Enhancement of platelet inhibition of ticlopidine plus aspirin vs aspirin alone given prior to elective PTCA

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Background In many patients today, elective percutaneous transluminal coronary angioplasty is followed by implantation of coronary stents to achieve optimal results. The current medical strategy to prevent early reocclusion is the inhibition of platelet aggregation by administration of ticlopidine, in addition to aspirin, immediately after the procedure. In order to inhibit platelet aggregation as early as possible, many centres begin to treat patients with additional ticlopidine the day before elective coronary intervention. The aim of this study was to determine the effect of this strategy on platelet aggregation before angioplasty.

Method Fifty-two consecutive patients admitted to hospital for elective balloon angioplasty were prospectively randomized to receive either standard oral aspirin 100 mg per day or standard therapy plus 250 mg ticlopidine at the time of admission and the morning before angioplasty. Adenosine diphosphate-, collagen- and epinephrine-induced platelet aggregation was measured immediately before the procedure by an investigator who was blinded concerning the arm of therapy.

Results The two groups of patients were comparable in terms of age, sex, body mass index, anginal state, time interval between application of study drug and coronary intervention. Patients on aspirin and ticlopidine had a mean maximal platelet aggregation of 36 ± 12% with adenosine diphosphate as agonist. For the control group, 54 ± 12% was measured (P < 0.001). Myocardial infarction or emergency coronary bypass grafting did not occur in either group. Local haemorrhagic complications at the arterial access site occurred in five (aspirin) and six (aspirin and ticlopidine) patients (P = ns) none of them requiring blood transfusion.

Conclusion The additional application of ticlopidine to chronic aspirin therapy the day before elective coronary balloon angioplasty leads to a significantly higher inhibition of platelet aggregation at the time of the intervention. It seems to be safe compared to the standard procedure.

Key Words: Ticlopidine, aspirin, platelet aggregation, percutaneous transluminal coronary angioplasty, stent.

In view of ticlopidine's additional antithrombotic effect and its potent inhibition of platelet adhesion to the endothelial surface, it appears to be a sensitive clinical concept to add this drug to routine premedication before elective percutaneous coronary balloon dilatation. However, little information on platelet function and clinical data are available to support this widely adopted approach.

This study was performed: (1) to determine the influence of the additional administration of ticlopidine to chronic oral aspirin on platelet aggregation in the setting before elective coronary angioplasty; (2) to document the safety of this therapeutic concept.

Methods

Patients

Fifty-two consecutive patients (>18, <80 years) with stable angina who were admitted to hospital for elective percutaneous transluminal coronary angioplasty were included in this study (Table 2). Table 1 gives the exclusion criteria for the two treatment groups.

Study protocol

Immediately after admission, informed consent was obtained and patients were randomized using a standard list of random numbers. All randomized patients were on chronic oral aspirin (100 mg per day) at the time of admission to hospital. In the treatment group, aspirin and ticlopidine patients received 250 mg ticlopidine orally. A second dose of 250 mg ticlopidine was given the next morning before scheduled coronary balloon dilatation. The consumption was confirmed and documented by a registered nurse. All relevant data on the interventional procedure were recorded. At hospital discharge all patients were seen by a doctor who was not aware of the treatment arm. Local bleeding complications at the site of arterial access were graded as follows: 1=local skin haematoma <10 cm in diameter; 2=local skin haematoma >10 cm in diameter; 3=local bleeding requiring transfusion; 4=local bleeding requiring surgical repair; 5=other complication.

Platelet aggregation

Before administration of the heparin bolus and immediately following the insertion of the arterial sheath, 40 ml of blood were carefully drawn in a sodium-citrate containing vial. Shear stress was avoided. Blood was centrifuged at 100 g for 15 min (Rotixa/RP, Hettich, Tuttingen, Germany). Platelet-rich plasma was then collected. Platelet-poor plasma was prepared by centrifuging the remaining blood at 1800 g for 10 min (Rotixa/RP, Hettich, Tuttingen, Germany). Platelet aggregation was measured by analysing optical absorbance at 650 nm with a PACK S-4 (Helena Laboratories, Texas, U.S.A.) by standard method. The investigator was blinded to the treatment arm of each sample. Induction of platelet aggregation was achieved by adding, successively, adenosine diphosphate (2·0; 1·5; 1·0; 0·5 μg), collagen (1·0; 0·75; 0·50; 0·25 μg), epinephrine (1·0; 0·75; 0·50; 0·25 μg ml⁻¹) and arachidonic acid (250 μg ml⁻¹) to the vial of platelet-rich plasma. Activating substances were used as supplied in the kit (Platelet Aggregation Kit, Helena Laboratories, Texas, U.S.A.).

