Pharmacologic Inhibition of Thromboxane Synthetase and Platelet Aggregation: Modulatory Role of Cyclooxygenase Products

By Vittorio Bertelé, Anna Falanga, Marian Tomasiak, Chiara Chiabrando, Chiara Cerletti, and Giovanni de Gaetano

Dazoxiben, an imidazole-derived selective inhibitor of thromboxane A₂ (TXA₂) synthetase, prevented TxB₂ synthesis in vitro in platelet-rich plasma from 16 normal subjects. Inhibition of TxB₂ synthesis was accompanied by increased generation of PGE₂, PGF₂α, and PGD₂, as shown by radioimmunoassay, thin-layer radiochromatography, and high-resolution gas chromatography-mass spectrometry. Even at dazoxiben concentrations (40–80 μM) above those inhibiting TxB₂ synthetase, platelet aggregation induced by threshold concentrations of arachidonic acid was inhibited in only 4 of 16 subjects, referred to as responders. The remaining 12 individuals were defined as nonresponders. The aggregating effect of arachidonic acid and of the prostaglandin-endoperoxide analog U-46619 was potentiated by PGE₂ and prevented by PGD₂ at concentrations within the range of those detected in dazoxiben-treated platelet-rich plasma. The antiaggregating effect of dazoxiben was counteracted by PGE₂ (in responders) and was potentiated by PGD₂ (in nonresponders). Platelets from responders and nonresponders did not differ in the amount of immunoreactive PGE₂ material or in their sensitivity to U-46619 or PGD₂. It is concluded that inhibition of thromboxane synthetase does not per se prevent platelet aggregation. The functional result of thromboxane suppression appears to be modulated by an interplay of the prostaglandin-endoperoxides, PGE₂ and PGD₂, which are formed in excess.

Arachidonic Acid (AA) induces human platelet aggregation. This requires oxidation of the precursor fatty acid to intermediate products, prostaglandin (PG) endoperoxides, which in turn are transformed into stable PGs: PGE₂, PGF₂α, and thromboxane A₂ (TXA₂). It is believed by some authors that the latter metabolite is responsible for platelet aggregation initiated by AA. Drugs inhibiting TXA₂ generation should therefore prevent platelet aggregation induced by AA. This is indeed the case for aspirin and other nonsteroidal antiinflammatory drugs that act on cyclooxygenase.

More recently, compounds with selective activity on TXA₂-synthetase have become available. These are theoretically more advantageous than aspirin-like drugs, as when administered in vivo, they should only prevent TXA₂ formation in platelets without affecting PG generation in other cells (for instance, the antiaggregating PG₁ in vascular endothelium). TX synthetase inhibition has therefore been proposed as an antithrombotic strategy. However, with dazoxiben, a selective Tx synthetase inhibitor, platelets from 2 of 3 healthy subjects were normally aggregated by AA despite complete inhibition of TX synthesis. Similar observations have been reported with dazoxiben and other TXA₂ synthetase inhibitors. Whether TXA₂ formation is essential for platelet aggregation by AA has therefore been questioned.

We have now extended our investigation to a larger number of individuals and confirm that, in the majority of cases, inhibition of TXA₂ generation is not, in fact, accompanied by prevention of platelet aggregation. We therefore investigated the possible mechanism by which platelet aggregation induced by AA may occur in the absence of TXA₂ generation. In particular, we examined the possible role of PG endoperoxides, PGE₂ and PGD₂, which are all produced in excess as a consequence of the pharmacologic blockade of TXA₂ synthetase.

An attempt was also made to assess whether platelets that do not aggregate in response to AA when TX synthesis has been inhibited differ in some way from platelets that react normally to AA in the absence of TXA₂ production.

