INFLUENCE OF A THROMBOXANE SYNTHESIS INHIBITOR ON THE MUSCLE TISSUE MICROCIRCULATION OF PATIENTS WITH INTERMITTENT CLAUDICATION

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THE main objective of our study was to evaluate the influence of dazoxiben (UK 37248), a thromboxane-synthetase-inhibitor, on oxygen supply in ischaemic muscle tissue of patients with chronic occlusive arterial disease (intermittent claudication). Additionally the flow properties of blood and some thrombocyte function parameters have been determined.

Before going into the details I would like to make some brief comments on the present state of the pathophysiology of chronic occlusive arterial diseases and on the method used to quantify a drug-induced increase in tissue microcirculation and tissue supply.

Changes have taken place during the past few years in the pathophysiology of chronic arterial diseases. Apart from stenoses or occlusions in the macrocirculation, the microcirculation has gained increasing interest. The microcirculation including arterioles, capillaries and venules seems to represent a weak point in the nutrition of tissue in chronic arterial disease. (Ehrly & Schroeder, 1979; Ehrly, 1980).

Different mechanisms have been described or suggested as being of importance in the pathophysiological processes that lead to arterial occlusive diseases.

Impaired flow properties of blood

It has been reported that the whole blood viscosity in patients with chronic vascular diseases can be increased. Moreover, red cell aggregation is mostly increased causing high blood viscosity values at low flow conditions (structural viscosity). In addition, red cell deformability as measured by an *in vitro* filtration test has been found to be decreased (Ehrly & Schroeder, 1976; Reid *et al.*, 1976). The increased aggregation tendency of red cells as well as the decreased deformability in patients with vascular diseases will influence the microvascular flow mostly in the poststenotic or postocclusive regions where low pressure gradients and low shear forces exist (Ehrly, 1981).

Impaired flow regulation and flow distribution in the microcirculation

Simultaneous measurements of muscle tissue oxygen

tension and quantitative blood flow measurements using venous occlusion plethysmography of the recumbent patient, showed almost normal blood flow values, whereas the tissue oxygen pressure values were only about 50% of normal values in healthy volunteers. This led us to the hypothesis of microcirculatory blood maldistribution (Ehrly, 1980; Ehrly & Schroeder, 1976). It seems obvious that an improvement in the flow properties of blood may also induce a more homogeneous flow distribution in the microcirculation.

Thrombocyte aggregation and microthrombi

Little is known about the influence of platelets, platelet aggregation or microthrombi in patients with intermittent claudication. However, in many ischaemic conditions these processes could be prime causes in the reduction of blood flow. These factors may also have some significance in the pathophysiology of intermittent claudication.

Since it is generally accepted that apart from stenoses or occlusions in the larger arteries, microcirculatory factors are responsible for the ischaemic symptomatology of patients with vascular diseases, drugs have been made that improve blood flow at the microvascular level. Thus, for example, rheologically active drugs like dextran, arvin or pentoxifylline have led to improved flow properties of blood, as measured *ex vivo*. The question is, however, how can these therapeutic effects be quantified *in vivo*. Fortunately we are now able to measure not only the quantity of blood flowing through the lower limbs but also the quality of blood flow. With this method we can measure an increased tissue supply whatever the mechanism of the drug may be (Ehrly *et al.*, 1979, 1980, 1981).

Influence of dazoxiben (UK 37248) on tissue pO₂ values

Dazoxiben 100 mg was given intravenously in patients with intermittent claudication, then orally 200 mg daily for 3 weeks. In an open study, after a placebo run-in period, patients who had fulfilled the criteria of inclusion were treated. Muscle tissue pO₂

(Ehrly *et al.*, 1975) was measured before, and 15, 30, 60 and 120 min after injection as well as weekly during oral treatment. Many further laboratory tests have also been performed. Plasma samples were obtained in order to measure the concentration of the drug. As the study is not yet finished, only about four patients and two others who have not completed the oral part of the treatment will be discussed.

In two patients there is a moderate increase in muscle tissue pO_2 with a maximum 30 min after the *in vivo* injection of the drug. In two others, muscle pO_2 values remain unchanged. The values obtained after oral treatment do not show a clear tendency to increase. In two further patients the experiments are not yet finished. Haemorheological values, prothrombin and thrombin remain unchanged. From the laboratory tests a moderate decrease in glucose concentration was found in four patients during the oral part of the treatment. No side-effects were seen whether in the intravenous or in the long-term treatment.

These results in only a few patients do not allow us to draw conclusions. However, in some patients the microcirculation seems to be improved by dazoxiben as measured using the tissue pO_2 method. Based on our new perspectives on the pathophysiology of vascular diseases, new drugs must be investigated with new and sophisticated methods to result in a better treatment of patients with chronic arterial diseases.

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