Rapid and selective inhibition of platelet aggregation and thromboxane formation by intravenous low dose aspirin in man

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1. One of the major problems in the clinical use of low dose aspirin for the prevention of vascular occlusion is that it takes about 3–5 days to become effective, a time too long for patients with unstable angina or coronary thrombolysis. Intravenous aspirin may be expected to exert a more rapid effect, but its influence on endothelial prostacyclin synthesis is uncertain.

2. In a single-blind, randomized, prospective study, we compared the effects of a single intravenous low dose (50mg) or high dose (500mg) of aspirin or placebo infused over a 60 min period on platelet aggregation, platelet thromboxane A₂ production and whole-body prostanoid synthesis in 10 healthy male subjects by gas chromatography–tandem mass spectrometry.

3. Before the study, blood flow rates in the basilic and subclavian veins were determined by sonographic colour velocity imaging; the infusion rate for low dose aspirin was calculated to avoid biologically effective plasma levels of aspirin in the systemic circulation.

4. Platelet aggregation induced by 1 mmol/l arachidonic acid was similarly inhibited by >85% within 30 min after the start of the infusion of high dose or low dose aspirin, respectively, and remained suppressed for 24 h. Platelet thromboxane A₂ release declined gradually after low dose aspirin, reaching a minimum of 93% inhibition after 60 min. High dose aspirin suppressed platelet thromboxane A₂ release to below the detection limit after 10 min.

5. Urinary excretion of the major urinary metabolite of thromboxane A₂ (2,3-dinor-thromboxane B₂) was equally suppressed by both dosages of aspirin [no significant difference between high dose (−83.2%) and low dose (−67.4%)]. The urinary excretion of the major urinary metabolite of prostacyclin (2,3-dinor-6-keto-prostaglandin F₁α) and of prostaglandin E₂ was also markedly decreased, by 79.2% and 63.5%, respectively, by high dose aspirin, whereas low dose aspirin suppressed 2,3-dinor-6-keto-prostaglandin F₁α excretion significantly less (−30.3%; P<0.02), and had no inhibitory effect at all on prostaglandin E₂ excretion, indicating that after intravenous low dose aspirin no biologically active acetylsalicylate was present in the systemic circulation.

6. These data show that intravenous low dose aspirin can inhibit platelet aggregation and thromboxane B₂ synthesis within less than 2 h while sparing systemic cyclo-oxygenase activity. Partial inhibition of prostacyclin formation seems to be an unavoidable consequence of effective inhibition of platelet cyclo-oxygenase by aspirin.

INTRODUCTION

Aspirin (acetylsalicylic acid), which is the best-investigated drug inhibiting platelet activation, has been shown in the last years to be effective in the long-term prevention of arterial occlusion and reocclusion [1–5]. In low doses there seems to be a relative biological selectivity for the inhibition of platelet thromboxane formation [6–8]. By leaving the antiaggregatory and vasodilator activity of prostacyclin intact, this might add further benefit to the antiplatelet effect of aspirin [9]. Accordingly, several dosage regimens have been proposed to optimize the selectivity of aspirin treatment, including the use of very low daily doses or of entericoated, slow-release oral formulations of aspirin [10–13]. Since it has been found that the thrombocyte and endothelial cyclo-oxygenase enzymes are equally sensitive to inhibition by a single dose of aspirin [14, 15], it has been suggested that the biological selectivity of aspirin for platelet thromboxane formation might be a pharmacokinetic rather than a pharmacodynamic effect. After oral low doses of aspirin, pharmacologically active
Thus, the dilution of the drug occurring in the systemic circulation. This was compared to previous studies indicating that the liver's function as a 'metabolic filter' preventing systemic prostacyclin activity after oral administration.

Effective inhibition of cyclo-oxygenase, both in platelets and endothelial cells, has been shown in vitro to occur in concentrations above 10 μg/ml [16, 32]. The aim of the present study has thus been to infuse low dose (LD, 50 mg) aspirin at a rate adapted to previously determined blood flow rates, in order to reach a plasma concentration above 10 μg/ml at the site of infusion, but well below this level in the systemic circulation. This was compared with high dose (HD, 500 mg) aspirin and with placebo. The 50 mg dose was chosen because it had been shown to have equal antiplatelet effects with 324 mg daily [9], and to differentially inhibit thromboxane (TX) A2 and prostacyclin formation after repeated oral dosages [25]. As parameters for the formation of thromboxane and prostacyclin in vivo, urinary excretion rates of the 2,3-dinor metabolites of TXA2 (2,3-dinor-TXB2) and prostacyclin (2,3-dinor-6-keto-PGF1α, where PG is prostaglandin) were determined because they had been shown to closely reflect biosynthesis of the respective prostanoids [33, 34]. Urinary PGE2 excretion was chosen as a reliable parameter of kidney, and thus systemic, cyclo-oxygenase activity [33, 35, 36].

