TREATMENT OF SEVERE SECONDARY RAYNAUD'S DISEASE

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ABSTRACT

The use of the drug Ancrod, a purified fraction obtained from snake venom, is discussed as a treatment in patients suffering from severe secondary Raynaud's disease. Results of a study using six patients are discussed.

THE DISEASE

Secondary Raynaud's syndrome or phenomenon is characterized by an ischemia of the skin of fingers or toes, caused by morphological disorders in the very small arteries. The common pathophysiological basis of all types of the secondary Raynaud's syndrome is the impaired microcirculation. Theoretically, the therapy of the different types of the secondary Raynaud's syndrome should be causal and should counteract the pathogentic factors of atherosclerosis, thromboangiitis obliterans, collagen disease, hard-arm vibration, and so on. Since in most of the types of secondary Raynaud's syndrome a causal therapy is unknown, we must try to improve the basic pathophysiological mechanism, namely, the impaired microcirculation.[1]

TREATMENT

Besides some common and unspecific methods such as exercise, application of heat, and psychological treatment, three paths could be useful in improving the impaired blood flow in the microcirculation:

- treatment of the vasospastic component of secondary Raynaud's phenomenon
- reconstruction (desobliteration) of occluded arteries, and
- improvement of the flow properties of blood.

1. Clinical experience shows that blood flow in secondary Raynaud's phenomenon can be improved by a reduction of the sympathetic vasomotor tone. This indicates that a functional component is present in many cases of the so-called secondary Raynaud's syndrome. Vasodilation can be achieved by heat application, sympathectomy, nitroglyceride, α-blocking agents, reserpine, and others. In some patients with secondary Raynaud's disease, sympathectomy is followed by an increase in the peripheral blood flow; usually the procedure must be repeated after 1 or 2 years. Reserpine is often said to be helpful. It can be given orally in a dosage of 0.5 to 1.5 mg/day,[2] intramuscularly,[3] and intraarterially (0.5 mg[4-6]). Tolazolin (Priscol) is said to have a temporary effect similar to reserpine. No exciting results have been reported concerning therapy with α-blocking agents[3] and steriods like methylandrostenediol.[7] The so-called vasoactive drugs seem to be ineffective.[8]

2. In some cases of secondary Raynaud's syndrome in which stenosis or occlusions of the larger arteries were angiographically detected, an increase in the blood flow of the peripheral circulation can be seen after surgical therapy (desobliteration, by-pass).

3. There is no doubt that the results of the treatment of patients with severe secondary Raynaud's phenomenon are unsatisfactory.[2,3,6,9] In most cases, the syndrome cannot be influenced by drugs or procedures discussed above. Now, I would like to discuss a new treatment, based on a new concept in the therapy of vascular diseases.[10-13] It is well known that peripheral blood flow is not only dependent on the blood pressure or the diameter of the vessels, but blood flow in the microcirculation depends mainly on the flow properties of blood, that is, blood viscosity, plasma viscosity, erythrocyte aggregation, and red cell deformability.[3]

In 1965 Pringle et al. found an increased viscosity of blood in patients suffering from Raynaud's disease.[14] Some years ago we suggested a local increase in blood viscosity in the arteries distally of occlusions or stenosis due to a shear-dependent increase in erythrocyte aggregation.[12-13] An increased blood viscosity as well as a normal blood viscosity can be reduced by specific drugs.[10,12,13] One of these drugs is Ancrod (Arwin®, a purified fraction of the venom of the Malayan pit viper, *Agkistrodon rhodostoma)*, which is able to decrease the fibrinogen concentration of blood. Since the fibrinogen concentration is a very important factor determining the flow properties of blood, a decrease in the concentration of fibrinogen leads to a decrease in blood viscosity and plasma viscosity and especially to a drastic reduction in eryth-

rocyte aggregation.[10,15] Indeed, Ancrod treatment of patients suffering from chronical occlusive disease (stage III and IV, according to Fontaine) was introduced in 1971[11] and was found to be very successful (see surveys, references 16, 17). There can be a statistically significant reduction of pain while at rest as well as a reduction in consumption of analgetic drugs.[18]

