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Conservative Treatment of Acute and Chronic Lymphoedema with Benzo-pyrones

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Summary

Generally, the success of conservative therapy is only limited to a transient reduction in oedema. Concomitant with this, subjective improvements such as a reduced feeling of heaviness, a lessening of pain and of the bursting feeling of the affected limb are frequently reported. Once the oedema is reduced, the reduction must be maintained by elevation, elastic compression bandages, and by careful attention to infection. A failure to observe these points results in a very rapid reformation of the oedema.

Experimental results have shown the benzopyrones to be very useful in reducing high protein oedemas, particularly those of lymph and thermal oedema. They do this by enhancing the lysis and removal of the abnormal accumulated protein from the affected part. They also enhance glucose uptake by the various cells, thus allowing them to survive in a viable state in severe conditions such as those of metabolic acidosis characteristic of stagnant tissue fluids.

Since the benzopyrones remove the excess protein, the tendency for further fibrotic tissue formation is reduced. In addition, like some other anti-inflammatory drugs, the benzopyrones may be able to enhance the removal of existing fibrotic tissue by causing its lysis. The cells involved in this action seem to be the macrophages.

The remarkable reductions of lymph and thermal oedemas obtained in animal experiments with the benzopyrones have not been reported in many clinical trials. There seem to be two main reasons for this. Firstly much lower doses are used than have been shown to be optimal. Secondly, the follow up periods of observations have usually only been short. Some clinical trials even with these lower doses have however been very promising, and this is especially enlightening when it is considered that such doses in animals only result in minimal changes in the oedema volume. This may be the reason for the high proportion of "subjective improvement only" reports in clinical trials.

The Rationale of Conservative Therapy

The conservative therapy of lymphoedema has two main aims. The first is to retard the formation of new oedema fluid. This is generally achieved by an external elastic support, diuretic or antibiotic drugs depending on the situation. The second is to increase the fluid movement from the limb by elevation, massage or muscle pump exercises. These conservative methods are well

reviewed by *Stillwell* (39). Once the oedema fluid is removed, the tissue hydrostatic pressure will be lowered. As the elasticity of the tissues is partially lost in lymphoedema, tissue hydrostatic pressures must be maintained at or near pre-lymphoedema levels by the use of an external elastic support. Continuous support is essential if the cutaneous tissues are to be assisted in regaining their lost elasticity.

When considering conservative therapy the patients attitude is extremely important, they must in fact "learn to live for their limb". There are many factors which may cause rapid reformation of the oedema fluid. Among the worst are constriction of the limb due to tight clothing, generalised heating, excessive use of the limb, local application of heat and unattended puncture wounds. The degree of success in avoiding these certainly depends strongly on the motivation of the patient.

Physiotherapy is very time consuming and usually does not suit the active person (3). In addition the benefits of physiotherapy are only transient and seem to be most effective in the early soft stages of lymphoedema before excessive fibrosis occurs (22). *Asdonk* has however reported good successes from long term physiotherapy treatment of cases of hard late stage lymphoedema (1). However, no matter how effective the therapy, the oedema fluid will very rapidly return if the appropriate care is not taken. *Stillwell* recorded a rapid redevelopment of oedema within one hour after rising from rest, while *Watson* observed 1/4 of the lymph removed by compression bandages in combination with elevation, to return within one hour (39, 41).

A new and recent addition to the armament of those who use conservative therapy is Venalot®. In its injectable form each ml contains 1.5 mg coumarin and 25 mg of sodium rutin sulphate; while in its oral form, the capsules contain 5 mg coumarin and 25 mg rutin and the tablets contain 15 mg coumarin and 90 mg troxerutin. *Clodius* has reported some promising results through the administration of Venalot, although as yet the period of follow up has only been relatively short (7). This drug, its components and related compounds and their application to the relief of lymphoedema is the main topic of this paper.

The major components of Venalot® belong to the group of drugs called the benzopyrones. Their mode of action has been investigated in some detail and is now well known (4). Based on these results and the general lack of success, and transient nature of other conservative methods for the treatment of most cases of lymphoedema, I propose to suggest that further use of these drugs would seem to be indicated.

The Mode of Action of the Benzopyrones in High Protein Oedemas

The benzopyrones act by enhancing proteolytic activity. Upon administration they bind onto proteins – in particular the albumins (11, 24). As an example *O'Reilly* found that one mole of coumarin was bound to one mole of albumin (24). At the site of oedema, the benzopyrones cause some additional endothelial junctions to open thus allowing small additional quantities of protein, fluid and drug into the affected part (5, 26). The junctions remain open for about 30 minutes, and are believed to be the consequence of the release of small quanities of amines which the drugs cause (4, 20).

