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The Use of a Tissue Tonometer as a Diagnostic Aid in Extremity Lymphoedema: A Determination of its Conservative Treatment with Benzo-pyrones

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Summary

With the aid of a tissue tonometer, we have been able to gain an estimate of the rate at which the lymphoedematous tissue loses its compressability and regains it upon treatment with the non-steroidal anti-inflammatory drugs: the benzo-pyrones. The values obtained by tonometry, unlike other objective methods of measurement of the effectiveness of a therapy, approximate closely to the patients subjective claims.

Introduction

Lymphoedema is the result of a disturbed lymph flow. The additional protein and fluid which exceeds the transport capacity of the lymph system accumulates in the tissues. Its high protein content enhances the activity of fibroblastic cells, resulting in subsequent fibrinogenesis and the closure of lymph pathways and further lymph stasis. The valves of the remaining overloaded and engorged lymphatics become incompetent and these vessels no longer function to remove tissue fluid (1). The affected limb becomes larger, harder and gradually pits less upon pressure. If left untreated for a long time the extremity slowly becomes fibrosclerotic and the tissue more resistant to compression (2). The characteristic hard brawny phase of lymphoedema becomes manifest, during which time further impairment of lymphatic and vascular function occurs as a consequence of the rapid growth of collagen bundles in close approximation to these vessels (3).

To date, with the exception of a few cases, reports of the conservative treatment of chronic primary or secondary lymphoedema are based upon measuring limb volume or circumference. This is due primarily to the problem of objectively measuring the limb and because there is a lack of definition as to what degree of swelling represents lymphoedema (6). We do not wish to enter into this argument, but only to present the results of a study of the long term treatment of chronic lymphoedema with the benzo-pyrone preparation, Venalot®, assessed by using a newly designed tissue tonometer (2).

Methods

Thirty-four patients with secondary lymphoedema of the arm were examined. The duration of their lymphoedema varied from a minimum of one year to a maximum of 21 years. Eighteen of the patients (with a mean duration of lymphoedema of 8.8 years) received two tablets of Venalot® (each containing 15 mg coumarin and 90 mg of troxerutin – *Schaper* and *Brümmer*, Western Germany) each morning for times varying from one month to 36 months (average time 16 months). In addition to this, the patients were regularly encouraged to elevate the extremity and to avoid excessive work, constriction of the limb by tight clothing, generalised heating, puncture wounds and anything which increases capillary filtration or leads to infection (5). Since infections so often can lead to a rapid worsening of the lymphoedematous condition and erysipelas, the pa-

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tients were told to meticulously avoid all infections and to report all instances of even minor cuts, scratches etc. (6).

The second group was treated similarly in all respects with the exception that they did not receive Venalot®. The average duration of lymphoedema of this group was 14.1 years. This was not significantly different from the duration of the Venalot® treated groups (t test, 32 d.f., 1.41). The patient's progress was assessed by measuring the tissue tonicity of both the normal and the affected limb. For measuring, the patient supports the extremity in a horizontal position on a table and is told to allow the muscles to relax. The actual process of measuring has been described previously (2). Three successive measurements were made and an average taken. Since the normal arm was measured at the same time as the lymphoedematous one, each patient is her own control. The total units of compressability for the lymphoedematous and normal limbs was then noted. The difference, either positive (lymphoedematous limb less compressable i.e. harder than the normal one) or negative (lymphoedematous limbs more compressable than normal one) was calculated and graphed.

Since each mm of compression of the tissue was represented by the movement of the pointer over one whole division (5 subdividions) a number of inferences could be made about the effect of the duration of lympoedema, the length of therapy etc. on actual tissue compressability.

In these observations one author (*Clodius*) performed all the measurements and recorded all the clinical observations while the other author (*Piller*) calculated all the results and drew all the conclusions, thus this is a double blind study.