**MATERIALS AND METHODS**

**Study design**

This single-blind, placebo-controlled, randomized and prospective study, which was approved by the Ethics Committee of the Medical School of Hannover, was performed in ten healthy male subjects (mean age 24.2 ± 0.5 years, height 1.82 ± 0.2 cm, weight 72.2 ± 2.5 kg) and consisted of 3 study days. On one day, placebo was infused into a cubital vein; on the other 2 days, 50 mg or 500 mg of aspirin were infused over 60 min. The sequence of the 3 days was randomized with a minimum of 7 days wash-out period between them, which has been shown to be sufficient for urinary 2,3-dinor-TXB2 excretion to return to basal values after cessation of aspirin [6, 37].

All participants had given their written informed consent and had denied having taken aspirin or any drug known to interfere with platelet aggregation or prostaglandin synthesis for 2 weeks preceding their participation in the study.

At the beginning of each study day the subjects emptied their bladders. A urinary sample was tested for salicylate content to further exclude that they had ingested any salicylate-derived drugs. A mild oral volume loading (herb tea) was started at 3 ml/kg initially and continued during the study period at 1–2 ml h⁻¹ kg⁻¹ adjusted to the individual hourly urinary volumes.

Before, as well as 10, 20, 30, 60 and 120 min after, the beginning of the infusion, 9 ml of venous blood was collected from the opposite arm into a syringe containing 1 ml of 3.13% (w/v) sodium citrate. For 2 h before and 2 h after the beginning of the infusion, urine was collected at hourly intervals and was immediately frozen for the determination of urinary prostaglandin and thromboxane metabolites. In six of the subjects an additional sample of venous blood was collected for platelet aggregation 24 h after the aspirin infusions.

Each subject remained in the supine position for the duration of the infusion.

Participants were asked on each study day whether they had noticed any aspirin-related side-effects.

**Sonographic measurements of blood flow**

Before the beginning of the study, each subject underwent a general physical examination and a sonographic determination of the diameters and blood flow rates of the basilic and subclavian veins (5 MHz transducer) under standardized conditions (room temperature 22 ± 0.5°C, supine position, 15 min rest period before examination). Blood flow velocity was measured with colour velocity imaging (Philips platinum; Philips). In contrast to the
Doppler method (a frequency domain method) colour velocity imaging is a time domain method [38]. After angle correction, velocity was measured by green tagging the maximum and minimum velocity values in the colour-coded bloodstream. From the average flow rates \(F\) and diameters \(d\) the mean blood volumes per minute \(V\) were calculated as
\[
V(\text{ml/min}) = F \pi \left(\frac{d}{2}\right)^2.
\]

**Platelet aggregation and thromboxane formation**

Platelet-rich plasma (PRP) was prepared by centrifugation at 200 g for 15 min. Platelet-poor plasma (PPP) was prepared from the remaining volume of blood by centrifugation at 2000 g for 10 min. Platelet aggregation was monitored at 37°C as the increase in light transmission by the method of Born and Cross [39] using an Apatc dual-channel aggregometer (LBor, Hamburg, Germany). The aggregometer was adjusted before each test so that in each patient the value of light transmission for PRP was 0% and for PPP was 100%. Aggregation was induced in duplicate using final concentrations of 1 mg/l collagen (Hormonchemie, Munich, Germany) and 0.5 and 1 mmol/l arachidonic acid (Sigma, Munich, Germany) in 250 μl of PRP. Aggregation was monitored for 3 min. In aggregations induced by 0.5 mmol/l arachidonic acid, the reaction was quenched by the addition of 0.5 ml of ice-cold ethanol to 250 μl of PRP. After centrifugation the supernatant was stored at −20°C until analysis of TXB₂, the stable hydrolysis product of TXA₂, by r.i.a.

