were seen between the two groups at follow up. The median ⁵¹Cr-EDTA clearance was lower in the 10 patients receiving cyclosporin who had an increased T₂₀ (80 ml/min/1.73 m² (range 33-90)) compared with the 11 patients with normal values of T₂₀ (95 ml/min/1.73 m² (range 61-116)) (p=0.011). The median plasma creatinine concentration in those with a raised T₂₀ taking cyclosporin was higher (99 µmol/l (range 70-150)) than in those with a normal T₂₀

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)*		Residual activity at 20 min (T ₂₀)**		Plasma creatinine concentration (μmol/l)
				Left kidney (min)	Right kidney (min)	Left kidney (%)	Right kidney (%)	
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.

**T₂₀ 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).*

***Mann Whitney test for unpaired data.

****Pratt's test for paired data: cyclosporin n=11, placebo n=9.

taking cyclosporin (83 $\mu\text{mol/l}$ (range 69-103)) ($p=0.023$).

An intraindividual comparison was made and the median increase in T_{20} from the initial examination to the final examination (with an average of the left and right kidney changes) was 61% (range -41% to 267%) in the group treated with cyclosporin. In comparison, the T_{20} of the patients who were given a placebo fell by 12% (range -75% to 43%) ($p=0.0062$). The decrease in ^{51}Cr -EDTA clearance was larger (median fall of 23%, range -39% to 6%) in patients in whom the T_{20} had increased above the median increase in T_{20} (61%) than in the remaining patients treated with cyclosporin (fall of 1%, range -6% to 48%) and all the patients receiving a placebo (1%, range -10% to 27%) ($p=0.015$).

Comments

Because the renal clearance of hippuran occurs predominantly by tubular uptake and secretion, the increased T_{20} most probably resulted from a tubulopathy. Recent studies have suggested, however, that cyclosporin is not directly toxic to the tubular cells but that the tubulopathy is secondary to primary changes in renal haemodynamics.¹ We found no difference in the final ^{51}Cr -EDTA clearance, and, though the exact p value suggested a type II error, no significant change was seen when the patients treated with cyclosporin served as their own controls. Furthermore, no changes in the time taken to achieve maximal activity on the renograms were found. We therefore concluded that in the short term low dose cyclosporin does not interfere appreciably with renal haemodynamics. Nevertheless, the finding of increased values of T_{20} in the patients treated with cyclosporin suggests that the

tubular cells might be sensitive to small, and thus by the methods used here not readily detectable, changes in renal blood flow. This is in keeping with a slight, but significant, increase in the median plasma creatinine concentration of the group treated with cyclosporin (table), as creatinine is cleared by glomerular filtration and by tubular secretion.

Although these preliminary results might prove to have no biological importance—as opposed to statistical significance—we suggest that hippuran renography is an additional way of monitoring renal function in patients without transplants who are treated with cyclosporin.

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- 1 Dieperink H. Cyclosporin A nephrotoxicity. *Dan Med Bull* 1989;86:235-48.
- 2 Blaufox MD, Britton KE, Nimmon CC, Wedeen RP. The radionuclide renogram. In: Blaufox MD, ed. *Evaluation of renal function and diseases with radionuclides. The upper urinary tract*. Basel: Karger, 1989:98-129.
- 3 Brynskov J, Freund L, Nørby Rasmussen S, et al. A placebo-controlled, double-blind, randomised trial of cyclosporine therapy in active chronic Crohn's disease. *N Engl J Med* 1989;321:845-50.
- 4 Mogensen P, Munck O, Giese J. ^{125}I -hippuran renography in normal subjects and in patients with essential hypertension. *Scand J Clin Lab Invest* 1975;35:301-6.
- 5 Bröchner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults. *Dan Med Bull* 1978;25:181-202.

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Split skin grafting in children with immune deficiencies

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A belief that healing will be poor in children with immunodeficiency disease may delay referral for surgical treatment of skin defects. We report on three children with an immunodeficiency or haematological disease complicated by chronic skin lesions in whom rapid healing was achieved by radical debridement and split skin grafting.

Case reports

Case 1—A 15 year old boy with a B cell leukaemia developed chronic graft versus host disease after receiving a bone marrow transplant. A large circumferential ulcer affecting most of his left lower leg resulted. Conservative treatment for six months was unsuccessful, and so surgical debridement and split skin grafting were undertaken; 75% of the graft took. The unhealed areas required further grafting, but complete healing was achieved in five weeks.

Case 2—A 4 year old boy with hyperimmunoglobulin E syndrome was referred with a three month history of a chronic soft tissue infection of the right thumb. An abscess at the site had been drained and debrided on several occasions. Conservative management with parenteral antibiotics did not produce any improvement. The thumb was then radically debrided and a split skin graft applied. Parenteral antibiotics were continued. The whole of the graft took, with complete resolution of the infection at one week.

Case 3—A 3 year old boy with a six week history of idiopathic acquired aplastic anaemia developed a necrotic ulcer over the right ulnar styloid. After one month of conservative treatment the lesion was excised and the defect covered with a split skin graft. Blood, platelets, granulocytes, and parenteral antibiotics were given perioperatively. The initial graft did not take, but further debridement and skin grafting resulted in complete healing at one week.

Comment

Two major phases are important in the success of skin grafting—namely, serum imbibition and vascularisation. The graft survives initially by absorbing serum from the host site, but within 48 hours endothelium grows into it and a circulation is established.¹ Any vascular bed may support a skin graft, but connective tissue denuded of its vascular covering will not (for example, tendon without paratenon).

In graft versus host disease immunocompetent T lymphocytes are introduced into an immunosuppressed, histoincompatible host. They recognise foreign host antigens, become activated, and attack host cells.² This occurs particularly in the skin. A healed skin graft will be susceptible to the same attack, but the initial take of the graft should not be compromised as T lymphocytes play no part in either serum imbibition or vascularisation. The hyperimmunoglobulin E syndrome is a primary immunodeficiency disease characterised by recurrent staphylococcal abscesses and an increased serum IgE concentration.³ This abnormal response to an antigen plays no part in the take of a skin graft and will not directly interfere with healing. Idiopathic acquired