Thrombolytic treatment and proteinuria

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Abstract

Objectives—To determine whether patients with acute myocardial infarction undergoing thrombolysis with streptokinase develop changes in renal function.

Design—Prospective assessment of renal function in 60 consecutive patients admitted with acute myocardial infarction.

Setting—Tertiary referral centre and city general hospital.

Patients—60 consecutive patients with acute myocardial infarction. Thirty eight were given streptokinase and 17 tissue plasminogen activator (alteplase) and five no thrombolytic agent (non-streptokinase group).

Main outcome measures—Proteinuria and creatinine clearance on admission (day 1) and on days 3 and 6; serum urea and creatinine concentrations on days 1 and 7; streptokinase IgG on days 1, 2, and 7.

Results—Significant proteinuria (> 0.15 g/24 h) was found in 31 (82%) of the 38 patients in the streptokinase group (mean 0.47 g/24 h (95% confidence interval 0.35 to 0.6 g/24 h)) in the 24 hours after admission compared with six (27%) out of 22 in the non-streptokinase group (mean 0.17 g/24 h (0.12 to 0.2 g/24 h); $P = 0.008$). In the streptokinase group this decreased to the normal range by day 3 (mean 0.15 g/24 h (0.1 to 0.22 g/24 h); $P = 0.0001$ v baseline). Electrophoresis of urine showed the proteinuria to be glomerular in origin. Creatinine clearance and serum creatinine and urea concentrations were similar in both groups. In the streptokinase group detectable streptokinase IgG titres were found in 28 out of 32 (87%) patients. The median titre on admission was 16 (range $0-110$); it fell to 3 (range $0-80$; $P = 0.001$) by day 2 and increased to 61 (range $0-7700$; $P = 0.0002$ v baseline) by day 7.

Conclusions—Streptokinase was associated with significant early onset proteinuria of glomerular origin. This started to resolve by day 3 and resulted in no deterioration in overall renal function. The temporal relation to the initial fall in antibody titre suggests that it could be the result of immune complex deposition in the glomeruli.

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Keywords: thrombolytic treatment; proteinuria; streptokinase; alteplase

Transient microalbuminuria is a non-specific proportional response to various stimuli, including acute myocardial infarction.¹ Recently clinically significant proteinuria has been reported in patients with acute myocardial infarction undergoing thrombolytic treatment with streptokinase,^{2,3} but whether the proteinuria was related to myocardial infarction or to the streptokinase is unclear. Streptokinase is a foreign protein (produced by β -haemolytic streptococci), and antibodies to streptokinase are widespread in the population as a result of previous exposure to streptococci.^{4,5} After treatment with streptokinase the antibody titre initially disappears and is followed by a typical secondary immunoglobulin response.⁶ A disadvantage to treatment with streptokinase is the occasional occurrence of immune reactions. More serious immune reactions such as serum sickness are related to specific antibodies against streptokinase,⁷ but, no relation has been found between the more frequent minor reactions—for example, hypotension and rigors—and streptokinase antibodies.⁸ Proteinuria may be a subclinical response to streptokinase that could be related to circulating specific antibody present at the time of treatment.

The aim of this study was (a) to determine whether streptokinase is associated with changes in renal function in excess of that expected in an acute vascular event and (b) to determine the nature and aetiology of any proteinuria found.

Patients and methods

Sixty consecutive patients (35 men; mean age 64, range 35-85) presenting with acute myocardial infarction were recruited. Myocardial infarction was diagnosed on the basis of typical chest pain and definite electrocardiographic changes (ST elevation of at least 1 mm in two limb leads or 2 mm in two adjacent chest leads) and confirmed by a subsequent rise in creatine kinase activity. Thrombolytic treatment, either streptokinase or alteplase (tissue plasminogen activator), was given to patients presenting within 12 hours of onset of symptoms, if they had no contraindications to thrombolysis. Urine was collected over 24 hours to measure protein loss and creatinine clearance in the first 24 hours after admission to the coronary care unit (day 1) and on days 3 and 6. The selectivity of any proteinuria was determined by sodium dodecyl sulphate polyacrylamide gel electrophoresis.⁹ A venous blood sample was taken on admission and on days 2 and 7 to measure streptokinase IgG by

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an enzyme linked immunosorbent assay as previously described.⁶ Serum urea and creatinine concentrations were measured on admission and again on day 7. Infarct size was estimated both from peak plasma creatine kinase and creatine kinase MB activities and from the area under the enzyme time-activity curve¹⁰ in the first 48 hours after presentation. The study was approved by the local ethics committee.

STATISTICAL ANALYSIS

Proteinuria is expressed as the mean value with 95% confidence interval. Antibody titres are expressed as medians and ranges. All other results are expressed as means (SD). Significance was determined by Wilcoxon ranking for paired and unpaired data and Student's *t* test.

Results

Streptokinase was given to 38 patients, and 22 patients received either tissue plasminogen activator (17) or no thrombolytic agent (5). The characteristics of the streptokinase and the non-streptokinase group were similar (table). However, streptokinase was more commonly given to patients with inferior myocardial infarction, although the size of infarction was similar in both groups. No patient treated with streptokinase developed an obvious clinical allergic reaction to streptokinase and the subsequent complications of infarction were similar in both groups (table).