For the determination of TXB₂, the samples were thawed, the ethanol was evaporated and the pellet resuspended in r.i.a. phosphate buffer. \([3H]TXB₂\) was supplied by New England Nuclear (Dreieich, Germany). The unlabelled standard and the TXB₂ antibody were purchased from Sigma (Munich, Germany). The detection limit of the assay was 20 pg/10⁸ platelets.

**Urinary prostanoïd excretion**

Urinary samples were kept at −20°C until analysis of their prostanoïd content. Quantification of urinary 2,3-dinor-TXB₂ (a major urinary metabolite of TXA₂), 2,3-dinor-6-keto-PGF₁α (the major urinary metabolite of prostacyclin) and PGE₂ was performed by negative chemical ionization gas chromatography–tandem mass spectrometry on a triple-stage quadrupole mass spectrometer TSQ 45 (Finnigan MAT, San Jose, CA, U.S.A.) as described elsewhere [40, 41]. Briefly, endogenous prostanoïds and their corresponding tetradeterated internal standards, which had been externally added to 50 ml aliquots of urine samples, were extracted from acidified urine samples (pH 3.0) by solid-phase extraction on octadecyl silica cartridges (J. T. Baker, Deventer, The Netherlands). After derivatization to their pentafluorobenzyl ester methoxyamine derivatives and separation by reversed-phase h.p.l.c. the analytes were converted to their trimethylsilyl ether derivatives. Gas chromatography–tandem mass spectrometry was performed by selected reaction monitoring of the characteristic daughter ions generated by collision-activated dissociation of the corresponding parent ions for endogenous prostanoïds and their stable-isotope labelled analogues.

Urinary creatinine was determined spectrophotometrically by the alkaline picric acid reaction with an automatic analyser (Beckman, Galway, Ireland), and excretion of prostanoïd metabolites was calculated as pg/mg of creatinine. To evaluate the differential influence of the treatments on urinary prostacyclin and thromboxane metabolite excretion, the ratio 2,3-dinor-6-keto-PGF₁α/2,3-dinor-TXB₂ was calculated from these values.

**Drugs**

Aspirin (DL-lysine mono-acetylsalicylic acid) was purchased from Bayer (Leverkusen, Germany) and diluted in 30 ml of 0.9% NaCl to give concentrations of 1.67 g/l or 16.67 g/l. These solutions were infused at a rate of 0.5 ml/min so that in 60 min 50 and 500 mg of DL-lysine mono-acetylsalicylic acid were infused, respectively. The pH of the solution was 5.0. It was freshly prepared immediately before use, although it was shown to be stable for at least 5 h. On the placebo day 30 ml of 0.9% NaCl were infused in 60 min.

**Salicylate levels in serum and urine**

Serum levels of salicylate, the hydrolysis product of acetylsalicylic acid, were determined in a blood sample drawn 15 min after the end of each infusion by a commercial fluorescence assay system (TDX; Abbott Diagnostics, Wiesbaden, Germany).

Urinary salicylate content was determined qualitatively as a compliance test by means of a reagent [4 g of HgCl₂, 4 g of Fe(NO₃)₃, 20 ml of HCl, 80 ml of H₂O] allowing the detection of ≤10 mg salicylate/litre of urine, or the previous ingestion of 100 mg of aspirin.

**Statistical analysis**

For the calculation of blood flow, median values of velocity measurements were calculated. All other data are given as means ± SEM. Statistical significance was assessed using the Scheffé f-test for two-way analysis of variance or the Wilcoxon matched-pairs signed-rank test. A P value <0.05 was considered significant in all cases.
Table I. Venous blood flow rates and corresponding calculated local aspirin concentrations. Blood flow was calculated from the vein diameters and blood flow velocities determined sonographically in the basilic and subclavian veins under standardized conditions (room temperature 22° ± 0.5°C, supine position, 15 min rest period before examination). Blood flow velocity was measured with colour velocity imaging. After angle correction, velocity was measured by green tagging the maximum and minimum velocity values in the colour-coded bloodstream. Average local aspirin concentrations were calculated from infusion rates and local blood flow.

