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Antiaggregative Therapy with Acetylsalicylic Acid and Diclofenac in Patients with Acute Myocardial Infarction

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ABSTRACT

A total of 109 male patients with acute transmural myocardial infarction (MI) were studied. 26 patients received a dose of acetylsalicylic acid (aspirin,ASA) 500 mg/d and 29 patients of 50 mg/d. 27 patients were given diclofenac (25 mg/d). 27 patients received no antiplatelet therapy. We observed thrombocyte hyperaggregation on the 1st MI day, a rapid increase in platelet activity by the 7th day and a considerable decrease in platelet aggregation during the 3rd and 4th weeks of illness in the group without antiaggregative treatment. The present study clearly demonstrated high antiaggregatory efficacy of ASA in dose of 50 mg/d which was significantly higher than that in daily dose of 500 mg ASA. Low-dose aspirin had fewer side-effects than aspirin 500 mg/d. However, although daily dose of 50 mg aspirin significantly inhibited platelet hyperaggregation on 7th day of MI, the hyperactivity of thrombocytes was not abolished. Diclofenac 25 mg daily had only a moderate antiaggregative efficacy in acute MI patients.

INTRODUCTION

The thrombotic contribution to MI is now universally recognized. An occlusive coronary thrombus on an ulcerated and ruptured atherosclerotic plaque is the underlying abnormality in more than 90 percent of patients with Q-wave MI (3). Platelet hyperactivity in MI patients has been shown in numerous previous studies (8,10,16). To prevent thrombotic occlusion of a coronary artery and to improve the rheological properties of blood in MI patients the antiplatelet treatment is beneficial.

Aspirin, by inhibition of platelet cyclooxygenase, is an effective inhibitor of thromboxane A2 (TxA2) formation and platelet aggregation (2,17). Low-dose aspirin (100 mg/d and less) has been used increasingly to preserve prostacyclin biosynthesis and reduce gastrointestinal toxicity (11,12). Several studies have found a protective effect of aspirin in primary and secondary prevention of MI (4,14). A powerful cycloxygenase inhibitor diclofenac has also been shown to prolong skin bleeding time and reduce platelet aggregation (13). However, there are only few papers concerning aspirin (5,18) and no data about diclofenac for evolving myocardial infarction.

In this study we have compared antiaggregative efficacy of aspirin (500 mg/d and 50 mg/d) and of diclofenac (25 mg/d) during the first 4 weeks of MI. No antiaggregatory treatment was used in the controls.

MATERIALS AND METHODS

Patients and control persons. 109 male patients (mean age 53.5 years, range 32-65) with acute transmural MI were selected from the myocardial infarction department of the Tartu University Hospital. The diagnosis of MI was established on the basis of the standard criteria (history, electrocardiography and elevated serum creatine kinase and lactic dehydrogenase activities). 26 infarction patients received a dose of aspirin 500 mg/d and 29 patients a dose of aspirin 50 mg/d. 27 patients were given diclofenac (25 mg/d). 27 patients with MI received no antiplatelet therapy with nonsteroidal antiinflammatory drugs. There were 18 chronic coronary artery disease (CCAD) male patients (mean age 49.8 years, range 29-64) and 23 healthy male volunteers (HV; mean age 47.0 years, range 26-65) in the control groups. None of patients and control subjects had taken nonsteroidal antiinflammatory drugs or corticosteroids for at least two weeks.

Blood sampling. Venous blood samples from the antecubital vein were collected. Samples of MI patients were drawn on the 1st, 3rd, 7th, 14th and 28th day of illness. Blood was anticoagulated with 3.8% trisodium citrate (9 parts blood to 1 part anticoagulant). Blood samples were drawn in the morning between 8 a.m. and 9 a.m. Patients and control persons were at rest for 20 min before sampling.

Preparation of platelet-rich plasma. Citrated blood was centrifuged at 160 g at room temperature for 10 min. The upper layer of platelet-rich plasma (PRP) was separated. The remaining blood specimens were centrifuged at 1400 g at room temperature for 20 min to prepare platelet-poor plasma (PPP). The platelet count in PRP was adjusted to $250 \times 10^9 \times l^{-1}$ using the autologous PPP and the PRP was thereafter stored for 20 min at room temperature before the platelet aggregation measurements.

Platelet aggregation studies. Platelet aggregometry was performed according to the method of Born (1) in an aggregometer at 37°C with a magnetic stirrer (1000 rpm). The aggregation studies were conducted 60 min after the venipuncture and were completed within 2 hours. The volume of PRP added to each cuvette was 450 µl. The aggregometer was adjusted before each experiment so that the PRP gave no light transmittance and the PPP gave 100 percent light transmittance. The spontaneous aggregation of platelets was recorded as the percentage fall in optical density during stirring the PRP in the aggregometer for 5 min. ADP (Reanal, Budapest, Hungary) and epinephrine (Sigma) were used as aggregating reagents. The final concentrations of ADP were 0.25 and 2.5 µM and of epinephrine 1 µM. Induced platelet aggregation

was expressed as the maximal percentage of aggregation achieved within 5 min after the addition of an agonist.