No patient in either group developed macroscopic haematuria.

Thirty one patients in the streptokinase group (82%) had proteinuria greater than the normal range (> 0.15 g/24 h) in the initial 24 hours after admission (mean 0.47 g/24 h (95% confidence interval 0.35 to 0.6 g/24 h)) compared with six (27%) in the non-streptokinase group (mean 0.17 g/24 h (0.12 to 0.2 g/24 h; *P* = 0.008)) (figure 1). By day 3 the mean value in the streptokinase group had decreased to 0.15 g/24 h (0.1 to 0.22 g/24 h; *P* = 0.0001) and was 0.15 g/24 h (0.13 to 0.22 g/1 h) by day 6 (*P* < 0.0001 *v* baseline). In the non-streptokinase group proteinuria was unchanged during the three time periods studied (day 3, mean 0.11 g/24 h (0.08 to 0.14 g/24 h); day 6, mean 0.14 g/24 h (0.1 to 0.18 g/24 h)). The electrophoretic pattern of the proteinuria in the streptokinase group was similar in all patients. The predominant protein was albumin (confirmed by densitometry and immunonephelometry), with numerous additional higher and lower molecular weight proteins (figure 2), indicating glomerular proteinuria. In the non-streptokinase group both the frequency and range of proteinuria (0.049–0.32 g/24 h) in the first 24 hours were less than in the streptokinase treated group (range 0.048–1.5 g/24 h). Creatinine clearance and serum urea and creatinine concentrations were similar in both groups and remained unchanged throughout the study (table).

Of those treated with streptokinase, 32 patients had serum samples for assessment of streptokinase IgG. Detectable antibody titres were found in 28 patients (87%). The median IgG titre on admission was 16 (range 0–110); it had decreased to 3 (0–80) by day 2 and increased to 61 (0–7700; *P* = 0.0002 *v* baseline) by day 7, indicating the beginning of the secondary immunoglobulin response.⁶ The median streptokinase IgG titre in the non-streptokinase group at presentation was 52.5 (0–3500) and was unchanged on day 7 (table). Although the titres in this group were unchanged, they were higher than in the streptokinase group on days 1 and 2 (day 1, *P* = 0.016; day 2, *P* = 0.0008) but were similar

Clinical characteristics of the study groups. Values are means (SD) unless stated otherwise

	Streptokinase (n = 38)	Non-streptokinase (n = 22)	P value
Mean age (years)	64	67	> 0.05
Male	21 (55)	14 (64)	> 0.05
Site of myocardial infarction:			
Anterior	11 (29)	9 (41)	0.0001
Inferior	25 (66)	10 (45)	0.0001
Lateral	1 (3)	1 (4.5)	> 0.05
Unknown	1 (3)	2 (9)	> 0.05
Complications of infarction:			
Left ventricular failure	4 (11)	4 (18)	> 0.05
Reinfarction	4 (11)	1 (4.5)	> 0.05
Death	1 (3)	2 (9)	> 0.05
Medical history:			
Previous myocardial infarction	2 (5)	9 (41)	0.005
Hypertension	7 (18)	4 (18)	> 0.05
Diabetes mellitus	2 (5)	—	> 0.05
Creatinine clearance (ml/s):			
Day 1	1.23 (0.7)	1.22 (0.79)	> 0.05
Day 3	1.13 (0.47)	1.22 (0.79)	> 0.05
Day 6	1.11 (0.47)	1.2 (0.7)	> 0.05
Serum creatinine (mmol/l):			
Day 1	0.09 (0.03)	0.1 (0.04)	> 0.05
Day 7	0.09 (0.03)	0.09 (0.04)	> 0.05
Serum urea (mmol/l):			
Day 1	6.7 (1.8)	6.7 (2.8)	> 0.05
Day 7	6.2 (3)	6.6 (5.8)	> 0.05
Creatine kinase:			
Peak value (IU/l)	1608 (1339)	1396 (1212)	> 0.05
Area under curve	33.6 (26.6)	26.4 (23.6)	> 0.05
Peak value (IU/l)	181 (205)	157 (169)	> 0.05
Area under curve	2.4 (1.9)	2.2 (2.2)	> 0.05
Median (range) streptokinase IgG (titre):			
Day 1	16 (0–110)	52.5 (0–3500)	0.016
Day 2	3 (0–80)	44 (6–2600)	0.0008
Day 7	61 (0–7700)	42.5 (13–1150)	> 0.05

Figure 1 Distribution of proteinuria in both patient groups over time.

Figure 2 Results of sodium dodecyl sulphate polyacrylamide gel electrophoresis of urine samples (obtained during the first 24 hours after admission) from patients treated with streptokinase. Tracks a-d are samples from patients; track e shows molecular weight markers. Several high molecular weight proteins are present, including albumin, indicating that the proteinuria is of glomerular origin.

by day 7. The high titres can be explained by the presence in the group of five patients treated with streptokinase between three days and three years previously for a previous infarction. No patient in the streptokinase group had previously received thrombolytic treatment.