Statistics

Data were collected on a personal computer (Pyramid, Germany) with a standard software (Microsoft Excel, Texas, U.S.A.).
Results

Patient characteristics

A total of 122 patients had to be screened to finally randomize and enrol 52 (42%) patients in this study. Twenty-two (17%) did not give their informed consent, 31 (24%) were on a continuous heparin treatment, 11 (9%) had unstable angina, five (4%) did not meet the inclusion age, one (1%) had malignant lymphoma, four (3%) had a history of peptic ulcer or gastrointestinal variceal bleeding, in one patient (1%) a Factor V Leiden mutation (heterocygote) was detected. A summary of the basic patient related information is presented in Table 2.

All patients were on a continuous oral aspirin therapy (100 mg per day) before admission to hospital. Ticlopidine was administered to all patients randomized to this arm of treatment and was subjectively well tolerated. The drug was given 22–28 h before scheduled coronary angioplasty in all except one of the group 1 patients, who underwent the intervention one day later than scheduled for organisational reasons. Percutaneous coronary angioplasty was performed in 53 of the 54 patients (98%) enrolled. One patient had a left main stem stenosis detected before passage of the guide wire and was transferred electively to surgery. One patient had acute coronary marginal branch occlusion proximal to an implanted stent. Aortocoronary bypass surgery was performed as an emergency procedure. Both patients were in group 2 (aspirin alone). Thirty-two intracoronary stents were implanted in 52 patients: 20 in 13 group 1 patients (50%), 12 in eight (31%) group 2 patients. Table 3 gives the procedural data of all patients enrolled. In all patients who had a stent implanted, ticlopidine was continued at 250 mg b.i.d. for 4 weeks. A full blood count was monitored at intervals of 2 weeks during ticlopidine administration.

Platelet aggregation

Platelet aggregation was measured as maximum aggregation in % compared to control (see above). As shown in Table 4 and Figs 1 and 2, adenosine diphosphate-induced platelet aggregation was significantly more inhibited in patients treated with ticlopidine and aspirin (36·1 vs 54·3%, P = 0·001) as compared to the group receiving aspirin alone. This was demonstrated at four different levels of concentration of the activating substance. Epinephrine-induced platelet aggregation was not influenced in this way. When collagen is used to induce aggregation there seems to be a trend towards a difference between the two groups that does not reach a level of significance in this study (Table 4, Figs 1 and 2).

Events and complications

No patient had a procedure-related myocardial infarction or fatal cardio-circulatory event during this study, or had to undergo surgical repair of blood transfusions for a local puncture-related complication. Grade 1 complications were documented in six patients of the ticlopidine/aspirin group and in five control patients.
Figure 1  Original tracings of adenosine diphosphate-induced platelet aggregation curves (patient 5, aspirin alone) at different concentrations of the activating substance (0·5 μM: lowest curve, 1·0: second curve; 1·5 μM: third curve; 2·0 μM: top curve).

Figure 2  Original tracings of adenosine diphosphate-induced platelet aggregation curves (patient 2, chronic oral aspirin plus ticlopidine) at different concentrations of the activating substance (0·5 μM: lowest curve, 1·0 μM: second curve; 1·5 μM: third curve; 2·0 μM: top curve).
Grade 2 local bleeding complications were seen in two group 1 patients and in three control patients.

**Discussion**

The protocol of this study was designed to investigate the influence on platelet aggregation of adding ticlopidine to chronic oral aspirin before elective percutaneous balloon coronary angioplasty and stenting. We chose a study design that reflects a therapeutic scheme already applied by many interventional cardiologists, although data on its actual influence on platelet aggregation are not yet published.

Pharmacological knowledge and clinical experience with chronic aspirin is longstanding[20,21]. Inhibition of platelet cyclo-oxygenase is the mechanism of its antiaggregatory effect. A cyclo-oxygenase inhibitor is generally recommended as routine premedication before interventional coronary procedures[22,23]. The first data on ticlopidine were published in 1974 by Mailrand and Eloy[24]. Information on pharmacokinetic and pharmacodynamic properties of ticlopidine and its clinical importance is still growing[25–27]. Ticlopidine is not a direct inhibitor of platelet surface receptors but inhibits the adenine diphosphate-induced exposure of the fibrinogen binding site of the glycoprotein IIb/IIIa receptor complex[16,28–31]. The drug also interferes effectively with platelet adhesion to the vascular endothelium on its antiplatelet effects[18,32]. An important observation was the delayed effect of ticlopidine on platelet aggregation. Inhibition of adenine diphosphate-induced platelet aggregation is measured 24–48 h after administration of a single dose of 250 mg of ticlopidine. The maximum antiaggregatory effect is measured at 72–96 h[31,33].

