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THE PATHOPHYSIOLOGY OF LYMPHEDEMA AND THE ACTION OF BENZO-PYRONES IN REDUCING IT

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ABSTRACT

The pathogenesis of lymphedema is briefly reviewed. Swelling secondary to lymphostasis shares the common deleterious effects of other edemas, especially those of chronic high protein edema, namely chronic inflammation with excess tissue fibrosis. Benzo-pyrones are the only known drugs which reduce the excess protein in the tissues with high protein edema including lymphedema. Once excess tissue protein is resorbed, edema subsides and the fibrosis slowly resolves by remodeling. Two of these benzo-pyrone drugs have been shown to reduce postmastectomy and primary lymphedema in randomized, double-blind, cross-over, placebo-controlled trials. One of these drugs (which is also inexpensive) has also been shown to reduce filaritic lymphedema and elephantiasis in a similar trial in India. The bigger the leg initially, the more rapid is the reduction. In this extreme condition about a 20% lessening of the excess volume occurs each year. The benzo-pyrones do not work rapidly, but they do convert a rapidly worsening condition into a slowly improving one. In addition, they have extremely low toxicity and are effective orally. They also seem to reduce the incidence of secondary acute inflammation.

Edema occurs when the lymphatic load of filtered fluid and protein from plasma exceeds the lymphatic transport capacity. In the setting of edema, tissue protein is as important as fluid since a surplus of macromolecules holds excess fluid in the tissues. The lymphatics are an important protective mechanism; however, tissue protein is removed by proteolysis as well as by lymphatic drainage (1). The various mechanisms promoting edema have been recently reviewed (1,2).

All edemas have deleterious effects (1). The swelling, pain and loss of function are often a great burden. Edema alters the structure of the interstitium and interferes both with cellular metabolism and with wound healing. Oxygen transport is also reduced as edema interrupts cell-to-cell contact. Tissue channels increase in size and number, but high-protein edemas stimulate fibrin deposition and tissue fibrosis.

The pathogenesis and effects of lymphedema

High-protein edemas have >1g/dl plasma protein in the tissues. If the edema lasts several weeks, this promotes chronic inflammation with its associated aftermaths (1,3): excess fibroblasts and collagen deposition in the tissue, altera-

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tion in tissue function, increased numbers of small blood vessels and lymphatics including damage to the vessel walls, a limited lymphocytosis, and increased numbers of tissue macrophages (probably a defense mechanism limiting accumulation of excess protein). The tissue changes found in chronic lymphedema are similar, and accordingly probably arise from excess protein deposited chronically in the tissue matrix. Chronic lymphedema also induces striking alterations in the collecting lymphatics--reflux of lymph, lipodermatosclerosis, Stewart-Treves angiosarcoma, autoimmune disease, secondary acute inflammation (sometimes incorrectly termed "erysipelas") (4), and in the extreme "elephantiasis" (1,2,5,6).

Acute lymphedema is transformed into chronic lymphedema over a latent period of variable length. This transformation probably derives from depletion of proteolytic macrophages and constriction of scar around collateral lymphatics perhaps traceable to excess protein passing through the lymphatic wall (1).

Treatment of high-protein edema, especially of a chronic one like lymphedema and elephantiasis includes non-operative or conservative therapy, a variety of operative procedures, drugs, or a combination of these alternatives (4). Because both non-operative and operative therapy has recently been reviewed (7,8), only drug treatment is examined here. Apart from use of antibiotics for associated infections, the benzo-pyrones thus far are the only drugs which seem effective in management of lymphedema and elephantiasis. Thus, diuretic agents are usually ineffective and are primarily indicated when lymphedema threatens life, or for an associated condition.

The rationale of benzo-pyrones

The benzo-pyrones comprise a large group of drugs (1). Most commonly used are 5,6 benzo-[alpha]-pyrone (coumarin) and 0-(β-hydroxy-ethyl)-rutosides, but diosmin and rutin are also available. They are active orally and topically, are remarkably free of side-effects, and are inexpensive (it should be noted that 'coumarin', while related to the anticoagulants has no anticoagulant activity). While even lower doses are also effective, the optimal doses in humans at present are 400mg per day for coumarin and 3g per day for the rutosides, diosmin or rutin. Higher doses may possibly be even more effective (1).

