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TREATMENT OF PATIENTS WITH SYMPTOMLESS LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

NORMAN SHARPE JUDY MURPHY
HEATHER SMITH SHARON HANNAN

Department of Medicine, University of Auckland School of Medicine, Auckland, New Zealand

Summary In a randomised, double-blind trial 60 patients with left ventricular dysfunction (ejection fraction <45%) but without clinical evidence of heart failure 1 week after Q wave myocardial infarction were given captopril 25 mg thrice a day, frusemide 40 mg daily, or placebo. Left ventricular volumes were measured at baseline and at 1, 3, 6, 9, and 12 months with cross-sectional echocardiography and Simpson's rule analysis of standardised apical views. The captopril group showed no significant change in left ventricular end-diastolic volume index but left ventricular end-systolic volume index was significantly reduced and stroke volume index and ejection fraction were significantly increased from 1 month on. In contrast, the frusemide and placebo groups showed significant increases in ventricular volumes, with stroke volume index unchanged and ejection fraction slightly reduced. The changes in the captopril group were significantly different from those in the other groups.

Introduction

THE treatment of congestive heart failure with angiotensin-converting-enzyme inhibitors is an important and widely applied advance. However, although definite clinical improvement and some reduction in mortality can be achieved with such treatment,[1-3] the prognosis for most patients remains poor. Frequently there is disparity between the symptoms of congestive heart failure and the degree of left ventricular dysfunction,[4] which is often advanced by the time of clinical presentation. Thus identification and early treatment of patients with ventricular dysfunction may prevent progression to clinical heart failure—as indicated by studies in which angiotensin-converting-enzyme inhibition seemed to prevent progressive ventricular dysfunction and heart failure and to improve survival in different animals.[5-7] The aim of our study was to determine the effects of an angiotensin-converting-enzyme inhibitor in patients with definite ventricular dysfunction but without clinical heart failure after myocardial infarction.

Patients and Methods

Patient Selection

Patients with recent Q wave myocardial infarction who were symptom-free and clinically stable and not on cardiac drugs before hospital discharge were considered for the study. The criteria for myocardial infarction were the appearance of new Q waves on serial electrocardiograms and raised serum creatine kinase levels. Those requiring treatment for myocardial ischaemia, arrhythmias, or heart failure were excluded, as were patients with atrial fibrillation, valvular heart disease, chronic lung disease, other serious systemic diseases, or renal impairment (serum creatinine >0·20 mmol/l). None of the patients considered had received thrombolytic agents or beta blockers at the time of infarction.

Eligible patients underwent cross-sectional echocardiography and those with adequate image quality and left ventricular ejection fraction less than 45% were entered into the study.

Study Design

Patients were randomised to receive, double blind, captopril 25 mg thrice a day (group 1), frusemide 40 mg daily (group 2), or placebo (group 3). The randomisation schedule had a block size of 30 patients.

An open test-dose of captopril 12·5 mg was given under observation before start of the trial regimen. The patients received medication from two bottles, one containing captopril or placebo and the other frusemide or placebo. Patients were reviewed clinically after 1 week of treatment, and clinical and

echocardiographic assessments were repeated at 1, 3, 6, 9, and 12 months. If symptoms or signs of heart failure occurred during treatment, the trial medication was doubled. If no improvement was evident after a further week, frusemide 40 mg daily was added openly and increased if required. Patients with recurrent myocardial ischaemia, reinfarction, arrhythmias, or severe heart failure requiring additonal treatment were withdrawn from the trial.

Methods of Assessment

The primary endpoints for the study were left ventricular volumes and function as measured by cross-sectional echocardiography. Echocardiography was standardised, with the same two operators conducting all examinations together. Patients were examined in the left lateral position, with the transducer operator seated on the left of the patient. Apical 4 and 2 chamber views were obtained by positioning the transducer in the space provided by a removable deep mattress section. The long axes of the apical views were maximised and recordings taken with respiration held at end-expiration or partial inspiration. Patient angulation, transducer position, and respiratory phase were recorded. Hard copies were taken and a dot tattooed on the chest at the apical transducer position for subsequent reference. A similar procedure was followed for every patient for all examinations, and patients had their own videotapes on which recordings were made. At each re-examination, earlier recordings and hard copies were reviewed to ensure that comparable views were obtained.

