Symptoms related to blood pressure, pulse rate, and blood concentrations of cortisol, zidovudine, and the 5-O-glucuronide of zidovudine (GAZT) in patient given zidovudine 200 mg and placebo

Time (min)	Patient supine: Blood pressure (mm Hg)	Patient supine: Pulse (beats/min)	Patient erect: Blood pressure (mm Hg)	Patient erect: Pulse (beats/min)	Plasma cortisol (nmol/l)	GAZT (μmol/l)	Zidovudine (μmol/l)	Symptoms
			Zidovudine 200 mg given at time 0					
−30	113/72	87	112/69	98		<2·0	<0·25	None
0	112/69	84	115/69	91	204	<2·0	<0·25	None
30	131/74	76	108/68	89		24·2	5·6	Slightly dizzy
40	111/65	80	Unrecordable					Very giddy, hungry, pale
50	123/74	74	118/65	83				
60	107/70	81	119/69	98	139	19·1	2·5	Less giddy, hungry
75	111/73	76	112/71	93				Not giddy, hungry
90	116/70	80	118/75	90	120	7·7	1·4	None
120	125/75	77	126/74	100	111	4·3	1·0	
150	129/77	73	123/67	89	171	2·5	0·6	
			Placebo given at time 0					
−30	108/66	86	109/58	93	233	<2·0	<0·25	
0	114/72	82	105/66	92	191	<2·0	<0·25	
30	119/73	81	117/74	92	147	<2·0	<0·25	
40	124/72	82	119/70	88				
50	120/71	79	122/69	90				
60	124/77	80	120/69	90	125	<2·4	<0·30	
75	114/72	78	117/66	94				
90	116/68	77	124/67	95	94	<2·0	<0·25	
120	117/71	75	115/68	90	99	<2·4	<0·30	
150	117/73	75	120/64	98	88	<2·0	<0·25	

Seven weeks later, at 7 am on consecutive mornings, a double blind placebo controlled challenge was performed. An intravenous cannula was inserted with the patient resting on an examination couch. Blood pressure and pulse rate were recorded with an electronic Colin sphygmomanometer (103 N Mark 3) half an hour before the drug was given; when the patient took two unmarked capsules; and at set intervals thereafter. The patient independently recorded any symptoms. Blood (20 ml) was taken via the cannula at set intervals and aliquots of plasma and serum immediately frozen at − 20°C. Blinded specimens were assayed for both zidovudine (limit detection 0·25 μmol/l) and a major metabolite, the 5-*O*-glucuronide of zidovudine (3-azido-3-deoxy-5-*B*-D-glucopyranuronosylthymidine; GAZT) (limit of detection 2·0 μmol/l), by high performance liquid chromatography (table). There was no appreciable abnormality or fluctuation in serial concentrations of sodium, potassium chloride, bicarbonate, urea, creatinine, calcium, phosphate, albumin, and magnesium.

There was no evidence of autonomic neuropathy: the response of blood pressure and pulse to the Valsalva manoeuvre was normal. The short tetracosactrin stress test showed a suboptimal response from a baseline value of 362 nmol/l to 517 nmol/l at 30 minutes.

Comment

Postural hypotension related to zidovudine has not been reported previously. Dizziness, however, was reported in a small number of patients in both the group given zidovudine and the group given placebo in a controlled trial, but the nature and timing of the symptoms were not stated.[4] In our patient the symptoms occurred only after he took zidovudine and coincided with the raised blood concentrations of both zidovudine and the metabolite that we measured. This drug profile corresponds with the published data on the pharmacokinetics and bioavailability of zidovudine in humans.[5]

We postulate that zidovudine or its metabolites, or both, have a direct but transient vasomotor effect related to dose that is not clinically apparent unless there is underlying adrenocortical insufficiency. Even allowing for normal diurnal variation, the mid-morning plasma cortisol concentrations were subnormal and there was no increase in cortisol concentration related to stress. Alternatively, zidovudine may have a direct effect on the autonomic system. We do not think that the patient's previous short course of ketoconazole and weak topical betamethasone were contributory.

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Dupuytren's contractures in patients infected with HIV

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A free radical mechanism for the pathogenesis of Dupuytren's contracture has been established,[1] and there is evidence for increased activity of free radicals in patients infected with HIV.[2] We compared the prevalence of Dupuytren's contractures in such patients with that in patients negative for HIV.

Patients, methods, and results

Fifty men (age range 19-54) serially admitted to hospital with complications of HIV infection were examined independently by two doctors for clinical evidence of Dupuytren's contractures. These were regarded as present only if both doctors agreed. A control group of 50 men seen as outpatients in a sexually transmitted disease clinic, who were negative for HIV antibody, were examined similarly.

The men's occupational histories and histories of alcohol consumption, epilepsy, diabetes mellitus, and all current medicines were obtained. Their livers were examined for hepatomegaly clinically and by ultrasonography or computed tomography; liver function was assessed by measurement of aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase activities; and fasting blood glucose concentration was measured. In the patients with HIV infection the date on which HIV antibody had first been detected was noted and plasma p24 antigen concentrations and CD4+ lymphocyte counts were measured (table).