MATERIALS AND METHODS

Chemicals

Aggregating agents employed were AA (sodium salt, >99% pure; Sigma, St Louis, MO), adenosine-5'-diphosphate (ADP, sodium salt, Sigma), U-46619 [[(15-S)-hydroxy-11,9-epoxy]methano]prosta (5Z, 13E)-dieneoic acid] (Upjohn Co., Kalamazoo, MI), and thrombin (Topostase, Roche, Milan, Italy). Stock solutions and dilutions of these agents were prepared as described. PGD₂, PGE₂, and EIP (9,11-epoxyiminoprostano-5,13-dieneoic acid), all from Upjohn, were dissolved in ethyl alcohol, stored at −20°C, and diluted in 0.15 M Tris buffer, pH 7.4, just before use.

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THROMBOXANE AND PLATELET AGGREGATION

SQ-22536, 9-(tetrahydro-2-furyl) adenine (Squibb, Princeton, NJ), was dissolved in ethyl alcohol and diluted in distilled water.

Aspirin (lysine acetylsalicylate, Flectadol Maggioni, Milan, Italy) and theophylline monohydrate (Carlo Erba, Milan, Italy) were freshly dissolved in distilled water. Dazoxiben [UK 37,248-01 (4-[2-[lH-imidazole-1-yl]ethoxy] benzoic acid hydrochloride] was dissolved in 0.15 M Tris buffer, pH 7.4.

Platelet Aggregation Studies

Platelet-rich plasma (PRP) was prepared as described17 from 16 healthy human volunteers (11 males and 5 females, 27–38 yr old) who had not taken drugs for at least 8 days before donating blood.

Platelet aggregation tests were made in an Elvi 840 aggregometer (Elvi Logos, Italy).17 Inhibitors and proaggregating agents or their vehicles were added to PRP samples 1 min before aggregating compounds. The aggregation tests were followed for 3 min and were evaluated by the criteria7 of the threshold aggregating concentration (TAC) and threshold inhibitory concentration (TIC). TAC was defined as the smallest amount of aggregating agent producing more than 70% of light transmission for AA and U-46619 or inducing two waves of aggregation for ADP. TIC was defined as the smallest amount of inhibitor causing more than 90% inhibition of aggregation induced by TAC of each aggregating agent.

Arachidonic Acid Metabolism

Radioimmunoassays. TxB2 and PGE2 immunoreactive materials were measured in PRP samples stirred for 3 min in the presence of AA (at concentrations indicated in the Results section). Radioimmunoassays employed either highly specific rabbit antibodies against TxB2 (provided by J.B. Smith, Cardeza Foundation, Thomas Jefferson University, Philadelphia, PA)19 or anti-PGE2 rabbit antiserum (provided by C. Patrono, Catholic University, Rome, Italy).20

Thin-layer radiochromatography (TLC). Analysis of AA metabolism by thin-layer chromatography was performed on washed platelets labeled with 14C-sodium arachidonate (Amersham) and stimulated with thrombin as described.21

High-resolution gas chromatography-mass spectrometry. Three different individual PRP samples were incubated at 37°C for 1 min with 40 μM dazoxiben or its solvent before addition of AA and further incubation for 3 min. PGE2, PGD2, and TxB2 were detected simultaneously in PRP samples using high-resolution gas chromatography coupled to mass spectrometry in the selected ion monitoring mode, as described by Chiabrando et al.21 Briefly, this method is based on single-step extraction of PG and TxB2 from acidified PRP samples (pH 3.5) on C18 reversed-phase cartridges (SEP-PAK C18, Waters, Millipore, Segrè, Italy), after addition of deuterated analogs as internal standards. This is followed by derivatization of functional groups and final analysis by high-resolution gas chromatography with selected ion monitoring using SE-54 WCOT persilanized Pyrex glass capillary columns (20 m long; internal diameter 0.35 mm). A LKB 2091-051 gas chromatography-mass spectrometer, equipped with a LKB 2130 computer system and a DANI 3800 gas chromatograph, were used as described.22

Statistical Analysis

Student’s t test was used.

RESULTS

Effects of Dazoxiben on Platelet Function

AA Metabolism

Figure 1 shows the effect of 20 μM dazoxiben on platelet AA metabolism studied by radio-TLC. Concomitantly with complete suppression of the TxB2 peak, three peaks appeared that were absent or very small in control platelets. These peaks comigrated with authentic PGF2α, PGE2, and PGD2; PGE2 was the highest. The peak corresponding to HHT was partially reduced by dazoxiben, whereas those comigrating with 12-HETE and unmetabolized AA were unmodified.