All echocardiographic recordings for each patient were analysed at the end of the study period, with all measurements being made by one observer. End-diastolic and end-systolic frames were outlined from both apical views by the use of a 'Franklin 2000' cardiac analysis system (Bruce Franklin Inc, Woodinville, Washington), and left ventricular volumes were obtained by a Simpson's rule method. The mean of three measurements on consecutive cycles from both views was taken from each examination. Left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and stroke-volume index (SVI) were derived by using body surface area estimated at each time-point.

The echocardiographic method described above gave the following mean (SD) findings for 50 normal adults: LVEDVI 56·2 (9·9) ml/m², LVESVI 25·7 (5·0) ml/m², SVI 30·5 (5·3) ml/m², ejection fraction 54·4 (3·4)%. These are similar to those reported by Wahr et al, who used a similar method.[8] Intraobserver variability was determined from a random sample of 30 study patients and repeated measurement of consecutive cycles from the baseline recording in each case. The standard error of repeated measurements[9] for LVEDVI was 1·8 ml/m², LVESVI 1·3 ml/m², SVI 1·5 ml/m², and ejection fraction 1·3%.

Statistical Analysis

The treatment effects were estimated by general linear modelling,[10] which included myocardial infarction site and treatment-site interaction in the model. Least squares means[10,11] were used to adjust for imbalance due to patient withdrawal during treatment, and adjusted mean differences from baseline, together with the appropriate least significant difference intervals, were calculated by the Tukey-Kramer method.[10,12] The significance of within-group changes from baseline and of between-group differences were sought by this method. Lack of overlap of baseline or comparable intervals denotes a significant difference with $p < 0.05$.

Results

Patient Population

The study group of 60 patients was obtained after assessment of 101 patients with recent Q wave myocardial infarction. 18 (18%) of these patients were excluded because of inadequate echocardiographic image quality and 23 (23%) because of an ejection fraction greater than 45%. No patient had symptoms of hypotension with the open test-dose of captopril. The three treatment groups had similar clinical characteristics (table I). Although left ventricular end-systolic volume was higher and ejection fraction was lower at baseline in the captopril group than in the frusemide group, there were no significant differences between the captopril and placebo groups or the frusemide and placebo groups in echocardiographic data (table II).

TABLE I—CLINICAL CHARACTERISTICS OF PATIENT GROUPS AT BASELINE

Characteristics	Captopril group	Frusemide group	Placebo group
Age (yr)			
Mean	59 (9)	57 (11)	53 (10)
Range	38–74	32–74	31–72
Sex			
Female	1	2	1
Male	19	18	19
Weight (kg)	74 (11)	72 (11)	78 (13)
Infarct site			
Anterior	11	16	12
Inferior	9	4	8
Peak creatine kinase (units/l)	2368 (1119)	2629 (2051)	2039 (1055)
No with previous myocardial infarction	0	0	3
No with previous hypertension	4	1	3
Time to entry post infarct (days)	9 (4)	8 (3)	9 (4)

Values are mean (SD).
Between-group comparisons are all non-significant.

TABLE II—BASELINE ECHOCARDIOGRAPHY MEASUREMENT OF LEFT VENTRICULAR VOLUME

Indices of left ventricular volume	Captopril group	Frusemide group	Placebo group
LVEDVI (ml/m²)	81·2 (3·6)	74·8 (2·5)	76 1 (2·9)
LVESVI (ml/m²)	52·2 (3·0)	44·9 (1·9)	47·5 (2·3)
SVI (ml/m²)	29·0 (1·1)	29·9 (1·1)	28·6 (1·1)
EF (%)	36·3 (1·2)	39·9 (1·2)	37·9 (1·2)

Values are mean (SE).
Between-group comparisons are all non-significant except for captopril *vs* frusemide for LVESVI and EF, $p < 0.05$.