The primary cells upon which the benzopyrones seem to act are the macrophages (2), although evidence for the involvement of other cells such as fibroblasts (28) and neutrophils (30) is accumulating. In lymphoedema there are certainly accumulations of these cells in the oedematous tissues (18, 23). In addition the benzopyrones are capable of rejuvenating old cells and causing the proliferation of existing ones at certain dose levels (17, 32). Thus in the oedematous limb there is concentrated the drug, the cells upon which it acts and the protein upon which the cells act.

Venalot® – (Schaper & Brümmer, Western Germany)

The drugs major action is to stimulate proteolysis of the accumulated abnormal protein of the extracellular compartment of the oedematous limb. *In vitro* tests of the incubation of macrophages with protein with or without coumarin have shown a 220 % enhancement of protein lysis in the drug treated group (2). An equivalent success with fibroblast cultures was not obtained due to difficulties in maintaining a viable culture (*Casley-Smith,* 1975 personal communication).

In vivo studies have shown an enhancement of radio protein removal in drug treated lymphoedematous limbs (returning to normal levels in some cases), increased protein fragment levels and increased enzyme activity levels (31, 33). One may at first think that the increased fragment levels would give rise to the accumulation of further oedema fluid, but because of their small size, a concentration gradient directed from the tissues and a high diffusion coeficient, their rapid removal from the tissues, thus freeing the osmotically held water is possible.

The importance of this drug induced proteolysis in the resolution of the oedema has been emphasized by the results from a comparison of the benzopyrones and other anti-inflammatory drugs. Not all drugs have the same effect on protease activity levels, and similarly not all drugs are equally effective in reducing the oedema. The calculation of the extent of correlation between these two parameters yielded some extra-ordinary results (28). There was a 86 % correlation between acid protease activity levels of the skin and oedema reducing ability, a 88 % correlation between acid protease activity levels of the oedema fluid and oedema reducing ability and a remarkable 99 % correlation between neutral protease activity levels in the skin and oedema reducing ability. This certainly suggests that drug induced proteolysis is a very important factor in the resolution of high protein oedemas.

Casley-Smith has also reported some interesting evidence which indicates that coumarin (and most likely other benzopyrones) is able to enhance proteolysis to such an extent that in both normal and injured limbs, the need for functioning lymphatics is removed (4). This is confirmed by animal experiments, which have shown coumarin to be very effective in reducing oedema fluid even when all the lymphatics were obstructed (33).

Although proteolysis is by far the most important mode of action of the benzopyrones, they are drugs of many actions, and some of these should also be considered (4). Some benzopyrones are known to protect red blood cells against lactacidotic rigidification, thus preserving their ability to be easily deformed even in metabolic acidosis (38). *Dannon and Elazar* have shown that hydroxyethylrutosides can increase glucose uptake by red blood cells thus protecting them in stagnant areas of the circulation, it also assists in the reformation of the interiorised plasma membranes (8). Most certainly this can also be applied to both the fixed tissue and circulating macrophages. Increased particle injestion by the macrophages has also been shown to enhance glucose transport (2a). Since the benzopyrones enhance the uptake and digestion of protein by these cells, benzopyrone treatment will permit them to remain viable in areas of stagnant fluid (6).

The increased incidence of streptococcal infections, acute erysipelas and chronic lymphangitis in lymphoedematous limbs, would seem to be the result of disruption of the immuno active function of the macrophages (7, 10). The condition is analogous to burn injury where the activity of the reticulo-endothelial system and in particular the macrophages are depressed (21).

Benzopyrone treatment, by removing the stagnant proteinacious fluid, by rejuvenating some of the cells (17), by enhancing macrophage activity and by improving glucose uptake and transport by the cells can only lead to a great reduction in the frequency of these annoying side effects.

The Pathophysiology of the Early and Late Forms of Lymphoedema

Lymphoedema is the result of a disturbed lymph flow, and is often accompanied by venous

blockade of varying severity. The accumulated extravasated lymph, rich in protein, gives rise to increased fibroblastic activity. The fibrination will then close the lymph pathways and give rise to further lymph stasis.

