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# Evidence of increased platelet activation after thrombolysis in patients with acute myocardial infarction

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## Abstract

***Objective*—To assess platelet activation after thrombolysis in patients with acute myocardial infarction.**

***Design*—Platelet function was assessed by measurement of the in vivo synthesis of thromboxane by gas chromatography-mass spectrometry of thromboxane's major urinary metabolite, 2,3-dinor-thromboxane-$B_2$.**

***Setting*—Coronary care unit of Huddinge University Hospital.**

***Subjects*—30 patients with acute myocardial infarction given either streptokinase 1·5 million units intravenously over one hour + 500 mg aspirin (n = 10), 500 mg aspirin (n = 10), or neither thrombolysis nor aspirin (n = 10).**

***Results*—Patients treated by thrombolysis had a 20-fold increase in thromboxane formation during thrombolysis compared with control patients not treated by thrombolysis (p = 0·0001). Until two days after thrombolysis thromboxane production in patients treated with streptokinase did not decrease to a value comparable with patients treated with aspirin but not given thrombolysis.**

***Conclusions*—Thromboxane production increased considerably during thrombolysis, possibly reflecting greatly enhanced platelet activation. The slow decrease in thromboxane formation after treatment with aspirin suggests that the efficacy of thrombolysis might be improved by more efficient antiplatelet treatment.**


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Platelet are activated in coronary thrombotic diseases such as acute myocardial infarction and unstable angina pectoris[1–3] and aspirin treatment was found to prevent myocardial infarction and deaths in patients with unstable angina and myocardial infarction.[4–6] Aspirin irreversibly acetylates the enzyme cyclo-oxygenase and thereby inhibits the synthesis of the potent platelet aggregator thromboxane $A_2$.[7] We found that aspirin was a very efficient inhibitor of thromboxane synthesis in patients with acute myocardial infarction.[8] These patient's however, were not treated with thrombolytic agents. The beneficial effect of thrombolysis on mortality[6 9] has made it the standard treatment for patients with myocardial infarction. The higher reinfarction rate in patients given streptokinase without aspirin[6 10 11] prompted us to study the effect of aspirin on the in vivo synthesis of thromboxane and prostacyclin in patients with acute myocardial infarction given thrombolysis.

## Patients and methods

We studied 10 patients with acute myocardial infarction admitted to our coronary care unit within six hours of the onset of symptoms (3·3 (0·5) h (mean (SE)). The patients had not taken aspirin or any other cyclo-oxygenase inhibitor in the 10 days before the infarction and all gave their informed consent to the study. Regular medications were continued—that is, patients were given β-blockers if there was no contraindication, and glyceryl trinitrate and diuretics were given as necessary. All patients were given streptokinase (Behring, Marburg, Germany) (1·5 million units intravenously over one hour). Immediately after this the patients were given

*Table 1 Data on 10 patients treated with streptokinase infusion (1·5 million units/60 min) within six hours after onset of symptoms of myocardial infarction (MI)*

| Case | Age | Sex | Smoker | Previous MI | Duration of pain (h) | CK-MB peak (μkat/l) | Time to enzyme peak (h) | Excretion during infusion of streptokinase (pg/mg creatinine) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $PGI_{2m}$ | $TxA_{2m}$ |
| 1 | 69 | F | — | — | 6 | 6·1 | 12 | 353 | 709 |
| 2 | 59 | F | Yes | — | 4·5 | 6·5 | 18·5 | 592 | 4922 |
| 3 | 37 | M | Yes | — | 6 | 8·9 | 18·5 | 1340 | 29196 |
| 4 | 59 | M | Yes | — | 2 | 6·5 | 12·5 | 772 | 3266 |
| 5 | 72 | M | — | Yes | 1 | 4 | 10 | 675 | 2716 |
| 6 | 50 | M | Yes | Yes | 2 | 5·2 | 10 | 937 | 5534 |
| 7 | 73 | F | — | Yes | 3 | 5·4 | 25 | 140 | 1021 |
| 8 | 72 | M | Yes | — | 5 | 3·7 | 13 | 1522 | 2158 |
| 9 | 74 | M | Yes | Yes | 2·5 | 0·7 | 8·5 | 391 | 1492 |
| 10 | 80 | M | — | — | 2·5 | 1·1 | 17 | 908 | 90737 |
| Mean (SEM) | 64·5 (3·4) | | | | | | | | |

CK-MB, creatine phosphokinase isoenzyme MB. $PGI_{2m}$, prostacyclin metabolite; T × $A_{2m}$, thromboxane metabolite.