<table>
<thead>
<tr>
<th>Flow</th>
<th>Basilic vein (mean diameter 0.38 cm)</th>
<th>Subclavian vein (mean diameter 0.96 cm)</th>
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<tr>
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<td>Velocity (cm/s)</td>
<td>Flow (ml/min)</td>
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<td>50 mg</td>
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<td>Median</td>
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<td>Minimum</td>
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<td>Maximum</td>
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**RESULTS**

**Blood flow measurements**

Sonographic measurements indicated a mean vessel diameter of 0.38 ± 0.02 cm and 0.96 ± 0.08 cm for the basilic and subclavian veins, respectively. In the basilic vein, the minimum flow velocity was 2.4 ± 0.4 cm/s and the maximum velocity was 5.1 ± 0.8 cm/s, resulting in a minimum volume of 18.0 ml/min and a maximum volume of 39.0 ml/min (median 28.5 ml/min). In the subclavian vein, the minimum flow velocity was 5.4 ± 0.8 cm/s and the maximum velocity was 17.3 ± 2.0 cm/s, resulting in a minimum volume of 305.0 ml/min and a maximum volume of 720.0 ml/min (median 512.0 ml/min). The dilution coefficient calculated from this data was 1:18, and the local plasma concentration of aspirin was calculated as 53.2 mg/l in the basilic vein and 3.0 mg/l in the subclavian vein after LD aspirin, and 532.1 mg/l and 30.2 mg/l after HD aspirin (Table 1).

None of the subjects reported any side-effects, neither systemically nor at the site of infusion, on any of the study days.

**Platelet aggregation and TXA₂ formation**

Both dosages of aspirin caused a cumulative, almost complete, inhibition of arachidonic acid-induced platelet aggregation within 30 min (Fig. 1). In both groups, aggregation remained suppressed 1 h after the end of the infusion and was still suppressed 24 h later (Fig. 2).

Collagen-induced aggregation was also significantly suppressed in both aspirin groups, although the effect was reached more rapidly after HD aspirin. At 60 min, aggregation was inhibited by almost 90% after both dosages (not significant; Fig. 3). Again, the effect was sustained after the end of the infusion, and was still present 24 h after the infusion, although a slight recovery was observed.

Platelet thromboxane release induced by 0.5 mmol/l arachidonic acid declined gradually during the infusion of 50 mg of aspirin, reaching
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Fig. 3. Maximum platelet aggregation induced by 1 𝜇g/ml collagen in PRP before (basal) and after the start of the infusion of 50 mg or 500 mg of aspirin or placebo at the time points indicated. Data points are means ± SEM for n = 10 subjects at 0-120 min (n = 6 at 24 h). Asterisks indicate statistically significant differences between the placebo-treated group and each of the aspirin-treated groups. Abbreviation: NS, not significant.

Fig. 4. Thromboxane release by platelets stimulated with 0.5 mmol/l arachidonic acid before (basal) and after the start of the infusion of 50 mg or 500 mg of aspirin or placebo at the time points indicated. Data points are means ± SEM for n = 10 subjects at 0-120 min (n = 6 at 24 h). Samples of PRP were incubated for 3 min at 37°C, the reaction was quenched by adding 0.5 ml of ice-cold ethanol to 150 𝜇l of PRP, and thromboxane release was determined by i. a. of the supernatant.

PGE₂. Interindividual variability was 21.4 ± 1.6% for 2,3-dinor-TXB₂, 31.2 ± 4.6% for 2,3-dinor-6-keto-PGF₁α and 24.7 ± 3.6% for PGE₂. Differences between the basal values of all three prostanoids on the 3 study days showed no statistical significance. No sequential effects were observed between the study days.

After the infusion of HD aspirin, urinary 2,3-dinor-TXB₂ excretion was diminished by 45.7% and 83.2% in the first and second hour after the start of the infusion, respectively (P < 0.01; Fig. 5a). Urinary 2,3-dinor-6-keto-PGF₁α excretion was similarly reduced by 51.6% and 79.2% in the first and second hour, respectively (P < 0.01) and the PGE₂ excretion rate was decreased by 13.4% in the first hour (not significant) and by 63.5% in the second hour (P < 0.01). No significant difference was found for the effect of aspirin on either of the prostanoids.