Figure 2 shows that reorientation of platelet AA metabolism toward PGF2α, PGE2, and PGD2 was apparent at concentrations of dazoxiben (0.6–1 μM) that only partially inhibited TxB2 synthesis. Raising the dazoxiben concentrations to 80 μM did not affect PG synthesis, thus confirming the lack of effect of this drug on platelet cyclooxygenase or PG isomerases.

TLC data were supported by high-resolution gas chromatography coupled to mass spectrometry on three individual samples of PRP incubated with and without 40 μM dazoxiben and stimulated with TAC of AA (0.25–0.35 mM); the absolute amounts of TxB2,
Platelet aggregation was overcome by TAC of AA. In PRP from the four subjects designated M. dazoxiben between 20 and 80 nM was completely prevented at concentrations of 0.1-20 μM. TxB2 generation (measured by RIA) was completely prevented by dazoxiben (up to 1 mM). TxB2 and PGE2 immunoreactive material rose to 78.5 ± 15.6 ng/10⁸ platelets. In 8 samples, TxB2 averaged 48.4 ± 13.1 ng/10⁸ platelets, and PGE2 averaged 13.5 ± 3.7 ng/10⁸ platelets (mean ± SEM). Dazoxiben (0.1-20 μM) induced concentration-dependent inhibition of TxB2 generation. The IC50 value was about 0.6 μM, and complete (≥95%) inhibition was obtained with 40 μM dazoxiben. In the latter condition, PGE2 immunoreactive material rose to 78.5 ± 15.6 ng/10⁸ platelets (n = 8).

**Aggregation Induced by AA**

After a 3-min incubation of PRP with TAC of AA (0.2-0.7 mM), both TxB2 and PGE2 immunoreactive material could be detected. In 8 samples, TxB2 averaged 48.4 ± 13.1 ng/10⁸ platelets, and PGE2 averaged 13.5 ± 3.7 ng/10⁸ platelets (mean ± SEM). Dazoxiben (0.1-20 μM) induced concentration-dependent inhibition of TxB2 generation. The IC50 value was about 0.6 μM, and complete (≥95%) inhibition was obtained with 40 μM dazoxiben. In the latter condition, PGE2 immunoreactive material rose to 78.5 ± 15.6 ng/10⁸ platelets (n = 8).

**Table 1. Quantitative Profiling of Prostaglandins and Thromboxane B2 Measured in PRP by High-Resolution Gas Chromatography-Mass Spectrometry**

<table>
<thead>
<tr>
<th></th>
<th>TxB2</th>
<th>PGE2</th>
<th>PGD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>32.7</td>
<td>18.0</td>
<td>ND</td>
</tr>
<tr>
<td>36.9</td>
<td>15.7</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>26.3</td>
<td>17.6</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Dazoxiben (40 μM)</td>
<td>ND</td>
<td>42.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Detection limit</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Values are ng/10⁸ platelets. ND, not detectable.

**Table 2. Effect of Dazoxiben on Platelet Aggregation and TxB2 Generation Induced by AA in PRP From Four Responders**

<table>
<thead>
<tr>
<th>AA</th>
<th>Platelet Aggregation</th>
<th>TxB2 (ng/10⁸ Platelets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>Dazoxiben Control</td>
<td>Dazoxiben Control</td>
</tr>
<tr>
<td>&gt;TAC</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TAC</td>
<td>TIC†</td>
<td>+</td>
</tr>
<tr>
<td>TAC</td>
<td>&lt;TIC</td>
<td>+</td>
</tr>
<tr>
<td>&gt;TAC</td>
<td>TIC</td>
<td>+</td>
</tr>
</tbody>
</table>

AA was used at three concentrations (mM): <TAC (0.25 ± 0.05), TAC (0.47 ± 0.03), >TAC (0.64 ± 0.07). Dazoxiben was used at two μM concentrations: TIC (64.4 ± 16.9), <TIC (47.5 ± 12.5). Platelet aggregation was indicated as positive (+) when light transmission was more than 70% and as negative (−) when it was less than 10%. Mean ± SEM; n = 4.