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*Table 2 Comparison of peak enzyme and protanoid concentrations (mean (SEM)) during myocardial infarction in patients given thrombolysis and aspirin (n = 10) with controls not given thrombolysis (but given aspirin (n = 10); and controls given neither (n = 10)*

| | Age (y) | Sex (female (%)) | Smokers (%) | CK-MB peak (μkat/l) | Peak (pg/ml creatinine) | |
|---|---|---|---|---|---|---|
| | | | | | $PGI_2m$ | $TxA_2m$ |
| SK + aspirin | 64·5 (3·4) | 30% | 60% | 4·8 (0·7) | 1187 (449) | 11966 (7514) |
| Aspirin | 60·7 (3·5) | 20% | 40% | 3·2 (0·6) | 1078 (491) | 522 (137) |
| Controls | 63·9 (2·1) | 10% | 30% | 3·1 (0·6) | 755 (268) | 650 (145) |

SK, streptokinase; CK-MB, creatine kinase isoenzyme MB; $PGI_2m$, prostacyclin metabolite; T × $A_2m$, thromboxane metabolite.

aspirin (500 mg) in buffered water solution (Bamyl-S, Hassle, Sweden) and this treatment was repeated every third day. Urine was collected before treatment, soon after thrombolysis, and then as 24 hour collections for days 1, 2, 3, and 7.

Table 1 gives data on the individual patients. As controls we used 20 patients with myocardial infarction who were not given thrombolysis. Those patients were recruited before thrombolysis and aspirin became the routine treatment at our coronary care unit. They had no contraindications to the use of aspirin and in all respects resembled the thrombolysis patients. Ten of the controls were given neither aspirin nor streptokinase and 10 were given aspirin in the same protocol as the patients treated with thrombolysis.

Otherwise all 30 patients were treated in an identical way—that is, were given β-blockers if there was no contraindication, and glyceryl and diuretics were given when necessary. Patient characteristics were matched. Acute myocardial infarction was diagnosed by the WHO criteria. The study was approved by the ethics committee at Huddinge University Hospital.

ANALYSIS

Urinary 2,3-dinor-$TxB_2$ and 2,3-dinor-6-keto-$PGF_{1\alpha}$ were analysed by gas chromatography-mass spectrometry, with tetra-deuterated carriers and internal standards.[12 13]

STATISTICAL METHODS

Results are given as mean (SE) and analysed by analysis of variance. Because thromboxane values after thrombolysis were not normally distributed the data were logarithmically transformed before analysis.

## Results

All patients had a transmural infarction. Baseline characteristics and infarction variables such as peak enzyme concentrations, age, sex, and previous treatment with β blockers were similar for patients given thrombolysis and for control patients (table 2). Infusion of streptokinase increased the initial thromboxane metabolite concentration 10-fold (fig 1) and the peak concentration was approximately 20 times higher than in the two control groups (fig 2; p = 0·0001).

As figs 1 and 2 show, thromboxane production fell after the first dose of 500 mg aspirin, but only to a concentraton similar to that found in control patients not treated with aspirin or thrombolysis. On the second day after thrombolysis thromboxane production had fallen to the same concentration as measured in the patients treated with aspirin but not thrombolysis (fig 2). Peak prostacyclin concentrations were increased to a similar extent in all groups (table 2).

One patient in the thrombolysis group died of severe congestive heart failure on the third day. There were no reinfarctions within a 30 day period. Furthermore, no side effects of aspirin were reported. Glyceryl trinitrate consumption was similar in the three groups.