Encouraged by these results, we started Ancrod treatment of patients with secondary Raynaud's syndrome in 1973.[19] Since then, six patients with severe secondary Raynaud's phenomenon have been treated with this drug. In all cases, the diagnosis was proved by angiography; in three cases, sclerodermia was present and proved by biopsy of the skin. All patients had severe pain and cyanosis of the fingers; in three patients, necrosis of the finger tips was present. Former treatment, including sympathectomy, reserpine, etc., were unsatisfactory. Ancrod was injected subcutaneously (1 unit/kg body weight per day) as described elsewhere.[16,19-21] In this way, the desired low fibrinogen level can be maintained for some weeks. When patients with severe secondary Raynaud's syndrome were treated with Ancrod, ischemic pains disappeared within 2 to 6 days. Blood and plasma viscosity as well as erythrocyte aggregation were decreased simultaneously. The peripheral circulation was improved; skin temperature and skin color were normalized. The treatment was maintained over a 2 to 4 week period. Within this time, there was a marked improvement in the healing of ischemic ulcers. Surprisingly, the beneficial effect continued even after the treatment had ended. The time interval between the successful therapy and the reoccurrence of the ischemic symptoms was usually a few months to 1 or 2 years. In one case, after a 1½-year pain-free interval, a second Ancrod treatment was successfully used.

The mode of action of Ancrod *during* the treatment can be explained by the improved flow properties of blood as described above. However, the permanence of the beneficial effects *after* the end of the treatment must be explained otherwise. We suggest that during the treatment and during an increased perfusion in the ischemic tissue, the fibrinolytic activity of the plasma can act and dissolve microclots in the low flow areas of the microvasculature.[16,17,22] The number of patients with secondary Raynaud's syndrome treated with Ancrod is too small to draw final conclusions; however, the clinical effect appears striking. Since disappearance of pains is a subjective parameter, the more objective parameters are needed to prove the validity of this new treatment. On the other hand, in patients with chronic occlusive arterial disease with severe intermittent claudication, the benefit of the Ancrod treatment now could be proved by a new, objective method.[23]

SUMMARY

Treatment of secondary Raynaud's disease must involve the treatment of the impaired microcirculation in the ischemic tissue. It can be performed in three ways: by treating the vasospastic component; by reconstruction of occlusions or stenosis in the greater arteries; or by improvement of the flow properties of blood.

Whereas the first two types of treatment often give unsatisfactory results, a new rheological therapy using Ancrod seems to be successful. This drug, a purified fraction of snake venom, lowers the fibrinogen concentration in blood and thereby improves the flow properties of blood and plasma. In six patients suffering from severe secondary Raynaud's disease, Ancrod was injected subcutaneously for a 2 to 4 week period. Some days after starting the treatment, the ischemic pains were reduced and finally disappeared. The beneficial effect continued even after ending the treatment. The mode of action of this new drug has been discussed.

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QUESTIONS, ANSWERS, AND COMMENTARY

Question (F. Dukes-Dobos, NIOSH): You have stated that you have tried Ancrod exclusively; perhaps you have tried other drugs as well. I wonder, if you have, and if so, with what results? It is known that aspirin as well as Persantin may have the same effect on preventing aggregation of blood. Have you tried these drugs? Have you found any effect?

Answer: We have not tried these drugs since we have no reason to try them. Aspirin, as well as Persantin, has solely an influence on the aggregation of platelets. These substances do not lower the viscosity of blood. We have proved this. So we have no reason to try it with our new method.

Question (M. Hoza, Dresser Industries): In lowering the viscosity of the blood is there not a possibility of increased hemorrhaging and possibly lack of coagulation?

Answer: That's a very good question, and if you decrease fibrinogen to zero, you have nonclottable blood. Now this, of course, is dangerous. With our dose schedule, we decrease the fibrinogen concentration down to 70 mg/100 ml of blood. At this concentration, we have a normal coagulation time and normal coagulation tests. And we have found no bleedings. But if you inject Ancrod intravenously, as we did in the beginning of these studies, then you may decrease the fibrinogen concentration to zero. But since we introduced subcutaneous administration of Ancrod, we see no bleedings.

Question (W. Taylor, University of Dundee): I wonder if I could ask whether it has an application in another field—namely, the coronary thrombosis problem?

Answer: In severe cases of acute coronary thrombosis or myocardial infarctions, there will often be some form of shock. And we know that in shock, we have a very labile coagulation. If you administer Ancrod, it will be counterproductive.

In the coronary thrombosis or myocardial infarction situation, I think one can administer another agent to improve the lack of microcirculation—an agent that also lowers the fibrinogen concentration, namely, streptokinase. We proposed this some years ago; unfortunately, in the United States, this therapy is not used. But in our country we do it, and some long-time studies have shown that by this treatment the mortality can be reduced some 20% to 30%.

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