Patient Withdrawals

In the captopril group, 1 patient required doubling of trial medication after 1 month, but no patient required additional open frusemide treatment. 2 patients were withdrawn because of re-infarction after 6 weeks and 10 months, and 1 patient because of ventricular arrhythmias after 2 weeks. In

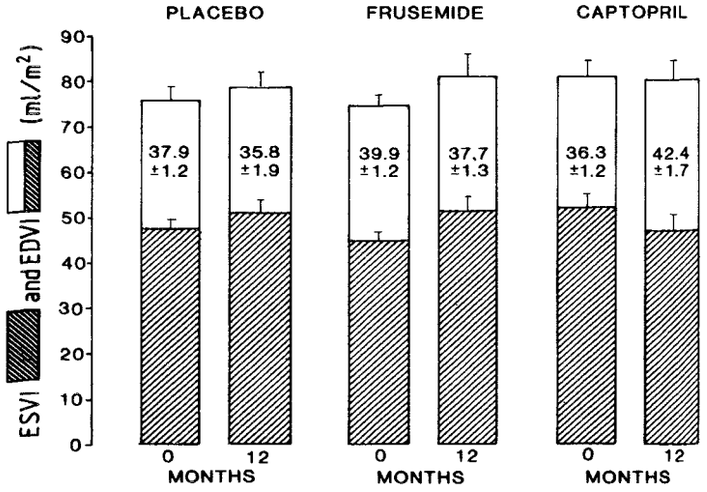

Fig 1—Unadjusted left ventricular volume data for treatment groups at baseline and 12 months.

Numbers in the columns refer to mean ± SE ejection fraction (%). Vertical bars represent SE.

TABLE III—ECHOCARDIOGRAPHIC DATA: DIFFERENCES FROM BASELINE FOR LEFT VENTRICULAR VOLUMES

Months	Captopril group	Frusemide group	Placebo group
ΔLVEDVI (ml/m²)			
1	−0·03 (2·47, −2·53)	2·13 (4·97, −0·71)	3·11 (5·59, 0·63)
3	−2·10 (1·09, −5·29)	2·46 (5·96, −1·04)	3·71 (6·96, 0·46)
6	−1·30 (1·47, −4·07)	1·04 (4·09, −2·01)	4·76 (7·71, 1·81)
9	−3·15 (0·09, −6·21)	1·39 (5·05, −2·27)	4·56 (8·01, 1·11)
12	−3·00 (0·44, −6·44)	3·89 (7·89, −0·11)	5·94 (9·82, 2·06)
ΔLVESVI (ml/m²)			
1	−2·03 (−0·01, −4·05)	2·11 (4·40, −0·18)	3·84 (5·84, 1·84)
3	−4·44 (−1·97, −6·91)	2·47 (5·18, −0·24)	5·34 (7·87, 2·83)
6	−4·42 (−2·00, −6·84)	1·76 (4·41, −0·89)	5·03 (7·60, 2·46)
9	−5·44 (−3·12, −7·76)	1·60 (4·37, −1·17)	4·81 (7·42, 2·20)
12	−7·24 (−4·41, −10·1)	3·84 (7·09, 0·59)	5·55 (8·74, 2·36)
ΔSVI (ml/m²)			
1	2·00 (3·21, 0·79)	0·07 (1·44, −1·30)	−0·76 (0·44, −1·96)
3	2·34 (3·91, 0·77)	0·03 (1·75, −1·69)	−1·64 (−0·04, −3·24)
6	3·12 (4·72, 1·52)	−0·73 (1·02, −2·48)	−0·26 (1·43, −1·95)
9	2·29 (4·07, 0·51)	−0·17 (1·96, −2·30)	−0·28 (1·73, −2·29)
12	4·26 (5·67, 2·85)	0·10 (1·72, −1·52)	0·40 (1·99, −1·19)
ΔEF (%)			
1	2·86 (3·98, 1·74)	−0·66 (0·61, −1·93)	−1·98 (−0·87, −3·09)
3	4·78 (6·20, 3·36)	−1·09 (0·47, −2·65)	−3·39 (−1·95, −4·83)
6	5·03 (6·61, 3·45)	−1·33 (0·41, −3·07)	−2·24 (−0·56, −3·92)
9	4·85 (6·44, 3·26)	−0·88 (1·02, −2·78)	−2·14 (−0·56, −3·94)
12	7·07 (8·63, 5·51)	−1·57 (0·22, −3·36)	−2·12 (−0·36, −3·88)

