FLUID of artificial blisters from erythromelalgic skin areas in primary thrombocythaemia contained a high amount of prostaglandin-E-like activity. Dazoxiben did not alleviate the erythromelalgia in patients with primary thrombocythaemia despite complete inhibition of platelet malondialdehyde and thromboxane B₂ synthesis and no inhibition of prostaglandin-E-like material. During a 10-day dazoxiben treatment period, persistent erythromelalgia was associated with a significant shortened mean platelet life span of 3.2 days. During subsequent treatment with low dose acetylsalicylic acid daily complete relief of erythromelalgia was associated with inhibition of platelet prostaglandin endoperoxide production and correction of platelet mean life span to normal, 7.9 days. These observations indicate that prostaglandin E₂, or another prostaglandin endoperoxide metabolite, is involved in the pathogenesis of erythromelalgia. The presented study does not give one single clue as to the origin (platelet, vessel wall or other) of the prostanoïd, but very likely originates from platelets because a very low dose of acetylsalicylic acid (250 to 500 mg every other day), which irreversibly inhibits platelet cyclooxygenase, is highly effective in the prevention of erythromelalgia in thrombocythaemia.

**Key words:** Aspirin, Cyclooxygenase, Dazoxiben, Erythromelalgia, Platelets, Prostaglandins, Thrombocythaemia, Thromboxane

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**Introduction**

Erythromelalgia is characterized by warm, red, congested extremities and painful burning sensations. In what appears to be the antithesis of Raynaud’s disease, warmth intensifies the discomfort and cold provides relief. Acroparesthesias e.g. tingling, pins and needles sensations, and numbness in the toes and fingers usually precede the disabling and burning distress. Erythromelalgia may lead to painful acrocyanosis and peripheral gangrene.¹

In previous studies we demonstrated that erythromelalgia is causally related to thrombocythaemia and results from platelet mediated inflammation and microvascular changes (Fig. 1).¹³ The histopathological vascular changes are confined to arterioles and characterized by aspecific inflammation, fibromuscular intimal proliferation and occlusive thrombi in the absence of pre-existing vascular disease.⁴ Both clinical signs and vascular lesions completely disappear by treatment with the platelet inhibiting drugs acetylsalicylic acid (ASA) and indomethacin, which inhibits platelet aggregation by inactivation of platelet cyclooxygenase activity.

To obtain more information of the pathophysiologic mechanism of erythromelalgia, prostaglandin activity in fluid from artificial blisters from erythromelalgic areas was investigated. Subsequently the authors evaluated the effects of dazoxiben, a selective inhibitor of thromboxane synthetase activity,⁵ on erythromelalgia, platelet kinetics and prostaglandin synthesis in patients with primary thrombocythaemia. Evidence is presented

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**Prostaglandin cyclooxygenase products but not thromboxane A₂ are involved in the pathogenesis of erythromelalgia in thrombocythaemia**

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that platelet prostaglandin E\textsubscript{2} or another prosta-
glandin endoperoxide metabolite is involved in the
pathogenesis of erythromelalgia in primary throm-
bocythaemia.

**Methods**

Clinical and haematological data were obtained
routinely. Thermography was carried out with a
Bofors Mark II (Karls Koga, Sweden) camera, that
registers the skin temperature indirectly. The skin
surface temperature was compared with a reference
source of fixed temperature.

Artificial dermal blisters were produced by a
suction blister device according to Kristella,\textsuperscript{6} which
was connected to the central suction unit of the
hospital. The suction pressure was adjusted to
100 mmHg. The suction cups were cleaned with
70\% alcohol and placed on the skin. Within a few
minutes the pressure was decreased slowly to
\(-200\) mmHg. Blisters of 3 mm developed after 1
to 2 h. Blisters were aspirated using a thin needle
and syringe.

Prostaglandin-like material was extracted from
blister fluid according to the method of Unger \textit{et al.}\textsuperscript{7} After resuspending the direct extracts in saline
(NaCl 0.9\%), PGE\textsubscript{2}-like material was assayed against
authentic PGE\textsubscript{2} (Upjohn Co., Kalamazoo, USA) on
the isolated rat stomach strip, using the oil-bath
technique of Ferreira and de Souza Costa.\textsuperscript{8} Both
standard and test prostaglandins were injected in
10 µl volumes directly into the Krebs’ solution
superfusing the tissue.\textsuperscript{9} All values for PGE-like
material were expressed as ng/ml blister fluid.