Statistical analysis. The results are presented as mean±SD. Statistical analysis was performed by one and two sample analysis and Student's t-test using STATGRAPHICS 2.6 software. A P value <0.05 was considered significant.

RESULTS

The effect of varying doses of ASA and diclofenac on spontaneous platelet aggregation in MI patients are shown in Fig. 1. The upper curve demonstrates platelet aggregation without antiaggregatory therapy. We observed a thrombocyte hypoaggregation on the 1st MI day, a rapid increase in platelet activity by the 7th day and a considerable decrease in the spontaneous aggregation during the 3rd and 4th weeks of illness. Spontaneous aggregation on the 1st MI day (2.07±0.65 %) was significantly (P<0.001) lower than in the CCAD patient group (5.30±2.25%), but higher than in the HV group (0.76±1.59%).

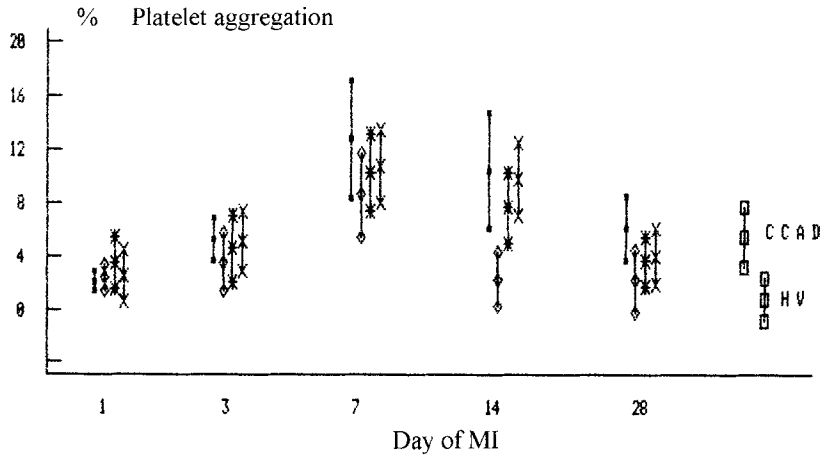

Fig. 1. Spontaneous platelet aggregation in patients with myocardial infarction receiving 500 mg/d (*; n=26) or 50 mg/d (◊; n=29) of acetylsalicylic acid, diclofenac 25 mg/d (x; n=27) or no antiaggregative therapy (•; n=27). On the right side spontaneous aggregation in chronic coronary artery disease (CCAD; n=18) and healthy volunteers (HV; n=23) groups are expressed. Data points are means±SD.

On the 28th day of MI spontaneous platelet aggregation (5.95±2.38%) did not differ from that in CCAD patients. Lower curves show that aspirin in the dose of 50 mg/d inhibited spontaneous aggregation of thrombocytes more effectively than in the dose of 500 mg/d. However, even the low-dose aspirin was insufficient to prevent the platelet hyperaggregation on the 7th day of MI. Spontaneous platelet aggregation on the 7th

day of illness in patients getting a dose of aspirin 50 mg/d was considerably higher than in the HV and CCAD groups. Diclofenac in a dose of 25 mg/d had only a limited antiaggregatory effect in MI patients. Spontaneous platelet aggregation was suppressed only on the 28th MI day (3.91±2.14% when compared with 5.95±2.38% in MI patients without antiaggregative therapy ($P<0.01$)).

Fig. 2. demonstrates the efficacy of aspirin and diclofenac to inhibit platelet hyperaggregation induced by 0.25 μM ADP during MI. Daily doses of 50 mg and 500 mg ASA both produced a fall in platelet aggregation on the 3rd, 7th 14th and 28th days of MI, although the effect was more pronounced in the low-dose aspirin group. Diclofenac suppressed 0.25 μM ADP-induced platelet aggregation on the 3rd, 7th and 14th MI day, but significantly less than 50 mg of aspirin.