The benzo-pyrones have multiple actions, many of which differ according to the specific compound. However, all benzo-pyrones tested (some 15 widely differing ones) have one consistent effect, namely, they uniformly reduce high-protein edema (as repeatedly shown in more than 50 different experimental models, both acute and chronic). While benzo-pyrones increase pumping of collecting lymphatics, their main action in alleviating edema is via macrophage stimulation (1). Normally, macrophages lyse some of plasma protein filtered into tissues but the benzo-pyrones increase macrophage lytic activity and induce many more of these macrophages to arrive at the local site of tissue swelling. In chronic lymphedema, moreover, the macrophages are dormant or less active, and the benzo-pyrones seem to restore normal activity.

In high-protein edema, the benzo-pyrones promote proteolysis and the fragments are resorbed directly back into the bloodstream. With removal of the excess protein edema subsides. In chronic lymphedema, removal of the protein eliminates the stimulus for excess fibrosis which gradually disappears as tissue collagenases facilitate remodeling. In more than 300 clinical trials of these benzo-pyrones in a variety of high protein edemas (1), and a few lymphedemas, their effectiveness has been repeatedly demonstrated.

The benzo-pyrones in lymphedema

In a randomized, double-blind, cross-over, clinical trial involving 40 patients, it was shown that 0-(β-hydroxy-ethyl)-rutosides reduced the volume of

the swollen limb, increased limb mobility, softness and comfort, and reduced the previously elevated skin temperature (9). All these changes were significant at the 1% to 0.01% level, after six months treatment using 3g of the drug per day. No other ancilliary treatment (e.g., compressing stockinettes) were used. The improvements were found in both patients with postmastectomy and primary lymphedema. During this period the mean excess volume in the arm was reduced from ~40% greater than the normal limb to ~20%. When the drug was combined with physiotherapy, prevention of postmastectomy lymphedema was more effective than with physiotherapy alone (10).

Twelve patients with postmastectomy lymphedema and 8 with lymphedema of the leg (from a variety of causes) were treated with 5,6 benzo-[alpha]-pyrone, using 200mg of drug per day for 6 months, in a randomized, double-blind, cross-over trial (11). (The numbers have since been increased to 20 with arm and 10 with leg lymphedema using 400mg per day with similar findings--Piller et al, unpublished observations) No other treatment was used. The edema of the limbs was reduced from a volume 48% greater to 32% greater than normal. The excess circumferences were reduced from 20% greater to 10%. The extremities were also softer as shown by an increase in surface tonometry (-10% to +5%). Elevated skin temperature was also lowered (+2.0% to -0.8%) suggesting a reduction in proliferation of capillaries. Patients had fewer episodes of secondary acute inflammation (so-called "erysipelas"). Subjectively the patients described greater comfort and freedom of limb movement. Twenty-eight of 30 patients preferred the active drug to the placebo.

An open, but controlled, trial of 5,6 benzo-[alpha]-pyrone (100mg per day) in postmastectomy lymphedema in 21 patients also showed considerable improvement (Clodius, et al, unpublished observations). This daily dose provided greater reduction than the 30mg of this agent with 180mg of troxerutin per day (12). However, the latter mixture dosage did reduce lymphedema in a similar earlier trial with 103 patients.

A double-blind, randomized, matched-pair trial of a 1-to-6 mixture of this benzo-pyrone drug and troxerutin (at 135mg of the former per day for 6 months, followed by 90mg/day for 18 months) in 91 patients with postmastectomy lymphedema (13) showed reduction in swelling at the wrist, forearm and upper arm (significant at the 2%, 1%, and 0.5% levels). Isotopic lymphography after 6 months even showed that fewer patients had blocked lymphatics in the axilla. A number of other workers have also found this drug mixture to be effective in lymphedema but the trials were uncontrolled (1).