Malondialdehyde production by arachidonic
stimulated platelets in platelet-rich plasma was
measured according to Smith \textit{et al.}\textsuperscript{10} Plasma
thromboxane B\textsubscript{2} (TxB\textsubscript{2}) and prostaglandin E\textsubscript{2}
(PGE\textsubscript{2}) were measured in 10 ml peripheral venous
blood samples collected under resting conditions in
polypropylene tubes, containing 20 µl of heparin
(500 µl/thromboliquine, Organon, the Nether-
lands) and 50 µl indomethacin (0.1 mg/ml in 0.1 M
phosphate buffer, pH 8.0). Blood samples were
centrifuged immediately at 1400 \times g for 10 min
and the plasma stored at \(-20^\circ\)C until assay. Two
ml of plasma was applied to a Sep-Pak C\textsubscript{18} cartridge
(Water Ass). The prostaglandin-like compounds were
eluted with 2 ml of absolute ethanol, and
200 µl aliquots dried under a stream of nitrogen at
40°C in a radioimmunoassay tube, then redissolved
in assay buffer. Antibody for TxB\textsubscript{2} and PGE\textsubscript{2} were
obtained from L’Institute Pasteur (Paris, France),
\textsuperscript{3}H-TxB\textsubscript{2} and \textsuperscript{3}H-PGE\textsubscript{2} from New England Nuclear
(Boston, USA) and standards of TxB\textsubscript{2} and PGE\textsubscript{2}
from Sigma. Normal values for TxB\textsubscript{2} and PGE\textsubscript{2}
were obtained from blood samples taken from
controls (aged 22–78 years) on two occasions.

Platelet survival studies were performed with
sodium \textsuperscript{51}Cr-chromate labelled autologous plate-
lets.\textsuperscript{11} The mean survival of platelets was calculated
according to the multiple hit model, as re-
commended by the International Committee for
Standardization in Haematology.\textsuperscript{12}

**Results**

Clinical and haematological data of three patients
with primary thrombocythaemia at the time of
study are summarized in Table 1. Thermographic
documentation of erythromelalgia in the left upper
leg and the sole of the right foot in Case 1 is shown
in Fig. 2. The skin surface temperature exceeded
31°C at places of red painful erythromelalgic hot

![Temperature](image)

**Table 1. Pertinent data at time of study**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Platelets ((\times 10^{10}/l))</th>
<th>[Presenting symptoms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>750</td>
<td>Disabling burning pain and red swelling of right forefoot sole and burning painful red spots in the skin of the left upper leg as shown in Fig. 2</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>M</td>
<td>1715</td>
<td>Burning pain and redness in toes and forefoot sole</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>M</td>
<td>930</td>
<td>Burning pain in red-bluish big toe, forefoot sole and lateral edge of the right foot</td>
</tr>
</tbody>
</table>

![Fig. 2](image)
Prostaglandin cyclooxygenase products in thrombocythaemia

Table 2. Prostaglandin E-like (PGE) activity in fluid of artificial blisters from skin areas with and without erythromelalgia in Patient 1 with primary thrombocythaemia as shown in Fig. 1.

<table>
<thead>
<tr>
<th>Volume of blister fluid (ml)</th>
<th>PGE (ng/ml)</th>
<th>Erythromelalgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.19</td>
<td>5.40</td>
<td>Present</td>
</tr>
<tr>
<td>1.29</td>
<td>6.53</td>
<td>Present</td>
</tr>
<tr>
<td>1.02</td>
<td>0.80</td>
<td>Absent</td>
</tr>
<tr>
<td>1.35</td>
<td>0.99</td>
<td>Absent*</td>
</tr>
</tbody>
</table>

*Erythromelalgic skin area during treatment with acetylsalicylic acid for 2 weeks.

spots, which completely disappeared by curative treatment with aspirin.

Prostaglandin measurements in fluid of artificial blisters from erythromelalgic areas in the left upper leg in Patient 1 with primary thrombocythaemia are shown in Table 2. PGE-like activities in blister fluid from skin areas with active erythromelalgia measured on two different occasions are evidently higher as compared with the value in blister fluid from skin areas without erythromelalgia. PGE-like activity in blister fluid from erythromelalgic areas during treatment with ASA declined to the level of the symptom-free skin area (Table 2).

The effects of platelet inhibiting drugs on erythromelalgia in typical cases of primary thrombocythaemia are shown in Fig. 3. Relief of erythromelalgic pain from one oral dose of ASA (500 mg) lasted 3 to 4 days, but from one oral dose of indomethacin (75 mg) less than 24 h. The analgesic effect of these drugs is in accordance with the length of inhibition of platelet malondialdehyde (MDA) production by arachidonic acid stimulated platelets in platelet-rich plasma (Fig. 3). Continued indomethacin (25 mg 3 times a day) relieved the erythromelalgia and inhibited MDA, and both reappeared within 24 h after discontinuation of the drug (Fig. 3).

Dipyridamole, 400 mg, sulphinpyrazon 800 mg, sodium salicylate 1500 mg (Fig. 3) and ticlopidine, 1000 mg (data not shown) for 4 days did not alleviate the erythromelalgic symptoms, but also had no effect on platelet MDA production (Fig. 3).

Treatment of Patient 2, who suffered from primary thrombocythaemia and erythromelalgia, with dazoxiben (200 mg orally every 6 h for 5 days) resulted in incomplete inhibition of platelet MDA synthesis of 90% at 2 h and of 75% at 4 h after each ingested dose of the drug (Table 3).