After the infusion of LD aspirin, urinary excretion of 2,3-dinor-TXB₂ was decreased by 19.3% in the first hour (not significant) and by 67.4% in the

Urinary prostanoid excretion

Basal urinary prostanoid excretion rates were 165.9 ± 18.8 pg/mg of creatinine for 2,3-dinor-TXB₂, 111.6 ± 23.1 pg/mg of creatinine for 2,3-dinor-6-keto-PGF₁α and 215.4 ± 42.5 pg/mg of creatinine for
second hour ($P<0.01$; Fig. 5b). These values were not significantly different from those after the infusion of HD aspirin. In contrast, urinary excretion of 2,3-dinor-6-keto-PGF$_{1\alpha}$ was only slightly, although significantly, reduced by 37.1% in the first hour ($P<0.01$), and remained at this level during the second hour (30.6% inhibition; $P<0.03$). The urinary excretion rate of PGE$_2$ was not affected by LD aspirin infusion: it was $+11.5\%$ in the first hour and $+17.0\%$ in the second hour after the infusion was started (not significant). After the infusion of placebo, no significant variation of the urinary excretion of either of the prostanooids occurred.

The ratio of urinary 2,3-dinor-6-keto-PGF$_{1\alpha}$/2,3-dinor-TXB$_2$ levels was largely unaffected by placebo and HD aspirin (from 1.0 to 1.1 and 1.2, respectively), whereas LD aspirin induced a marked increase in the ratio from 1.0 to 2.1 in the second hour.

**Serum salicylate levels**

No participant of the study had ingested any salicylate-derived drugs before the study, as no salicylate was detectable in the first urine sample of each study day and platelet aggregation was above 50% at the beginning of each study day. Fifteen minutes after the end of HD aspirin infusion, serum salicylate levels in peripheral venous blood were $22.3 \pm 1.2$ mg/l, whereas after LD aspirin and after placebo, no salicylate was detectable in serum, the detection limit of the assay being 2 mg/l.

**DISCUSSION**

This study represents the first successful attempt to induce a rapid inhibition of platelet aggregation and TXA$_2$ formation by an intravenous low dose of aspirin while maintaining systemic cyclo-oxygenase activity, as documented by unchanged urinary PGE$_2$ excretion.

By adapting the infusion rate to the venous blood flow previously determined by sonographic colour velocity imaging, we could expect to reach biologically active plasma concentrations after LD aspirin only in the relatively small segment of the venous circulation between the basilic and subclavian veins. The dilution in the blood stream thus mimicked the effect of the liver as a 'metabolic filter' after the oral ingestion of aspirin. The validity of this concept was proved by the determination of serum salicylate concentration, which was less than the detection limit of the assay (2 mg/l) after the 50 mg dose as well as after placebo, and was more than tenfold higher after the 500 mg dose.

Platelet aggregation and platelet TXA$_2$ release were cumulatively inhibited after both dosages of aspirin. Thirty minutes after the start of the infusion no significant difference in the inhibitory effect of 50 or 500 mg of aspirin on platelet aggregation was present. The inhibitory effect of LD aspirin on platelet TXA$_2$ synthesis also cumulated during the infusion time, reaching a maximum inhibition of 93.8% after 60 min, at which time point there was no significant difference between LD and HD aspirin. After both dosages, the inhibitory effect was maintained for 24 h, although after LD aspirin a slight tendency to increase was observed; however, inhibition of platelet thromboxane formation was still 85% 24 h after a single intravenous dose of 50 mg of aspirin. This effect was comparable in extent with the 67% inhibition observed after repeated oral low dose aspirin [6, 12], but compared with the oral administration of low dose aspirin which takes days to become equally effective [23], this was indeed a very rapid effect.

The effects on platelet activity were mirrored by a similar inhibition of urinary 2,3-dinor-TXB$_2$ excretion with both dosages. But whereas after the 500 mg dose the excretion of all three prostanoïds was suppressed to the same extent, the 50 mg dose had only a <40% inhibitory effect on 2,3-dinor-6-keto-PGF$_{1\alpha}$ excretion; PGE$_2$ excretion was not affected at all. Urinary PGE$_2$ excretion was chosen as an index for systemic cyclo-oxygenase activity because, in contrast to 6-keto-PGF$_{1\alpha}$ and other prostanoïd metabolites, it has been shown to be derived exclusively from the kidney [33, 36], which facilitated the unequivocal interpretation of our results. The fact that it was not suppressed by intravenous LD aspirin may allow one to draw the conclusion that cyclo-oxygenase activity remains intact in other organs too, and points to a decreased likelihood of renal and other side effects which have been ascribed to inhibition of systemic prostaglandin synthesis [18, 19, 42].