The benzo-pyrones in filaritic lymphedema and elephantiasis

Postmastectomy and primary lymphedema usually have much less pathological alteration than filaritic lymphedema and elephantiasis (especially in India). It is remarkable that benzo-pyrones are also effective in alleviating the latter condition. Preliminary unpublished results (Jamal, et al) are now available in a randomized, double-blind, matched-pair trial of 5,6 benzo-[alpha]-pyrone using 400mg per day orally, and no other therapy for this condition, in India. A total of 160 patients have been studied, most for six months but some as long as two years. The excess limb volumes were reduced from ~40% to ~25% above normal over two years *(Fig. 1)*. It is also noteworthy that the rate of limb reduction was greatest when the amount of edema was most prominent; the correlation coefficient (r) between the initial size and the rate of reduction = 0.38. There were also significant (5% levels) reductions in the circumference and improvements in softness. The filaricide, diethyl carbamazine (DEC), did not significantly reduce edema, when given with or apart from the 5,6 benzo-[alpha]-pyrone *(Fig. 1)*.

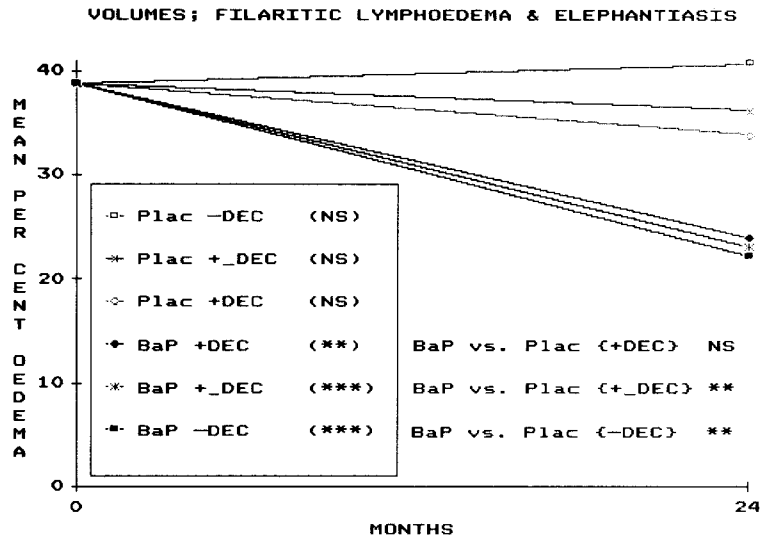

*Fig. 1. Preliminary results of the effect of 5,6, benzo-[α]-pyrone (BaP) on volumes of filaritic lymphedematous and elephantitic limbs. The trial was randomized, double-blind, matched-pair, placebo-controlled, involving 160 patients. The volume of edema is expressed as a percentage greater than the volume of a normal limb. To increase legibility, the initial and final values have been multiplied by scaling factors so that all initial values of each line are identical to the average initial value. Results are complex because diethyl carbamazine (DEC) was also tested, separately and combined with BaP. Because DEC was not shown to have value, its comparisons with a placebo were omitted, but groups with or without DEC have been shown separately. There were 3 placebo groups: the BaP placebo without DEC (Plac -DEC), that with DEC (Plac+DEC), and the two combined (Plac+-DEC). There were 3 similar groups taking BaP. Significances are indicated: 'N.S.' means p>0.05; * means 0.05>p>0.01; ** means 0.01>p>0.001; *** means 0.001>p. Those shown (in round brackets) after the identifiers in the Legend refer to the differences between the slopes of these lines and zero. To the right of the Legend are shown the significances of the differences between the slopes of the various groups taking BaP compared with those taking the placebo. The taking, or not, of DEC is shown {in curved brackets}. Two of the groups show a significant difference (1% level); the +DEC ones do not. This last effect probably signifies that DEC has only a small beneficial effect.*

CONCLUSION

It must be emphasized that the benzo-pyrones are only slowly effective--much more slowly than complex physiotherapy or surgery. However, these latter two methods of treatment are expensive and are not available in sufficient quantity in countries where filaritic lymphedema is most common. The benzo-pyrones are safe and effective orally and some are very inexpensive. They seem to convert a gradually worsening clinical condition into a slowly improving one and substantially diminish the likelihood of secondary acute inflammation.

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