Results

Tissue Compressability vs Duration of Lymphoedema Figure 1

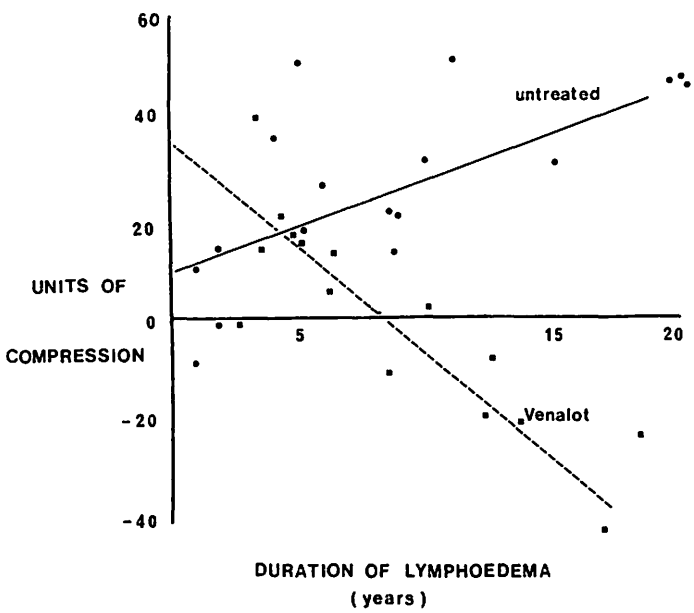

Fig. 1 Tissue compressability vs. duration of lymphoedema.

In the untreated group the slope was positive suggesting that the lymphoedematous tissues became more resistant to compression with time. A least mean squares analysis gave the following information. Slope 1.772, intercept 9.54, correlation coefficient .582 $F(1,14)$ 7.70, $.01 < p < .05$). The first obvious point is that the positive slope is significantly greater than zero. Thus the tissue be-

comes more resistant to compression with time. Knowing that 5 subdivisions (major division) on the tissue tonometer scale represent 1mm of compression by the central column, we can say that on average the tissue becomes harder by 18 mm for every 10 years of lymphoedema using this system of measurement. There is some evidence (to be presented later) which suggests that beyond 15 years this rate of increase falls off and in fact plateaus.

If the Venalot® treated group is examined, ignoring the length of treatment, but taking the duration of lymphoedema into account we find the following. Slope -4.599, intercept 34.16, correlation coefficient $-.75$, $F(1,16)$ 12.89, $.001 < P < .01$. This negative slope differs significantly from zero and it shows that irrespective of the length of Venalot® treatment, as long as it is given, that the lymphoedematous tissues become softer by 45 mm for every 10 years duration of lymphoedema. A comparison of slopes between the untreated and Venalot® treated group showed a very significant difference ($P < .001$).

Tissue Compressability vs Length of Benzopyrones Treatment Figure 2

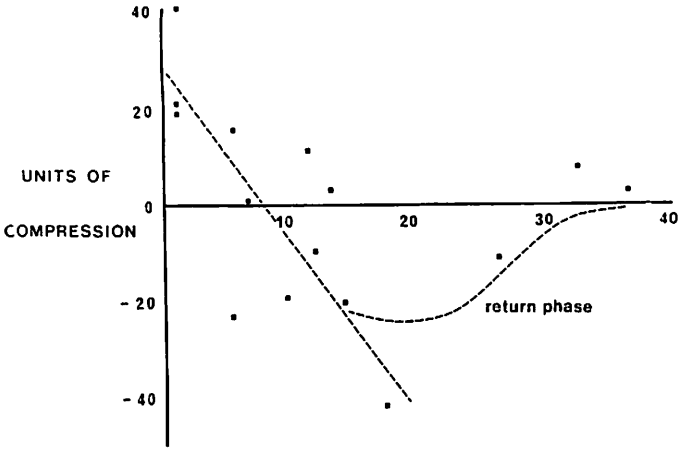

Fig. 2 Tissue compressability vs. length of Venalot® treatment

A least squares analysis gave the following result. Slope -3.28, intercept 28.56, correlation coefficient -.6934, $F(1,9)$ 8.33. Again, this negative slope differs significantly ($01. < P < .05$) from zero indicating reduced resistance to compression with increasing length of Venalot® treatment. The rate is 33 mm every 10 months. Obviously, the tissue does not become less resistant to compression at that rate for the whole length of time that Venalot® is given. In fact it seems that this rate may only apply for the first 6–10 months, thereafter the tissue compressability returns slowly to normal as the data from the patients treated for more than 20 months suggests.