Treatment of Patient 3, who suffered from primary thrombocythaemia and erythromelalgia, with dazoxiben (400 mg every 6 h for 10 days) resulted in nearly complete inhibition of MDA synthesis and complete inhibition of TxB2 formation, but no inhibition of PGE2 synthesis in exposed platelets (Table 4).

Dazoxiben treatment (400 mg 4 times a day for 10 days) did not relieve erythromelalgia and was associated with a significant shortened mean platelet survival of 3.7 days, indicating platelet consumption. Subsequent treatment with one low dose of ASA 500 mg daily, resulted in prompt and complete relief of erythromelalgia, correction of platelet mean survival to normal (7.9 days) and a change of platelet disappearance curves from curvilinear to a linear pattern.

Discussion

Erythromelalgia in thrombocythaemia is a platelet mediated syndrome of arteriolar inflammation and thrombosis of usually acral areas (Fig. 1).
which inhibit platelet cyclooxygenase activity, 15-18 melalgia. 13'14 The drugs ASA and indomethacin, evidently increased during active erythro-supravascular activation. Platelet consumption and may occur in the skin of the leg simulating superficial thrombophlebitis. 2 Platelet consumption is evidently increased during active erythromelalgia. 13'14 The drugs ASA and indomethacin, which inhibit platelet cyclooxygenase activity, 15-18 induce complete relief of the erythromelalgic symptoms and recovery of the ischaemic circulation disturbances. The diagnostic long-lasting effect of a single low dose of ASA on erythromelalgia can readily be explained by its irreversible inhibition of platelet cyclooxygenase activity. One single dose of indomethacin improves erythromelalgia for less than 24 h, which corresponded with its reversible inhibition of platelet cyclooxygenase activity. In contrast, sodium salicylate and the platelet inhibiting drugs sulphinpyrazone, dipyridamole, ticlopidine and dazoxiben neither inhibit platelet cyclooxygenase activity. 19'20 nor alleviate erythromelalgia. 2 Curative treatment of erythromelalgia with ASA (500 mg per day) resulted in a significant increase of shortened platelet survival to normal. 13'14 In contrast, dazoxiben neither affected erythromelalgia nor corrected the shortened platelet survival. These data are consistent with the concept that prostaglandin cyclooxygenase products but not thromboxane A2 are necessary for the development of erythromelalgia.

Evidence of intravascular activation, secretion and aggregation of hypersensitive platelets in thrombocythaemia, taking place at high shear rate conditions in the end-arterial microvasculature, stems from the histopathological demonstration of fibromuscular intimal proliferation and thrombotic occlusions of arterioles and small arteries in skin areas of active erythromelalgia (Fig. 1). 1,4 The release of platelet derived growth factor during secretion and aggregation of platelets is supposed to account for the fibromuscular intimal proliferation. The release and activation of vaso-active substances, e.g. prostaglandins, during platelet mediated processes in thrombocythaemia may be responsible for the inflammatory symptoms of erythromelalgia. 1,2 This assumption is supported by the finding of increased PGE-like activity in blister fluid from erythromelalgic areas (Table 2). The presented study does not give one single clue as to the origin (platelet, vessel wall or other) of the prostanooid, but very likely originates from platelets, because a very low dose of ASA (250 to 500 mg every other day) is highly effective in the prevention of erythromelalgia—a most disabling condition. It is thought that cyclooxygenase activity in the platelets lacking nuclei is irreversibly inhibited by ASA, whereas the production of prostacyclin, which has an antiaggregation effect, is much less affected in the endothelial cells containing nuclei for protein synthesis of cyclooxygenase. 21,22 Evidence exists that prostaglandin endoperoxides are important mediators of inflammation. 23,24 Therefore, the presented clinical and experimental observations indicate that not thromboxane A2, but its direct precursors, the prostaglandin endoperoxides or another prostanooid, prostaglandin E2 in particular, are responsible for the pain and inflammation associated with erythromelalgia in primary thrombocythaemia.

### Table 4: The effect of dazoxiben (400 mg every 6 h for 10 days) on platelet malondiadehyde (MDA) synthesis, plasma thromboxane B2 (TxB2) and prostaglandin E2 (PGE2) levels in Patient 3 who suffered from primary thrombocythaemia and erythromelalgia

<table>
<thead>
<tr>
<th>Day</th>
<th>MDA (nmol per 10^8 platelets)</th>
<th>TxB2 (pg/ml)</th>
<th>PGE2 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C*</td>
<td>2 h**</td>
<td>4 h</td>
</tr>
<tr>
<td>1</td>
<td>20.1</td>
<td>2.0</td>
<td>3.06</td>
</tr>
<tr>
<td>3</td>
<td>1.7</td>
<td>1.9</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>0.2</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**Pretreatment value.

**Time lapse in hours after intake of dazoxiben.

References

Prostaglandin cyclooxygenase products in thrombocythaemia


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