Effect from Prophylactic Administration of Pentoxyphylline (Trental) on the Development of Neuropathic Pain Syndrome and on the Associated Microcirculatory Disturbances

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Prophylactic injection of pentoxyphylline into rats with a neuropathic pain syndrome produced by sciatic nerve transection delayed and weakened the development of this syndrome, improved the microcirculation and venular permeability, and reduced mast cell degranulation. The findings of this study recommend pentoxyphylline for clinical use in the multidrug treatment of neuropathic pain syndromes.

Key Words: *pentoxyphylline; neuropathic pain syndrome; microcirculatory disturbances*

Our previous studies on rats showed that the development of a neuropathic pain syndrome (NPS) caused by sciatic nerve transection is accompanied by generalized disturbances in the microcirculatory system [5,9], and that clinical manifestations of the syndrome correlate with the severity of such disturbances [4]. Observations in patients with trigeminal neuralgia [6] or root pains [1] indicate that the microcirculatory system is implicated in the pathogenesis of pain syndromes.

The NPS produced in rats through sciatic nerve division was found to develop more rapidly and to be more severe in rats if the local circulation and microcirculation in the operated limb were impaired by ligation of the femoral artery [10]. Clinical observations show that limiting a local blood flow may elicit ischemic pains. Disturbances of local circulation and microcirculation may therefore trigger the development of pain syndromes in addition to playing a role in their pathogenesis.

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In this study, we sought to establish whether prophylactic administration of pentoxyphylline to rats might delay and weaken the development of an NPS as well as mitigate the associated microcirculatory disturbances, given the known ability of this drug to improve the microcirculation by dilating peripheral vessels and improving the rheological properties of the blood.

MATERIALS AND METHODS

A total of 50 male Wistar rats weighing 140-160 g were used. An NPS was produced by transecting the left sciatic nerve as described [9], and its severity was evaluated by the degree of autotomic damage to the denervated limb as expressed in scores, assigning score 1 to removal of the distal half of one or more claws; 2 to removal of the proximal half or one or more claws (up to the phalanx); 4 to removal of the distal phalanx in each digit; 6 to removal of the proximal phalanx in each digit; 2 to removal of skin from the foot; 4 to removal of muscle from the foot; and score 6 to removal of bone.

The terminal blood flow was examined by biomicroscopy in the mesentery of rats under

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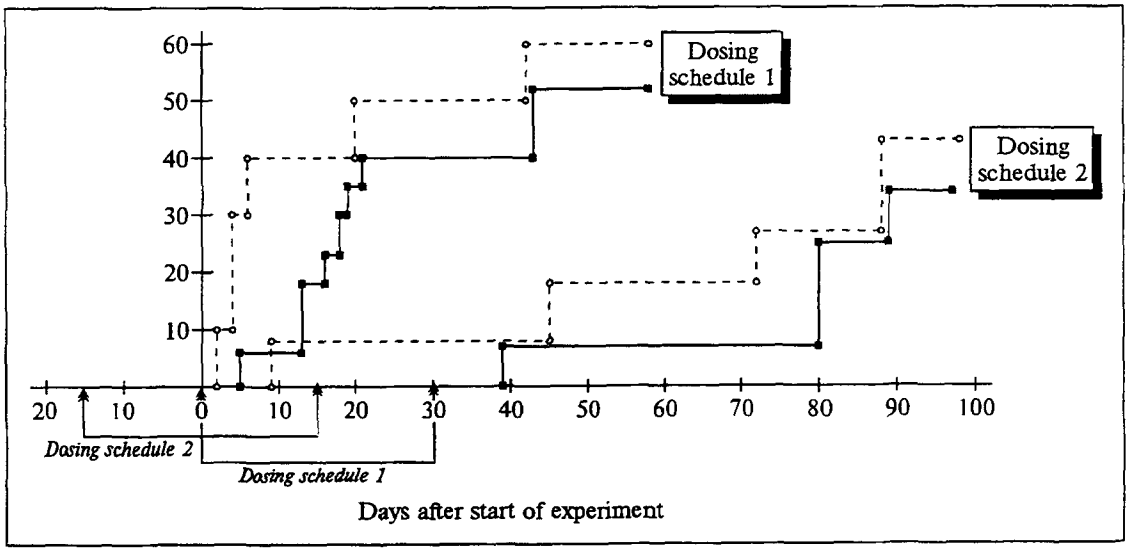

Fig. 1. Effect of pentoxyphylline on the development of a neuropathic pain syndrome. Ordinate: percentage of rats with autotomies relative to the total number of rats in the group. Solid line: rats given pentoxyphylline; dashed line: rats given saline. The beginning and termination of dosing are shown by arrows.

Nembutal anesthesia (5 mg/100 g). Venular permeability and the morphofunctional state of mast cells in the mesentery were assessed as previously described [3].