Values are least squares means with upper and lower least significant difference intervals in parentheses ($p < 0·05$).

the frusemide group, no patient required doubling of trial medication or additional frusemide, but 1 patient died suddenly after 1 week and another patient withdrew himself after 8 months. In the placebo group, 2 patients required doubling of trial medication and additional frusemide after 1 and 4 months, and the latter patient died suddenly at 7 months; 2 patients were withdrawn because of angina after 1 and 6 months and another 2 patients because of re-infarction after 3 and 7 months. 1 patient proved non-compliant after 2 months.

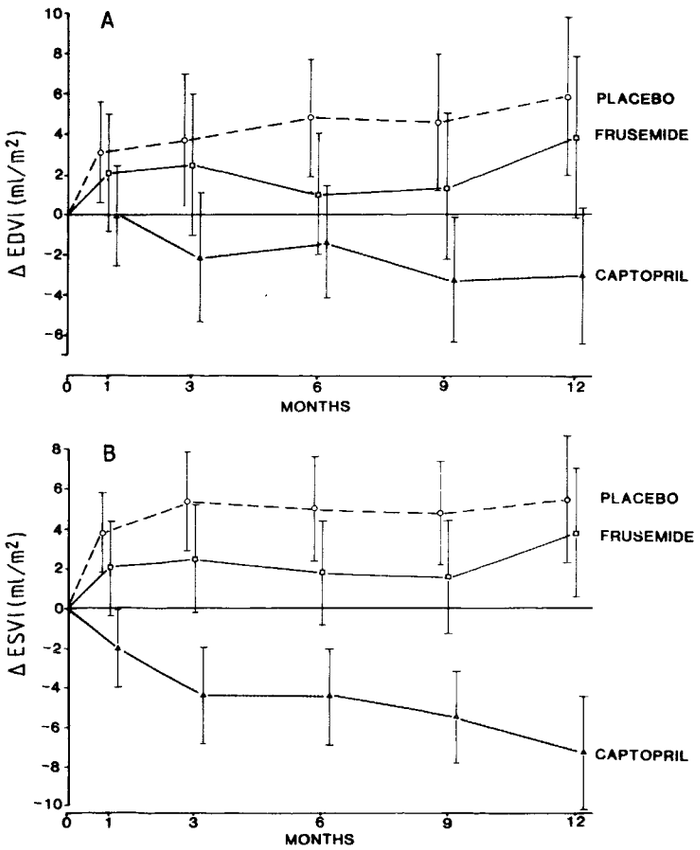

Fig 2—Adjusted mean differences from baseline at 1, 3, 6, 9, and 12 months for the three treatment groups for (A) LVEDVI and (B) LVESVI.

Values shown are least squares means with upper and lower least significant difference intervals ($p < 0·05$).

Echocardiographic Results

A pronounced treatment effect was observed amongst the groups ($F = 19·50$, 2df, $p = 0·0001$), and infarct site was also shown to be important ($F = 2·90$, 1df, $p = 0·096$). The unadjusted data for the treatment groups at baseline and at 12 months is shown in figure 1. The adjusted mean differences from baseline are shown in table III and figures 2 and 3.

In the placebo group the increase in LVEDVI from baseline was significant at 1 month and thereafter, and that in the frusemide group was of borderline significance at 12 months. There was a reduction in LVEDVI of borderline significance in the captopril group at 9 and 12 months. Placebo and frusemide groups did not differ significantly in LVEDVI but the change in the captopril group was significantly different from that in the placebo group from 6 months on and of borderline significance compared with the frusemide group at 12 months.

The increases in LVESVI were similar to the increases in LVEDVI for the placebo and frusemide groups, but in the captopril group the reduction in LVESVI was more pronounced than that for LVEDVI. The increase in the placebo group from baseline was significant at 1 month and thereafter, and in the frusemide group the increase was of borderline significance at 1 and 3 months and significant at 12 months. The reduction in the captopril group was significant at 1 month and thereafter. There was no significant difference between placebo and frusemide groups but the change in the captopril group was significantly different from both the other groups after 1 month.