* Threshold aggregating concentration.
† Threshold inhibitory concentration.

In 12 of 16 individual PRP samples tested, platelet aggregation induced by TAC of AA was not affected by any concentration of dazoxiben (up to 1 mM). TxB2 generation (measured by RIA) was completely prevented in all 12 subjects at concentrations of dazoxiben between 20 and 80 μM; these subjects were considered to be nonresponders to dazoxiben.

In the remaining 4 individual PRP samples, all from male donors, platelet aggregation induced by TAC of AA was inhibited by dazoxiben at concentrations between 40 and 80 μM. In all 4 subjects, TxB2 synthesis was completely prevented at concentrations of dazoxiben between 20 and 80 μM. These 4 subjects were considered to be responders to dazoxiben.

At intervals from 1 day to 6 mo, at least one further blood sample was collected from all 16 volunteers. In PRP from the 12 subjects designated as nonresponders, dazoxiben never inhibited aggregation induced by TAC of AA. In PRP from the four subjects designated as responders, dazoxiben occasionally did not inhibit the aggregation induced by TAC of AA.

As summarized in Table 2, the inhibitory effect of dazoxiben on platelet aggregation was overcome by raising the AA concentrations above the TAC. Under these conditions, dazoxiben still inhibited TxB2 generation by more than 90%. The antiaggregating activity of dazoxiben also disappeared when the TAC of AA was unchanged, but dazoxiben concentrations lower than the TIC were used. In the latter condition, dazoxiben was slightly less effective as an inhibitor of TxB2 synthesis. However, the absolute amount of TxB2 generated in the presence of the lower dazoxiben concentration was less than in control platelets challenged with subthreshold (nonaggregating) concentrations of AA. Thus, lowering the dazoxiben concentration resulted in restoration of aggregation despite the presence of nonaggregating levels of TxA2.

AA-induced platelet aggregation was inhibited in all 16 PRP samples by EIP, a PGH2/TxA2 receptor antagonist, at concentrations between 9 and 30 μM. The TIC of EIP reduced TxB2 generation by 72.6% ± 3.6% (n = 10). AA-induced platelet aggregation in both responder and nonresponder PRP samples was completely prevented by 100 μM aspirin (data not shown).

**Aggregation Induced by U-46619 and ADP**

In all subjects, platelet aggregation induced by either U-46619, a stable endoperoxide analog and TxA2 mimic, or ADP was not modified by dazoxiben at any concentration used. In contrast, EIP prevented aggregation induced by U-46619 and ADP (second wave). All individuals were considered to be nonresponders to dazoxiben as regards the ADP-induced second wave of aggregation.

**Modulatory Role of Cyclooxygenase Products**

**PG Cyclic Endoperoxides**

Because endoperoxides may accumulate when TxA2 synthetase is inhibited by dazoxiben, we investigated whether sensitivity of platelets to the aggregatory activity of the endoperoxide analog U-46619 was dif-
different in responders and nonresponders. The TAC of U-46619 were 450, 480, 750 and 840 nM in 4 responders and 300, 450, 480, and 600 nM in 4 nonresponders ($p > 0.05$).

**PGE$_2$**

As reported in Figs. 1 and 2 and Table 1, Tx synthetase blockade was accompanied by a marked increase of PGE$_2$. This increase, however, did not distinguish between 4 responders and 4 nonresponders, as similar amounts of PGE$_2$-immunoreactive material (74.0 ± 23.3 and 83.1 ± 23.9 ng/10$^8$ platelets) were produced in PRP from the two groups when platelets were challenged with AA in the presence of dazoxiben.

However, addition of 20–100 nM PGE$_2$ to PRP from a responder reversed the inhibitory effect of dazoxiben on AA-induced platelet aggregation (Fig. 3).

Moreover, anti-PGE$_2$ antiserum turned nonresponder PRP into responder. As shown in Fig. 4, the antiserum neutralized about 75% of the PGE$_2$ formed in excess after inhibition of Tx synthesis.