Pentoxyphylline (Trental; Servo, Yugoslavia) was injected intramuscularly at 10 mg/kg in a volume of 0.1 ml once daily using two schedules. In schedule 1, the drug was administered for a total of 40 days starting with day 1 after sciatic nerve transection (n=19), while in schedule 2 it was administered for 14 days before and 14 days after the operation (n=12).

The two comparison groups consisted of rats with transected sciatic nerve that received daily intramuscular injections of physiological saline (0.1 ml) according to schedule 1 (n=9) or 2 (n=10).

The rats were monitored over a period of 2.5 months postsurgery.

RESULTS

Pentoxyphylline treatment using schedule 1 delayed the onset of the NPS and reduced its severity. In this group, the syndrome had developed only in 6% of the rats by day 5 after surgery, in 18% by day 13, and in 41% by days 21 and 40 *versus* 30, 40, 50, and 60% of the rats, respectively, in the comparison group (Fig. 1).

In the group treated with pentoxyphylline using this schedule, NPS severity, expressed in scores as described above, was 1.1 on postoperative day 20 and remained at this level over the next 20 days, whereas the respective comparison group showed a score of 1.5 on postoperative day 20 with a subsequent rise to 1.75 by day 40.

The use of schedule 2 was more effective in delaying the onset of the NPS and reducing its severity. Thus, only 8% of the rats were found to have developed the syndrome by postoperative days 40, 60, and 70 *versus* 9, 18, and 27%, respectively, in the comparison group (Fig. 1). NPS severity on days 40, 60, and 70 had an average score of 1 in the treatment group *versus* 2, 2, and 1.5, respectively, in the comparison group.

The microcirculatory system was evaluated in rats selected from both treatment groups, the main criterion for selection being that the degree of autotomies be similar to that in the comparison groups.

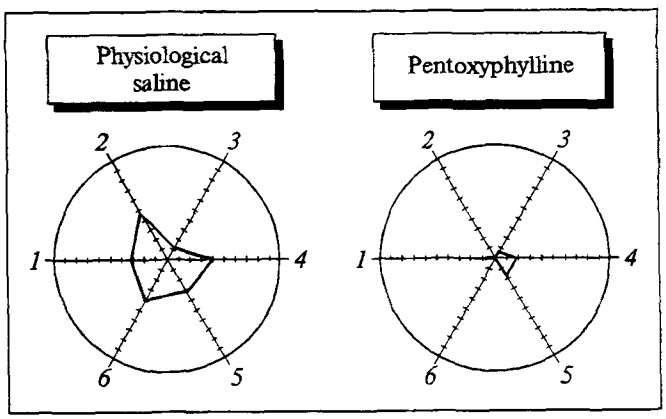

Fig. 2. Effect of pentoxyphylline on signs of disordered microcirculation in rats with a neuropathic pain syndrome. The five radii in these circular diagrams each represent the percentage of rats with one of the following signs (the presence of a given sign in all rats being taken as 100%): *1*) erythrocyte aggregation in capillaries; *2*) erythrocyte aggregation in venules; *3*) vessels with abundant plasma cells; *4*) leukocyte adherence to venular walls; *5*) extent of venular permeability distur-bances; *6*) severity of venular permeability disturbances.

Mesenteric biomicroscopy showed that pentoxyphylline reduced erythrocyte aggregation in capillaries and venules and made the venules less permeable for colloid charcoal particles (Fig. 2), as well as significantly reducing the proportion of degranulated mast cells from 4.2±0.2% to 1.2± ±0.2% ($p<0.001$).

This study on rats thus showed that prophylactic treatment with pentoxyphylline may delay the development of an NPS, lessen its clinical manifestations, and improve the microcirculation.

Such beneficial effects of pentoxyphylline are associated with its ability to inhibit cAMP and cGMP phosphodiesterases in vascular smooth muscle cells, erythrocytes, and platelets, which results in the accumulation of cyclic nucleotides inside the cells and hence in the relaxation of smooth muscle cells, an increased propensity of erythrocytes for deformation, and decreased platelet aggregation. All this leads to diminished blood viscosity and better perfusion of tissues. These mechanisms, along with the inhibition of α-adrenergic receptors and the potentiation of β-adrenergic receptors, underlie the improvements in blood flow, the increase in oxygen tension in tissues, and the normalization of tissue metabolism [2].

The development of an NPS is known to depend on the emergence of generators of pathologically enhanced excitation in various parts of the central nervous system [7] and to be accompanied by generalized microcirculatory disturbances [4,5,9]. However, neuronal hyperactivation may be elicited by the ischemization process itself [8]. The mechanisms of pentoxyphylline action described above suggest that the normalization of the microcirculation, oxygen tension in tissues, and tissue metabolism brought about by this drug reduces neuronal hyperexcitability and lessens the clinical manifestations of the NPS.

The results of this study indicate that prophylactic treatment with pentoxyphylline delays and weakens the development of an NPS by correcting microcirculatory disturbances which may play an important role in the pathogenesis of pain syndromes. Pentoxyphylline (Trental) may therefore be recommended for use as part of a multidrug therapy administered to patients with pain syndromes of neurogenic origin.

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