

SHORT REPORTS

Healing of Ischaemic Ulcers by Intravenous prostaglandin E₁ in a Woman with Thrombngitis Obliterans

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In 1973 Carlson reported that prostaglandin E₁ (PGE₁) administered intra-arterially to subjects with severe ischaemia of the lower limbs had a pain relieving and ulcer healing effect (1). A preliminary report on the same beneficial effects on ischaemic symptoms of the lower limbs by PGE₁ intravenously was published in 1976 (2). Studies on the effect of PGE₁ when administered intra-arterially or intravenously have since been extended and the healing effect on ischaemic ulcers by both routes have been confirmed, although hitherto completed studies are uncontrolled. Here we report a healing effect of PGE₁ on chronic ischaemic distal ulcers in a woman with symptoms of thrombngitis obliterans present for more than 20 years.

CASE REPORT

A 47-year-old unmarried female clerk (born 1930). Normal menstruations. Her father had rheumatoid arthritis—otherwise no chronic illness known in the family. She was a rather heavy smoker through the years 1947-49 and 1969-76 (about 20 cigarettes/day). During most of the 'sixties she smoked only occasionally. At the age of 23, infiltrates and nodules were found on dorsa of left foot and on lower left leg. Recurrent infiltrates and nodules during the next years. At age 26, symptoms of Raynaud's phenomenon appeared on the hands and claudication on walking. She also got slowly healing paronychiae on the left foot. Arteriography failed to show any pathological changes but oscillometry demonstrated low amplitudes over the calves. The patient was treated with vasodilating drugs and was encouraged to stop smoking. During the 'sixties she was in rather good condition so far as her ischaemic problems were concerned. However, she occa-

sionally had fissures between the toes and eczematous lesions on the feet and hands. She was also found to have contracted an allergic contact dermatitis and that she had been sensitized to formalin and certain rubber chemicals.

After taking up smoking in the early 'seventies, her feet became acrocyanotic and cold sensitive. Ulcerating nodules of the dorsa of the left foot occurred in 1974. Oscillometrical and plethysmographical signs of obliterating lesions could now be found in the arteries in both lower legs. Pathological plethysmography also on left hand. The ulcer on the foot caused intense pain and healed only slowly during the course of one year. She was given topical treatment by dermatologists and for some months prednisolone was also given orally.

In February 1976 the patient got ulcers on the first and second toe of the left foot after a minor trauma. The ulcers increased gradually and became extremely tender and painful. Continuous pain both day and night. Had to hang the left leg outside the bed during night. Admitted to hospital in July 1976. Arteriography showed advanced arterial obstructions and occlusions from below the knee of the left leg and also of the right leg. Treated with infusions including penicillin because of septic infections and with the thrombolytic drug Brinastrase® (Astra Läkemedel AB, Sweden) containing the proteolytic enzyme Brinase from *Aspergillus oryzae*. The treatment had no effect on either resting pains or ulcers. The situation seemed desperate, with incipient gangrene of the toes. Amputation of the lower leg was seriously considered by a consulting orthopedist. Considering the reported promising results achieved with prostaglandin E₁, it was decided to give this treatment a trial. At the start of the treatment, the patient had on the first and second toe dark-coloured infected ulcers with β -hemolysing streptococci group A and some Klebsiella (Fig. 1). X-ray revealed signs of osteitis in both digit I and II of the phalanges.

Treatment with prostaglandin E₁ (PGE₁) was given in a dosage of 1 ng/kg/min for 72 hours at each treatment. In all, five treatments were given, at approximately one month intervals. PGE₁ was administered as an infusion diluted in 1000 ml saline over 24 hours. Stored frozen PGE₁ was thawed and diluted every day. It was disposed in four 250 ml vials, which were stored in a refrigerator. Thus PGE₁ was never in room temperature more than 6 hours.

THERAPEUTIC RESULTS

The *subjective* effect of the remedy made it appearance as early as during the first 24-hour infusion. The main subjective effect was an almost immediate pain relief. Even the first night the patient no longer needed to keep the leg outside the bed, as had been necessary every night for several months

prior to treatment. The tenderness also disappeared and the patient could support herself on the foot without pain during the second day of infusion.

The *objective* effects were evident also during the first 24-hour treatment. The oedema subsided. Drying of the ulcers was noted during the first days of treatment. Healing started with pink dry granulations and the ulcers were continuously epithelialized (Fig. 2). Non-vital parts of the distal phalanx of the left big toe were slowly delimited and finally demarcated spontaneously 8 months after the first treatment. The ulcers healed completely. The pain was gone and has not recurred. The patient is still free of pain and ulcers in March 1978 (Fig. 3).

DISCUSSION

Thrombngitis obliterans in women is very rare, the ratio women/men being about 1.5:100 (4). The diagnosis in this case seems well established. Early onset with recurrent infiltrates and nodules on the feet and lower leg, after several years of claudication with oscillometrical, plethysmographical and finally radiological signs of advanced arterial obstructions, Raynaud's phenomenon of the hands and also pathological plethysmography on the left hand. The symptoms have also been correlated to smoking.

Before the treatment with PGE₁ was started the patient had had ulcers on the toes for 9 months. Conventional dermatological treatment as well as treatment with a thrombolytic drug given intravenously had no effect on the pain, nor did it heal the ulcers. The effect of the PGE₁-treatment was dramatic. The mechanism behind the beneficial action of PGE₁, however is, so far unknown. PGE₁ is a potent vasodilator (3). Intravenous PGE₁ in such dosages as given influence the microcirculation to the feet in subjects with peripheral artery disease more than does saline alone (5). However, both increases and decreases in skin temperature can be seen after PGE₁. A fall in temperature indicates a

steal phenomenon induced by PGE₁ whereby blood is drained from area where the temperature decrease occurred. The effect on blood flow, however, is very transitory and disappears soon after administration of PGE₁ is withdrawn.

PGE₁ inhibits platelet aggregation. This effect might be of importance in improving the microcirculation in the tissue around the ulcer edges.

There is also one report on a stimulating effect of PGE₁ on epidermal growth, which effect might play a role.

So far, only one controlled study has been performed with PGE₁ in subjects with peripheral artery disease (5). This showed that PGE₁ affected the microcirculation to a greater extent than did saline.

It has been questioned whether the beneficial effect of PGE₁ infusions could be attributed to the vehicle saline, as this has been suggested as a treatment in peripheral vascular disease (6). In this case infusions of antibiotic and thrombolytic drugs had preceded the PGE₁ infusions without any healing effects. Consequently this mechanism seems improbable in explaining the beneficial effect of PGE₁ infusion.

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Fig. 1. Ulcers before treatment with prostaglandin E_1 .

Fig. 2. Healing after 4 months. The patient was given intravenous infusions of prostaglandin E_1 in the dose of 1 ng/kg/h for 72 hours with one month intervals. Picture after 3 treatments.

Fig. 3. Complete healing of ulcers. Picture taken one year after the 5th and last treatment.