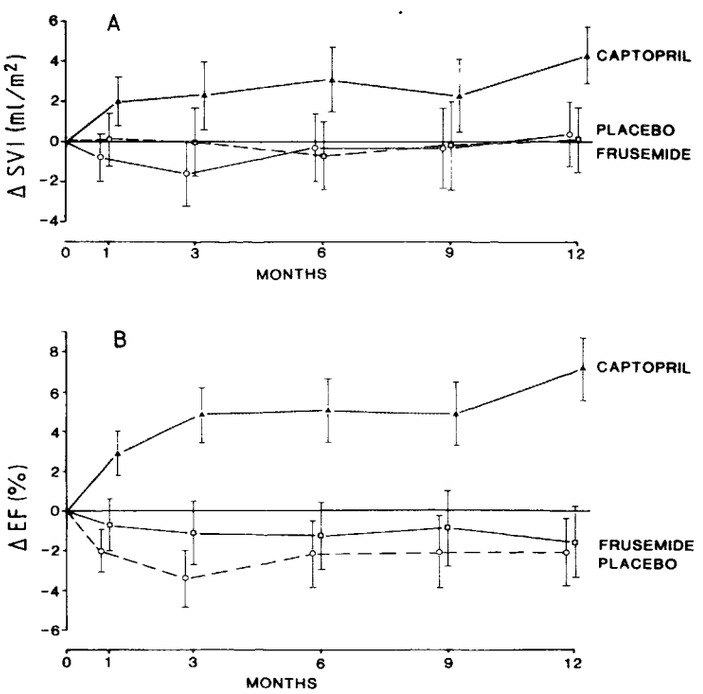

Fig 3—Adjusted mean differences from baseline at 1, 3, 6, 9, and 12 months for the three treatment groups for (A) SVI and (B) ejection fraction.

Values shown are least squares means with upper and lower least significant difference intervals ($p < 0·05$).

TABLE IV—DIFFERENCES FROM BASELINE FOR EJECTION FRACTION IN ANTERIOR AND INFERIOR INFARCT SUBGROUPS

—	Captopril	Frusemide	Placebo
Anterior infarct	7·0*←p < 0·001→	−2·6←NS→	−4·6
	↑ NS ↓	↑ NS ↓	↑ p < 0·05 ↓
Inferior infarct	7·1†← p < 0·01 →	−0·5←NS→	0·3

Findings are mean difference (%) in ejection fraction from baseline.
*p < 0·001 between captopril and placebo group.
†p < 0·01 between captopril and placebo group.

Accordingly, SVI was maintained unchanged in the placebo and frusemide groups whereas the captopril group showed a significant increase from baseline throughout the study period, with a 15% increase at 12 months. This increase in the captopril group was significantly different from both the other groups at 6 and 12 months. Ejection fraction was significantly reduced from baseline in the placebo group from 1 month on and slightly but not significantly reduced in the frusemide group. The captopril group showed a significant increase in ejection fraction from 1 month on, and this change was significantly different from that in the other groups throughout. At 12 months there was an 8–9% difference in the change in ejection fraction from baseline between the captopril and other groups.

The improvement in the captopril group was progressive, there being a further significant reduction in LVESVI and increases in SVI and ejection fraction between 1 and 12 months after the initial changes between 0 and 1 month. The changes in LVESVI and ejection fraction in the other groups, however, did not change further after 1 month.

The change in ejection fraction from baseline to 12 months was also analysed for anterior and inferior infarct subgroups within each treatment group (table IV). There was a significant increase for both subgroups with captopril treatment, no significant change for either with frusemide treatment, but a significant reduction for the anterior infarct subgroup with placebo treatment. There were no significant differences between the corresponding subgroups with placebo or frusemide treatment. However, the improvement for anterior and inferior infarct subgroups with captopril treatment was significantly different from the change for the corresponding subgroups with the other treatment.