Very little recently published experimental data exist on the haemostatic effect of the combined therapy with these two drugs. Data from animal studies are provided by Herbert and co-workers[34] who demonstrated an additive influence of the antiaggregating and antithrombotic effects of this combination therapy in rats treated with conventional doses of aspirin and ticlopidine. Splawinska et al.[35] describe a similar finding in an experimental study performed with 32 healthy volunteers. These authors speculate that, in the presence of aspirin that blocks the formation of thromboxane A₂, the inhibition of adenine diphosphate-induced platelet aggregation by ticlopidine is facilitated. They made this observation, of a ‘potentiated’ antiaggregatory effect even at a relatively low dosage of aspirin and ticlopidine. Press et al.[36] demonstrate a serial investigation of platelet aggregation in patients immediately after transcatheter coronary revascularization. They found that a significant inhibition of adenine diphosphate-induced platelet aggregation could be measured by day 2 of an oral combination therapy compared to aspirin alone.

The therapeutic strategy of inhibition of platelet aggregation by combining two antiplatelet agents, ticlopidine and aspirin, has been demonstrated to be clinically very effective in preventing subacute thrombotic closure after stenting of coronary arteries[10–13,19,36]. Hæmorrhagic complications seem to be rare compared to traditional oral anticoagulation with coumarin. Therefore, accompanied by this antiplatelet regimen, the clinical use of coronary stenting could expand significantly[14,16]. Results of recently published studies on the monoclonal antibody to the glycoprotein IIb/IIIa receptor, abciximab, in patients with unstable coronary syndromes, support the concept of platelet passivation before transcatheter coronary intervention[38–40]. As the routine application of the monoclonal antibody (ReoPro®) is an extremely cost intensive therapeutic strategy, orally applicable alternative treatments are needed.

In our study, we demonstrate that the addition of ticlopidine to chronic oral aspirin the day before elective coronary angioplasty can significantly increase the inhibition of platelet aggregation at the time of the interventional procedure, compared to aspirin alone. The effect was not accompanied by a higher incidence of local bleeding complications.

Our results show that this combination therapy leads to more intense platelet passivation and that this inhibition is achieved earlier than expected by the pharmacological studies on ticlopidine alone. This enhancement of platelet inhibition, by the combination of the two orally applicable antiplatelet agents, has been observed by other authors in experimental and clinical studies[34,35,37]. The value of our data is increased as patients were randomly assigned to the treatment groups and the investigator of platelet aggregation was blinded towards the treatment arm until the final evaluation of the data.

Our results are relevant for interventional cardiologists as we demonstrate that by adding ticlopidine to aspirin the day before balloon angioplasty the ‘antiaggregatory gap’ between stent implantation and maximum platelet passivation can be significantly reduced. The advantage of administering the additional dose of ticlopidine the day before the interventional procedure means that experienced cardiologists could select patients after admission to the interventional department. This already widely adopted therapeutic strategy is supported by the data from our study. Whether this concept leads to a reduction of early stent occlusions or fewer thrombotic complications during coronary intervention has to be proven in larger clinical studies that focus on clinical endpoints.

**Conclusion**

With the increasing use of intracoronary stents in interventional cardiology, pharmacological intervention in platelet aggregation to prevent local thrombus formation becomes a very prominent aspect of the procedure. Our data demonstrate that by giving ticlopidine in
addition to chronic aspirin one day before elective percutaneous transluminal coronary angioplasty, platelet aggregation can be more effectively inhibited, as compared to the standard treatment. In this group of patients with a relatively low procedural risk, this appears to be a cost effective way to inhibit platelet aggregation and, thus, thrombotic occlusion, as compared to inhibition of the glycoprotein IIb/IIIa receptor by monoclonal antibodies. Whether this approach reduces the rate of acute and subacute stent thrombosis has to be proven in larger clinical trials that focus on clinical outcome to confirm the importance of this observation.

References


Enhancement of platelet inhibition prior to PTCA 101