PGE$_2$ (20–100 nM), inactive by itself on platelet aggregation, markedly potentiated the aggregating effect of AA or U-46619 (Fig. 5, left panel). In contrast, PGE$_2$ did not potentiate AA, but did enhance U-46619-induced aggregation of “aspirinated” platelets (thus unable to generate platelet endoperoxides) (Fig. 5, right panel).

**PGD$_2$**

As reported in Figs. 1 and 2 and Table 1, Tx synthetase blockade was accompanied by increased PGD$_2$ generation. Because PGD$_2$ is a potent inhibitor of platelet aggregation, we tested whether platelets from responders were more sensitive to the antiaggregating effect of PGD$_2$ than platelets from nonresponders. This was not the case, as the average TIC of PGD$_2$ was 21.5 ± 2.9 nM in responders and 26.7 ± 7.1 nM in nonresponders ($p > 0.05$). However, PGD$_2$ at nanomolar concentrations turned the PRP from a nonresponder into a responder (Fig. 6).

PGD$_2$ inhibits platelet aggregation by stimulation of adenylate-cyclase and subsequent increase of intracellular cyclic-AMP. Figure 7 (right panel) shows that in fact the inhibitory effect of PGD$_2$ was prevented by SQ-22536, an inhibitor of adenylate-cyclase. This figure (left panel) shows that SQ-22536 counteracted the inhibitory activity of dazoxiben in responder PRP.

On the other hand, phosphodiesterase inhibitors,
Fig. 6. Representative AA-induced platelet aggregation in nonresponder PRP. PGD₂ (22 nM) slightly prevented platelet aggregation in control platelets, but completely suppressed it in dazoxiben (40 μM) pretreated platelets. In these experiments, the concentration of AA was 0.4 mM.

such as theophylline, by preventing c-AMP degradation, potentiate the antiaggregating effect of adenylate-cyclase activators. Figure 8 shows that theophylline, at concentrations that did not affect platelet aggregation, turned a nonresponder PRP to dazoxiben into a responder.

In additional experiments (not shown here), lower concentrations of theophylline did not potentiate dazoxiben, except in the presence of ineffective concentrations of PGD₂.

DISCUSSION

This study shows that selective inhibition of platelet TxA₂ synthesis need not result in prevention of platelet aggregation. Dazoxiben, an imidazole derivative and selective inhibitor of TxA₂ synthetase, completely prevents platelet TxB₂ synthesis in vitro at concentrations between 20 and 80 μM. At these concentrations, however, platelet aggregation induced by AA was only inhibited in 4 of 16 individual PRP samples. Aggregation in the remaining 12 samples was invariably and repeatedly unaffected, even by concentrations of dazoxiben as high as 1 mM. This confirms and extends previous observations by ourselves⁶ and others.⁸⁻²⁵

Based on structure–activity studies with different endoperoxides and TxA₂, Raz et al.⁷ also concluded that conversion of PG endoperoxides to TxA₂ is not an essential biochemical step in the induction of platelet aggregation by endoperoxides and/or AA. In contrast, Fitzpatrick et al.¹² suggested that endoperoxides must be converted to TxA₂ in order to induce platelet aggregation. This conclusion was mainly based on the observation that the synthetic prostaglandin analog, 9,11 azoprosta-5,13-dienoic acid (azo analog I), inhibited both TxA₂ synthetase and platelet aggregation. Further studies, however, have shown that azo-analog I is not only a TxA₂ synthetase inhibitor, but also a PGH₂/TxA₂ receptor antagonist.²⁶ It is conceivable, therefore, that the inhibitory effect of this compound on platelet aggregation was not due to its TxA₂ synthesis inhibiting capacity. Azo analog I thus behaves like another synthetic prostaglandin analog used in the present study, 9,11-epoxyimino prosta-dienoic acid.²⁷ This compound inhibited TxA₂ synthesis less effectively than dazoxiben, but prevented platelet aggregation induced by AA, ADP (second wave), or U-46619 in all 16 subjects.