Blood Biochemistry

There were no significant differences amongst the groups for serum urea, creatinine, or electrolytes at any time during treatment.

Discussion

This study demonstrates that angiotensin-converting-enzyme inhibition can improve symptomless ventricular dysfunction occurring after Q wave myocardial infarction. The treatment effect was highly significant, the reduction in cardiac volumes and improvement in ejection fraction with captopril contrasting with the increased dilatation that occurred with both frusemide and placebo. The patients selected for study were symptom-free, had no clinical signs of cardiac failure, and were not on cardiac medication other than the trial treatment.

Although the patient groups were well matched clinically at baseline, some minor differences, although not statistically significant, warrant comment. 3 patients in the placebo group, but none in the other groups had had previous myocardial infarction. However, the placebo group had the lowest mean peak creatine kinase values, and baseline echocardiographic left ventricular volumes were smaller than those for the captopril group. The frusemide group had more patients with anterior infarction than did the other groups, and also the highest mean peak creatine kinase values, but the smallest baseline left ventricular volumes. The captopril group had slightly more severe ventricular dysfunction than the frusemide group and might have been expected to have shown a greater tendency to subsequent deterioration rather than the actual improvement that occurred. In the comparison of changes between the groups, adjustment was made for patient withdrawals and also for the proportion of anterior and inferior infarcts within each treatment group, as is appropriate even in the absence of statistically significant baseline differences.

The study does not permit firm conclusions on the mechanism of improvement. However, the contrasting effects of captopril and frusemide suggest that afterload reduction in this context is beneficial. The cycle of progressive cardiac dilatation and dysfunction that may follow an initial increase in afterload seems to have been reversed with captopril. In contrast, the effect of diuretic treatment was not different from that of placebo.

Ventricular dilatation following infarction may occur in acute and chronic phases. Early infarct expansion may occur between 3 days and 2 weeks after infarction,[13] with further dilatation continuing during later months.[14] The trial regimen was begun several days after infarction, following the initial phase of infarct expansion and acute dilatation. Baseline echocardiographic measurements indicated moderate ventricular dilatation and dysfunction at the time of entry with LVEDVI more than 30% increased above normal, LVESVI more than 75% increased, and ejection fraction 35–40% decreased. Thus treatment was directed predominantly towards the later phase of progressive ventricular dilatation and dysfunction, and it is possible that earlier treatment may have been even more effective. It is notable that improvement during treatment with captopril seemed to be progressive whereas the dilatation in the frusemide and placebo groups occurred predominantly in the first month. Also, whereas reduction in ejection fraction in the frusemide and placebo groups was evident mainly in the anterior infarct subgroup, the improvement in ejection fraction with captopril was equally evident in both anterior and inferior infarct subgroups.

Ventricular dilatation is an adverse prognostic factor for survival in the year after infarction.[15] A recent study in which left ventricular volumes and function and severity of coronary disease were assessed angiographically 1–2 months after infarction showed that end-systolic volume at that time had the greatest predictive value for survival.[16]

The cross-sectional echocardiographic method of assessment of ventricular volumes used in this study gives an underestimate of absolute volumes.[17] However, this is not disadvantageous for evaluation of serial changes in a double-blind controlled study. Patient selection was such as to ensure adequate echo image quality, and the technique of recording was carefully standardised for each individual. Although there may be considerable interobserver variability in measurement with this method, intraobserver variability in our laboratory is small, and the method is well able to demonstrate a treatment effect.

The findings from this clinical study are consistent with

the laboratory studies showing improved ventricular performance and survival in rats treated with captopril after coronary ligation and myocardial infarction.[6,7] In those studies benefit was greatest for rats with moderate-sized infarcts (20–40% of left ventricular surface area) accompanied by moderate ventricular dilatation and ejection fraction in the range 30–40%, whereas those with small infarcts and also those with large infarcts did not benefit. In our study patients with small infarcts and ejection fraction greater than 45% were excluded, and patients with very large infarcts were also generally excluded since they tend to have clinical heart failure and require treatment.