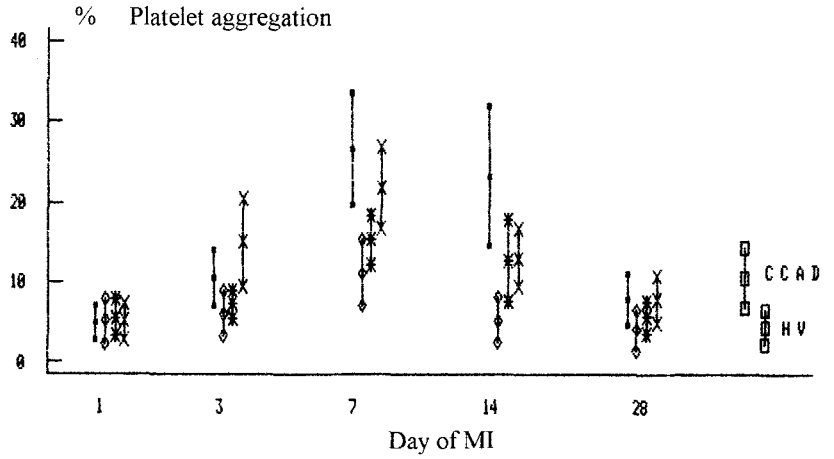

Fig. 2. Platelet aggregation induced by 0.25 μM ADP in patients with myocardial infarction receiving 500 mg/d (*; n=26) or 50 mg/d (◊; n=29) of acetylsalicylic acid, diclofenac 25 mg/d (x; n=27) or no antiaggregative therapy (•; n=27). On the right side spontaneous aggregation in chronic coronary artery disease (CCAD; n=18) and healthy volunteers (HV; n=23) groups are expressed. Data points are means±SD.

The changes in platelet aggregation induced by 2.5 μM ADP and 1 μM epinephrine in MI patients receiving 500 mg and 50 mg of aspirin, 25 mg of diclofenac or nothing are presented in Fig. 3 and Fig. 4. The sensitivity of these aggregation methods to evaluate platelet hyperaggregability in MI patients in comparison with 0.25 μM ADP-induced and spontaneous thrombocyte aggregation is lower. Nevertheless, similar results were obtained, applying all aggregation methods. The most pronounced platelet hyperaggregation occurred on the 7th MI day and low-dose aspirin was more effective to suppress platelet aggregation in comparison with 500 mg of aspirin and diclofenac.

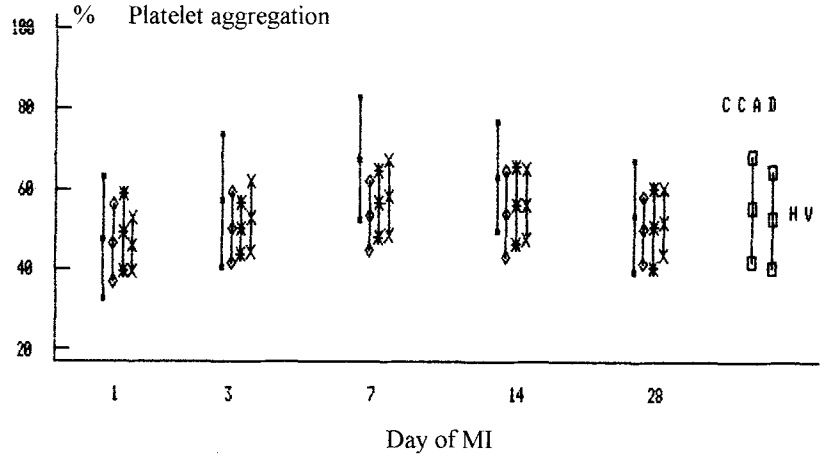

Fig. 3. Platelet aggregation induced by 2.5 μM ADP in patients with myocardial infarction receiving 500 mg/d (*; n=26) or 50 mg/d (◊; n=29) of acetylsalicylic acid, diclofenac 25 mg/d (x; n=27) or no antiaggregative therapy (·; n=27). On the right side spontaneous aggregation in chronic coronary artery disease (CCAD; n=18) and healthy volunteers (HV; n=23) groups are expressed. Data points are means±SD.