If TxA₂ is not necessary for platelet aggregation, what is the mechanism by which AA induces platelet aggregation? The most likely explanation is that PG endoperoxides or other cyclooxygenase products may be sufficient to induce aggregation by AA, when TxA₂ synthesis was inhibited.¹³⁻¹⁵,²⁵

The results reported here support this, offering evidence that, besides endoperoxides, both PGE₂ and
PGD₂ may play a modulatory role on platelet aggregation when TxA₂ synthetase is blocked. As in previous studies, both prostaglandins may be synthesized in excess in dazoxiben-treated platelets. The present study shows, by the use of high-resolution gas chromatography-mass spectrometry, that both prostaglandins may be synthesized in dazoxiben-treated platelets. The present study shows, by the use of high-resolution gas chromatography-mass spectrometry, that both prostaglandins are indeed produced in this condition. PGE₂ may potentiate the aggregatory activity of endoperoxides (see Fig. 5), and PGD₂ may potentiate it (see Fig. 6). PGE₂ was previously shown to stimulate ADP-induced platelet aggregation. 28-30

The possible role of endoperoxides in mediating AA-induced aggregation in dazoxiben-treated platelets is supported by the observation that aspirin prevented AA-induced aggregation of platelets whose Tx synthesis had already been completely blocked by dazoxiben, so, presumably, aspirin does not act by preventing TxA₂ synthesis. 14

Results reported in Fig. 5 indicate that the aggregating effect of endoperoxides is strongly potentiated by nanomolar concentrations of PGE₂. These are within the range of PGE₂ detectable in dazoxiben-treated platelets (see Table 1). Thus, the combination of these compounds, both produced in excess when TxA₂ synthetase is blocked, may be responsible for AA-induced platelet aggregation in dazoxiben-treated platelets.

This combined effect could be counteracted, or reduced, by PGD₂. Because this prostaglandin stimulates adenylate cyclase, its antiaggregating activity can be more easily shown in the presence of compounds inhibiting phosphodiesterase, such as theophylline (see Fig. 8). The amount of PGD₂ that inhibits AA-induced platelet aggregation is within the range of concentrations of this PG produced in dazoxiben-treated platelets (see Table 1).

Despite the evidence that PG endoperoxides, PGE₂ and PGD₂, modulate platelet function in the absence of TxA₂, we were unable to explain the responder and nonresponder behavior to dazoxiben. No difference could be found in the sensitivity to this drug of platelets from either group. Platelets from responders and nonresponders appeared equally sensitive to the aggregating effect of U-46619, an endoperoxide analog and TxA₂ mimic. 18 The amount of immunoreactive PGE₂ generated in the presence of dazoxiben was very similar in responder and nonresponder platelets, and they showed the same sensitivity to inhibition of platelet aggregation by PGD₂.

Difficulties in identifying characteristics that clearly distinguish responders and nonresponders were also encountered by Heptinstall et al. 25,31 and are increased by the fact that the former may behave the same way as the latter if slight modifications are made to the experimental conditions, for instance, in the concentration of AA used (see Table 2).

Thus, although on the basis of repeated determinations dazoxiben had a fairly constant effect in PRP challenged with threshold concentrations of AA, the division of the subjects into responders and nonresponders might be arbitrary. It could depend, at least in some subjects, on the experimental conditions used, rather than reflecting a truly repeatable qualitative difference between subjects. Nonetheless, different effects of dazoxiben on platelets under different experimental conditions may be relevant for a better understanding of the role of AA metabolites in the physiopathology of platelet function.

In conclusion, inhibition of TxA₂ synthetase is usually not accompanied by apparent modification of platelet aggregation. In some particular individuals, the complex balance between PG endoperoxides, PGE₂ and PGD₂, and their interactions with specific receptors might result in prevention of platelet aggregation associated with TxA₂ synthesis inhibition. Thus, TxA₂ synthesis is not necessary for platelet aggregation initiated in vitro by AA.

The question as to whether drugs inhibiting TxA₂ synthesis exert an antithrombotic effect will only be answered by in vivo investigations and by carefully conducted clinical trials. 32

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