All 50 patients with HIV antibodies had advanced disease (48 had stage IV, as classified by the Centers for Disease Control, and two stage III). Eighteen of these patients had Dupuytren's contractures (nine bilateral). One clinician thought that a thickening of the palmar aponeurosis was present in a further six patients (these were not included in the analysis). None of the 50 control patients had Dupuytren's contractures. Among the patients infected with HIV raised fasting blood glucose concentrations, biochemical abnormalities of liver function, hepatomegaly, high alcohol

*Data on 50 patients infected with HIV**

	No of patients	No with Kaposi's sarcoma	No with opportunistic infections	Mean CD4+ lymphocytes ($\times 10^6$/l)	Mean HIV p24 antigen (U/l)	No with epilepsy or taking anticonvulsants	No with alcohol consumption >2 units/day	No with clinical or radiological hepatomegaly
Patients with Dupuytren's contracture	18	6	15	59	152 000	1	3	5
Bilateral	9	3	7	43	121 000		2	2
Unilateral	9	3	8	75	182 000	1	1	3
Patients without Dupuytren's contracture	32	11	25	52	75 000	2	5	4
Total	50	17	40	54	103 000	3	8	9

*None of the patients had diabetes mellitus.

consumption, history of epilepsy or diabetes mellitus, and use of anticonvulsant drugs were no more common in those with Dupuytren's contractures (Student's *t* test). The presence of Dupuytren's contracture was not correlated with immunological function as measured by absolute CD4+ lymphocyte count, concentration of p24 antigen, time since HIV antibody was first detected, particular opportunistic infections, any drug, or tumours associated with HIV.

Comment

The prevalence of Dupuytren's contracture in the general population is 4% to 5·6%[3] and increases with age and a family history of the condition.[4] It is associated with heavy manual labour, trauma, epilepsy, diabetes mellitus, and alcoholic liver disease. None of these risk factors accounted for the condition in our patients, among whom the prevalence was 36%.

Oxidation by free radicals may be a cause of Dupuytren's contracture as ischaemia related conversion of xanthine dehydrogenase to xanthine oxidase, which reduces oxygen to yield superoxide free radicals, has been shown in surgical specimens of Dupuytren's contractures.[1] These free radicals are thought to induce proliferation of fibroblasts and production of type III collagen, which lead to fibrosis of the palmar aponeurosis. Furthermore, treatment with allopurinol may improve Dupuytren's contractures by binding xanthine oxidase and preventing production of the free radicals.[5] Possibly, increased production of free radicals also occurs in patients infected with HIV. Free radicals derived from oxygen are responsible for oxidation of unsaturated fatty acids in cell membranes, and increased plasma concentrations of malondialdehyde, which indicate high basal peroxidation of lipids, have been shown in patients with HIV infection.[2]

The prevalence of Dupuytren's contractures in patients infected with HIV may, therefore, be an important marker of disturbed metabolism of free radicals derived from oxygen, which in turn may be an important intermediary mechanism in the development of AIDS. This suggests that treatment with a scavenger of free radicals such as ascorbic acid may have a role in preventing some manifestations or progression of the disease.

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Training in accident and emergency: views of senior house officers

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There is no nationally accepted training programme for senior house officers in accident and emergency. Teaching varies from comprehensive instruction before and during tenure of the post to no formal instruction at all, and some medical schools do not provide any undergraduate training in the specialty. Yates and Wakeford showed that senior house officers were poorly prepared for the work that they were about to undertake[1]; when tuition was provided the format was determined by the senior staff. We undertook a study to gain a perspective of teaching from the trainees' view point.

Methods and results

We distributed a questionnaire to 60 senior house officers at eight different hospitals who had had more than three months' experience in accident and emergency work. The questionnaire assessed their personal preparation for the post, the amount of teaching provided, and the effect that teaching had had on their confidence. A linear analogue scale from 0 to 9 was used to assess their clinical confidence.

Before starting the post three doctors had done more than 20 hours' reading, 15 between 11 and 20 hours, 18 up to 10 hours, and 24 none. Twenty eight had attended an introductory weekend course and 16 an introductory day course.

All 60 doctors received one to two hours of teaching each week from senior staff in the accident and emergency department and other specialist staff. Eighteen, however, had not received any teaching on multiple or minor injuries, nine on resuscitation, and 37 on spinal injuries.

χ^2 Analysis was used to study any correlation between the score for clinical confidence and formal teaching on various subjects (table). A figure for overall confidence was obtained by adding individual scores for the 10 broad subject categories and a further 10 specific acute clinical problems—namely, acute anaphylaxis, myocardial infarction, the sudden infant death syndrome, managing violent patients, acute epiglottitis, 60% burns, multiple injuries, finger tip injuries, patients with head injuries refusing admission, and cardiac arrest. Overall confidence was not significantly correlated with previous postgraduate experience, but was with the number of months spent working in accident and emergency (Kruskal-Wallis test, H value = 11·44; $p<0·01$) and the number of hours spent in personal preparation (H value = 7·23; $p<0·05$). Fifty seven of the doctors thought that accident