The overloaded and engorged lymphatics can no longer function to absorb the excess fluid (4), thus further oedema fluid accumulation accompanied by further fibrination occurs. If left untreated, the swollen limb slowly becomes fibrotic, eventually forming the hard brawny form of lymphoedema. Lymphatic and vascular function is further impared by the growth of compact collagen bundles and cells in close approximation with these vessels (23).

What can the Benzopyrones do?

In the early soft pitting stage of lymphoedema, benzopyrone administration will enhance protein removal from the area. They do not need functional lymphatics to do this (33). The protein is lysed and leaves the way it originally entered – via the endothelial junctions. Molecules with a molecular weight up to 40,000 can pass through closed endothelial junctions (19, 36), thus the extent of protein lysis by the drugs does not have to be great. Since the accumulation of protein seems to be a prerequisite for the formation of fibrotic tissue, its removal will halt further fibrotic development.

In the late hard, brawny cases of lymphoedema a similar situation applies. This together with the restoration of the weakened immunological protective mechanisms may reduce the incidence of streptococcal infection and erysipelas. What of the existing fibrotic tissue? Its rate of formation or destruction is determined by the balance between collagen deposition and collagen lysis. Any drug which turns the balance in favour of lysis, will theoretically eventually remove the fibrotic tissue.

Houck and Jacob, Houck and Sharma have shown a number of anti-inflammatory drugs are capable of inducing collagenase activity in the fibroblasts of the skin (14, 15, 16). Recently a number of similarities in modes of action have become evident between these drugs and the benzopyrones (4).

Although all of the available evidence indicates that the fibroblasts synthesize collagen, everyone seems to have a different notion as to the cells which cause its resorption. However there is some very substantial evidence which suggests that the macrophages can play a vital role. *Salthouse and Matlaga* have shown maximal collagen lysis at a time when histological examination has shown macrophage proliferation (37). *Parakkac* has also confirmed the collagen lysing ability of the macrophages by electron microscopial examination (25). It is well documented that in the presence of the benzopyrones the macrophages are responsible for enhanced protein lysis. In light of the above evidence it also seems possible that they will do this in their drug activated state. Although the effect of the benzopyrones on collagen absorption has yet to be done, it seems very likely that the macrophages will play a vital role, not only in halting fibrotic development on the lymphoedematous limb, but also in causing the regression of any existing fibrotic tissue.

Clinical Trials

There are unfortunately few. Generally they show some good results, although they are certainly nowhere near as promising as those obtained in analogous animal experiments. *Clodius* using Venalot®, has reported that 52% of his patients claimed less bursting feelings, a reduction in pain and a reduction of the feeling of heaviness in their affected limb (7). A reduction of oedema in addition to these subjective improvements was reported in 36 %. Unfortunately the follow up period was only 18 months. *Fabre and Rudhardt* and *Volkner* have reported similar results (9, 40). *Piller and Clodius* however have reported an increasing percentage of objective and subjective improvements with longer follow up periods of up to 40 months (34).

Why aren't the clinical reports of the benzopyrone therapy as enthusiastic as the laboratory ones? The primary reason seems to be due the use of very much lower doses than have been shown to promote optimum oedema resolution. Of secondary importance is the control of environmental temperatures (27). The length of follow up also seems important (34).

The optimum determined doses of the various benzopyrones may seem high however they are certainly very safe (29). In fact the LD_{50} of the rutosides and coumarin are so high that it would be impossible to accidentally administer it (35, 13). No teratogenic effects have ever been found for any of the benzopyrones even with doses which are near the LD_{50} (12).

There is unfortunately some reluctance to use the benzopyrones, especially those containing coumarin. The reason, as *Casley-Smith* has so nicely put is "the singularly stupid use of coumarin for dicoumarol in some publications and conferences" (4). Coumarin he emphasizes "has no anticoagulant activity".

The possibility of combination of the benzopyrones with other drugs should also be carefully considered. *Houck and Sharma* present evidence which shows prednisolone, indomethicin and oxyphenylbutazone can reduce collagen by inducing collagenase activity (16). Since the benzopyrones would seem to stop further collagen formation by removing the excess accumulated protein, and since the macrophages (the cells on which the benzopyrones act) can also facilitate collagen resorption, simultaneous administration of these drugs should be even more benificial. *Clodius* (1975, personal communication) has in fact recorded some very promising results in the treatment of some lymphoedema patients using a combination of Venalot and oxyphenylbutazone.

No doubt benzopyrone therapy will add additional armament to the somewhat depleted array of measures for the conservative therapy of lymphoedema.

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