Although evidence has accumulated in the last years from clinical studies that low dose aspirin decreases the rates of vascular re-occlusion and of cardiovascular mortality [1, 2, 5], the effect of low dose aspirin treatment on vascular prostacyclin synthesis still appears uncertain, as some authors have found no decrease in prostacyclin formation [7, 9], while others have found a short-lived inhibition [25, 36, 37, 43] by low dose aspirin. However, recently the following pieces of evidence have been presented on the mechanism that probably underlies the interaction of aspirin with endothelial prostacyclin formation. (1) Clarke et al. [12] reported that basal prostacyclin biosynthesis fell slightly after 75 mg of controlled-release aspirin daily for 3 weeks, but the capacity of the endothelium to increase prostacyclin formation after intravenous stimulation with bradykinin was preserved. (2) Recently, Chiarando et al. [36] demonstrated that vascular prostacyclin formation is partly inhibited even with 30 mg of aspirin daily. Thus a certain decrease in prostacyclin levels seems to occur with any aspirin dose. This may be due to a unidirectional transfer of platelet-derived prostaglandin endoperoxides from activated platelets to the endothelium, which had earlier been shown to occur *in vitro* [44, 45] and is
thought to be the cause of increased prostacyclin levels in atherosclerotic patients in vivo [46]. Consistent with this concept, Reilly and Fitzgerald [47] showed that low dose aspirin induces a decline in prostacyclin formation which is abolished by addition of a thromboxane synthase inhibitor, probably by shifting of accumulated endoperoxides from platelets to endothelial cells after blockade of their metabolism to TXA2. (3) In the present study we show that prostacyclin formation is decreased after intravenous LD aspirin, although systemic cyclooxygenase activity, estimated as urinary PGE2 excretion, remained intact. Thus, the decrease in prostacyclin levels seems to be in part an unavoidable consequence of inhibition of platelet cyclooxygenase by aspirin at any dose and route of administration. Consequently, more important than leaving the absolute prostacyclin levels unimpaired may be increasing the ratio of prostacyclin to thromboxane levels, thus relatively favouring the vasorelaxant and antiaggregatory properties of the former.

In this study, the ratio was unaffected after the infusion of HD aspirin, pointing to its similar effect on both prostanoids which was comparable with the values after the infusion of placebo. In contrast, after LD aspirin the ratio increased in the second hour after the infusion, indicating that the slight inhibitory effect on 2,3-dinor-6-keto-PGF1α excretion was greatly outweighed by the marked inhibition of 2,3-dinor-TXB2 excretion. This is in accordance with the increased prostacyclin/TXA2 ratios after repeated oral low dose aspirin determined in several studies [12, 36, 48–50] and the unchanged ratios seen after higher aspirin doses [51]. Moreover, Wilson et al. [31] have shown a cumulative effect of prolonged aspirin infusion on thromboxane formation, which also points to similar kinetic effects after intravenous or oral low dose aspirin administration.

In conclusion, a single intravenous administration of low dose aspirin exerts its inhibitory action with the same relative biological selectivity for platelet thromboxane formation as repeated oral dosages, as long as systemic biologically active aspirin levels are avoided. Although, as we could demonstrate, systemic cyclo-oxygenase activity is not affected by this treatment, it seems impossible to effectively block TXA2 synthesis while at the same time fully maintaining prostacyclin production. This is probably due to the inhibition of endoperoxide release from the platelets, thus depriving the endothelium of one of its sources for prostacyclin synthesis. However, the ratio of prostacyclin to thromboxane is increased after low dose but not after high dose aspirin, suggesting a higher antithrombotic potential for the low dose. The intravenous administration of low dose aspirin may offer a possibility to rapidly achieve the aim of maximally inhibiting platelet activity when this is necessary, and an improved starting point for prolonged oral aspirin treatment.

Recently, immediate postoperative (oral) aspirin has been shown to increase vein graft patency early and late after coronary bypass surgery [4], and a beneficial effect of 250 mg of aspirin, given as an intravenous bolus to patients with acute myocardial infarction with 6 h after the onset of pain, on the incidence of ventricular tachycardia has been demonstrated by Gressin et al. [52]. The benefit of intravenous low dose aspirin treatment will have to be subject to further clinical evaluation.

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