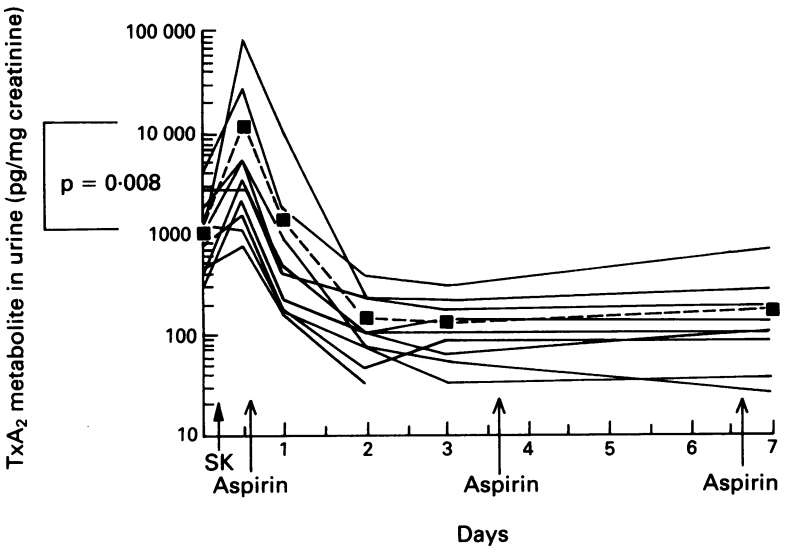


*Figure 1 Urinary excretion of a thromboxane ($TxA_2$) metabolite (2, 3 dinor-$TxB_2$) in 10 patients treated with infusion of streptokinase (SK) followed by an intermittent dose of aspirin (500 mg each third day). Mean is shown by a broken line.*

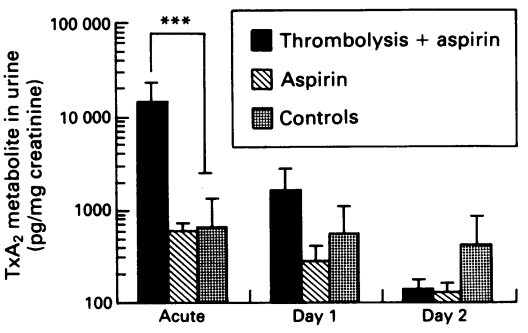


*Figure 2 Urinary excretion of a thromboxane ($TxA_2$) metabolite (2, 3-dinor-$TxB_2$) in patients with an acute myocardial infarction treated with streptokinase (SK) and aspirin: thrombolysis + aspirin (n= 10); only aspirin (n = 10), or neither (n = 10). Values are mean (SEM). ***p < 0·001.*

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## Discussion

We found a 20-fold increase in thromboxane formation when patients with acute myocardial infarction were treated with thrombolysis. The most obvious explanation for this finding was that platelet activation was increased during thrombolysis. Fitzgerald *et al* reported a similar tendency for thromboxane production to increase during thrombolysis in two patients.[14]

Patients given thrombolysis without antiplatelet therapy are reported to have an increased reinfarction rate,[6 10 11] probably reflecting reocclusion of previously opened coronary arteries. Furthermore, repeated angiography has shown evidence of early reocclusion.[15] In a study reported by Six *et al* there was evidence suggesting that the higher the dose of streptokinase the higher the initial patency rate but also the higher the reinfarction rate.[16]

Our findings accord with the suggestion that the increase in reinfarction rate is caused by greatly enhanced platelet activation/instability (as shown by the increase in thromboxane formation). In the ISIS-2 study the addition of aspirin to streptokinase reduced mortality even further.[6] The dose of aspirin given in ISIS-2 was only about a quarter of the dose we gave. Despite the higher dose of aspirin in our study it was not until day 2 that thromboxane production fell to values found in patients with acute myocardial infarction who were treated with aspirin but not thrombolysis. These results indicate that the efficacy of thrombolysis could be improved if patients were also given more effective antiplatelet therapy. Perhaps the initial high patency rate could be better preserved if aspirin were given before thrombolysis or if a thromboxane receptor antagonist were given with a cyclo-oxygenase inhibitor or thromboxane synthase inhibitor.[17] Our results may help to explain why treatment with low dose aspirin (80 mg) in conjunction with thrombolysis was relatively ineffective.[18]

We found that thromboxane formation increased 20-fold when patients with acute myocardial infarction were given streptokinase. This increase probably reflects a considerable platelet activation. Our results strongly suggest that the combination of thrombolysis with efficient antiplatelet therapy would improve results in patients with myocardial infarction, especially when thromboxane receptor antagonists become available.

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