There was no correlation between the degree of proteinuria in the initial 24 hour period and the serum streptokinase IgG titre at presentation in the streptokinase group ($r = 0.09$; $P = 0.6$) or with the fall in titre from day 1 to day 2 ($r = 0.16$; $P = 0.4$). No correlation was found between baseline proteinuria and peak creatine kinase activity in either group (streptokinase, $r = 0.1$; $P = 0.8$; non-streptokinase, $r = 0.1$, $P = 0.9$) or between baseline proteinuria and the area under the creatine kinase time-activity curve (streptokinase, $r = 0.16$, $P = 0.4$; non-streptokinase, $r = 0.1$; $P = 0.07$). There was also no correlation between proteinuria and peak plasma creatine kinase MB activity or area under the time-activity curve for this enzyme. The degree of proteinuria did not relate to the frequency of left ventricular failure or reinfarction complicating acute myocardial infarction in either group.

Discussion

Significant proteinuria was found in a substantial proportion (82%) of patients treated with streptokinase but in only 27% of those not receiving streptokinase. Among those in the non-streptokinase group the range of proteinuria was also less than in the streptokinase group. The proteinuria was a temporary phenomenon and started to improve by day 3, though it was not completely resolved in all patients by day 6. A longer follow up period would be necessary to ensure resolution. Some patients, however, may have had a degree of renal impairment before infarction, but data were not available to confirm this. The proteinuria was not associated with a

deterioration in renal function as determined by changes in creatinine clearance or serum urea or creatinine concentration. Acute myocardial infarction may be complicated by factors that can cause poor renal perfusion (left ventricular failure, arrhythmias, etc), but both groups of patients were similar in age, size of infarct, and prevalence of complications of acute myocardial infarction.

The groups differed in the site of infarction and in the prevalence of previous myocardial infarction. The predominance of inferior infarction in the streptokinase group can be explained by the results of a recent major trial in which streptokinase was recommended in the management of inferior infarction and tissue plasminogen activator in anterior infarction.¹¹ The higher incidence of previous myocardial infarction in the non-streptokinase group can be explained by the frequent avoidance of repeat treatment with streptokinase. This may also explain the higher streptokinase IgG titres found in the non-streptokinase group, which remained unchanged throughout the period of the study. The high titres reflect the development of a secondary immunoglobulin response to the previously administered streptokinase. The extent of myocardial infarction and its complications were similar in both groups, and the excess of proteinuria in the streptokinase group could not be explained on the basis of acute myocardial infarction and its complications or by any differences between the two groups. Proteinuria can also be associated with an acute phase response, which is well documented in acute myocardial infarction,¹² but, the onset and resolution of the proteinuria were more rapid and the degree of proteinuria greater than would be usual in an acute phase response. The small protein load contained in a bolus dose of streptokinase would be unlikely to cause proteinuria as a result of protein load.¹³

Seven patients in the non-streptokinase group had proteinuria in excess of the normal range, that resolved over the next six days (overall results were not significant). Proteinuria had not completely resolved in all patients and again may indicate previous renal impairment (no data available) or renal impairment after infarction, though not associated with changes in creatinine clearance or serum creatinine concentration. Gosling *et al* showed microalbuminuria in patients with acute myocardial infarction,¹ and this would account for the mild proteinuria (< 0.32 g/24 h) in the non-streptokinase group but not the excess of proteinuria in the other group.

The occurrence of proteinuria in the streptokinase group coincided with the fall in antibody titre from day 1 to day 2. Firstly, the fall in titre could be explained by immune complex formation, as 87% of patients had detectable specific circulating streptokinase IgG before they were given streptokinase. Circulating IgG containing immune complexes have been shown immediately after treatment with streptokinase.¹⁴ These immune

complexes may deposit in the glomeruli before being removed, and this could result in proteinuria. This would account for the glomerular proteinuria found in those treated with streptokinase and not observed in those not receiving streptokinase. The degree of proteinuria was not related to antibody titre at presentation, although most patients had low titres at presentation (median 16).

Secondly, antibody mediated activities, including immune complex formation, are more importantly determined by antibody affinity than by antibody concentration.¹⁵ The resolution of the proteinuria probably follows removal of the immune complexes by phagocytosis.

Although we found no relation of antibody titre to proteinuria, antibody titres were generally low. Further studies would be necessary to evaluate (a) whether patients with high antibody titres, such as patients previously treated with streptokinase or those who had had a recent streptococcal infection, would be at risk of developing greater degrees of proteinuria and (b) whether patients with pre-existing renal disease might be at risk of deterioration in renal function after administration of streptokinase.

We conclude that streptokinase treatment in patients with acute myocardial infarction is commonly associated with transient proteinuria in excess of that expected with an acute vascular event. The proteinuria was starting to resolve by day 3 and was not associated with a deterioration in renal function. The onset of proteinuria coincides with the fall in streptokinase IgG, suggesting that deposition of glomerular immune complex could account for this phenomenon.

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