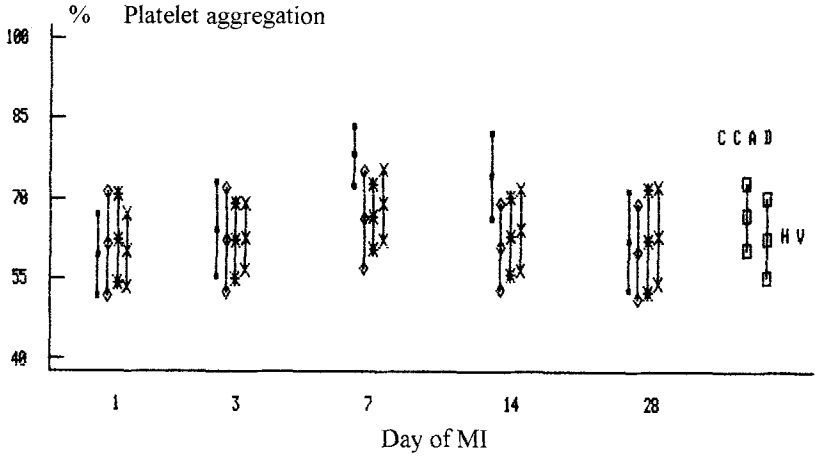

Fig. 4. Platelet aggregation induced by 1 μM epinephrine in patients with myocardial infarction receiving 500 mg/d (*; n=26) or 50 mg/d (◊; n=29) of acetylsalicylic acid, diclofenac 25 mg/d (x; n=27) or no antiaggregative therapy (·; n=27). On the right side spontaneous aggregation in chronic coronary artery disease (CCAD; n=18) and healthy volunteers (HV; n=23) groups are expressed. Data points are means±SD.

DISCUSSION

Numerous experimental and clinical studies have indicated platelet hyperaggregation in MI patients. Nonsteroidal antiflogistic drugs were demonstrated to inhibit thrombocyte aggregation (17). Low-dose ASA was shown to have a more pronounced antiaggregative effect when compared to high doses of aspirin (10). However, there are only few papers concerning antiaggregatory therapy in acute MI patients. ISIS-2 (the Second International Study of Infarct Survival) showed a highly significant 23% reduction of the risk of total vascular death among the acute MI patients taking 162 mg/d aspirin during 5 weeks when compared to a placebo group (5). The question whether heparin is also necessary to treat acute MI patients if aspirin is given was studied in ISIS-3 trial (6). There was no significant difference in the endpoint of the 35-day mortality (10.3% aspirin plus heparin versus 10.6% aspirin alone).

The most effective and safe dose of ASA during the first month of MI is still unclear. Recently, it was shown that early intervention with low-dose aspirin (100 mg/d) reduced infarct size and decreased the risk of reinfarction (18). Another study demonstrated that treatment with aspirin 75 mg daily reduced the risk of MI by 50% at 3 months after an episode of unstable CAD in men (15). Nevertheless, the major gastrointestinal bleeds have been reported in patients taking aspirin 75 mg/d (9).

Assuming that a daily dose of 50 mg aspirin would suffice in blocking platelet thromboxane A2 (TxA2) production (7), we examined the efficacy of this dose in acute MI patients. The present study clearly demonstrated the high antiaggregative efficacy of aspirin in a dose of 50 mg/d which was significantly more pronounced than that in the daily dose of 500 mg aspirin. Moreover, we found that low-dose aspirin had fewer side-effects than aspirin 500 mg/d. Five patients in the 500 mg/d group and only one in the low-dose aspirin group had moderate gastrointestinal side-effects. There was no need to finish the administration of aspirin. Spontaneous platelet aggregation and that induced by ADP and on the 3rd and 4th MI weeks in the patient group getting low-dose aspirin did not differ significantly from that in CCAD patients. We also found that antiplatelet activity of low-dose aspirin was too low to abolish thrombocyte hyperaggregation in the acute phase of MI. Despite of ASA administration in the dose of 50 mg/d spontaneous and 0.25 μM ADP-induced platelet aggregation on the 7th MI day both remained to be elevated in comparison with CCAD patients. To avoid the complications which often occur in this stage of MI, a more effective antiaggregative treatment is needed. It was previously shown that the inhibition of platelets following 50 mg/d aspirin was complete only after three days while the total effect of 500 mg of aspirin was attained after 24 hours (7). Correspondingly, the antiplatelet effect of low-dose aspirin can be enhanced by using the dose of 500 mg/d during 2 initial days of antiaggregative treatment. Nevertheless,

since we established platelet hypoaggregation on first days of MI, an earlier cumulation of ASA might have no big advantage in antiplatelet therapy of MI.

Another powerful cyclooxygenase inhibitor diclofenac has also been shown to inhibit platelet aggregation (13). To our knowledge the efficacy of diclofenac in antiaggregative treatment of AMI has not been studied before. We found that a daily dose of 25 mg diclofenac produced only a moderate inhibition of platelet aggregation. The antiaggregative efficacy of diclofenac was significantly lower than that of aspirin in doses of 50 mg/d and 500 mg/d.

In conclusion, our results demonstrate that the antiaggregative treatment of AMI with aspirin 50 mg daily is effective and safe. Aspirin 500 mg/d had significantly lower efficacy to suppress the platelet hyperaggregation in MI patients. However, although low-dose aspirin significantly inhibited the platelet hyperaggregation on the 7th day of MI, the hyperactivity of thrombocytes was not terminated. Diclofenac 25 mg daily had only a moderate antiaggregatory effect in acute MI patients.

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