Haemodynamic benefit and improvement in symptoms can be achieved with angiotensin-coverting-enzyme inhibition in patients with advanced congestive heart failure,[1,2] and improvement in survival has been demonstrated.[3] However such treatment is essentially palliative and the prognosis, which is related to the underlying severe ventricular dysfunction, remains poor. There is now a sound basis for including an angiotensin-converting-enzyme inhibitor in the initial treatment of patients presenting with congestive heart failure and ventricular dilatation. The difficulty remains that moderate to severe ventricular dysfunction may have been present for a time in symptom-free patients before becoming clinically manifest. Echocardiographic examination of select patient groups may allow detection of ventricular dysfunction and guide management. Although our findings will require confirmation, they provide a clinical basis for the preventive treatment of symptomless ventricular dysfunction.

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Correspondence should be addressed to N. S.

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HUMAN IMMUNODEFICIENCY VIRUS DETECTED IN BOWEL EPITHELIUM FROM PATIENTS WITH GASTROINTESTINAL SYMPTOMS

JAY A. NELSON[1] CLAYTON A. WILEY[2]
CATHERINE REYNOLDS-KOHLER[1] CHARLES E. REESE[3]
WILLIAM MARGARETTEN[3] JAY A. LEVY[3]

Department of Immunology, Research Institute of Scripps Clinic, La Jolla, California 92037, USA;[1] Department of Pathology, University of California, San Diego, La Jolla;[2] and Departments of Pathology and Medicine, University of California School of Medicine, San Francisco[3]

Summary Infectious human immunodeficiency virus (HIV) was recovered from two out of four bowel biopsy specimens from acquired immunodeficiency syndrome (AIDS) patients with chronic diarrhoea of unknown aetiology. In-situ hybridisation of biopsy specimens from rectum and duodenum of other AIDS patients with gastrointestinal complaints showed the presence of HIV-infected cells in both the base of the bowel crypts and the lamina propria. The type(s) of epithelial cell(s) infected could not be determined definitively. However, the association of in-situ labelling of HIV RNA in argentaffin staining cells strongly suggests that enterochromaffin cells derived from neural crest tissue are among the target cells. This evidence that HIV can directly infect the bowel raises the possibility that the virus causes some of the gastrointestinal disorders of AIDS patients.

Introduction

INDIVIDUALS infected by the human immunodeficiency virus (HIV) can suffer various gastrointestinal symptoms including chronic diarrhoea.[1,2] In Africa this disorder has been associated with "slim disease", a term that describes the great loss of weight that accompanies diarrhoea.[3,4] Infectious HIV has been recovered from human T cells and macrophages, as well as from several body fluids including semen.[5-9] We and others have also recovered the virus from brain tissue and noted its presence in brain macrophages and capillary endothelial cells.[10-13] Because a known gastrointestinal pathogen cannot be identified in some HIV seropositive patients with chronic diarrhoea, we investigated the possibility that HIV might directly infect bowel tissue.

Subjects and Methods

Our study population included thirteen HIV-infected individuals with a history of chronic diarhoea and one HIV seropositive patient with no gastrointestinal complaints (no 14). They underwent an endoscopic biopsy at either the AIDS clinic at the University of California Medical Center in San Francisco or at San Francisco General Hospital. One specimen was obtained at necropsy (patient 14). Histological examination of the bowel specimens from most but not all of these individuals showed acute or chronic inflammation with areas of monocyte infiltration in the lamina propria.

To examine bowel tissue for infectious virus, a rectal mucosal biopsy specimen was taken from four HIV seropositive homosexual men with a history of chronic watery diarrhoea. Within 1 h, a 2–3 mm piece of this tissue was washed extensively in Hank's balanced salt solution containing antibiotics. The tissue was then minced with forceps and added to cultures of peripheral mononuclear cells (PMC) from seronegative individuals.[10] These PMC were pretreated for three days with phytohaemagglutinin (3 μg/ml) and then washed before use in culture. The presence of virus was assayed in culture fluids by a standard reverse transcriptase procedure.[14] Positive fluids were passed to fresh normal mitogen-stimulated PMC and identified by production of high reverse transcriptase activity and viral antigen in the cells.[10,15]