Tissue Compressability vs Circumference Difference Figure 3

A least mean squares analysis of the effect of circumference in untreated limbs gave the following information: slope 1.922, intercept 17.37, correlation coefficient .4084, $F(1,14)$ 2.60, ns. It should be mentioned before we deal with this, that the circumference difference referred to is the difference between the lymphoedematous limb and the normal one measured by tape, in the same place, at the same time. Although the analysis showed that the slope of the untreated group was not signi-

ficantly different from zero, the data is suggestive that the lymphoedematous limb may become more resistant to compression by ~1 mm for every cm increase in circumference above the normal limb.

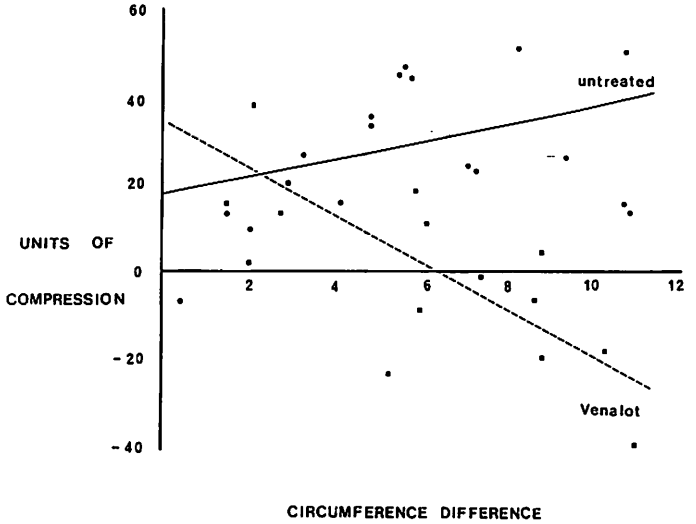

Fig. 3 Tissue compressability vs. circumference difference.

A least squares analysis of the effect of circumference in tissue compressability of the Venalot® treated group gave the following information: Slope -5.32, intercept 33.75, correlation coefficient -.557 and F(1,14) 5.40, $.01 < P < .05$. The slope is significantly different from zero and indicates that the tissue becomes less resistant to compression by ~5 mm for every cm that the lymphoedematous limb above the normal one. A comparison of the slopes of the untreated and Venalot® treated group showed them to be significantly different (F 1,30; 8.704; $.001 < P < .01$).

Discussion

During the course of progressive high protein oedema, the tissues gradually become fibro-sclerotic. This is partly the consequence of the high protein concentration of the stagnant oedema fluid and partly because of repeated attacks of infections to which the unwieldy limb is easily susceptable. During the development of lymphoedema the protein-rich fluid is gradually replaced by the fibro-sclerotic tissue. The elasticity of the tissue is lost and the tissues become more resistant to compression (2, 7). Therefore tissue tonometry is better than difference of circumference measurements.

During this time the growth of compact collagen bundles in close approximation with the lymph and vascular vessels further impairs the functioning of the few remaining overloaded lymph collectors (3). Simultaneously, the progressive connective tissue overgrowth widens the distances between the adjacent capillaries resulting in further accumulation of protein-rich fluid and so the progressive histopathological state of lymphoedema continues (1). It is documented that as lymphoedema progesses the epifascial tissues become brawny or stone-like in appearance, in fact, the evidence of Figure 1 confirms this. Likewise, as lymphoedema develops and tends towards the chronic stage, the arm generally becomes bigger, up to a point. This point is determined by the number of functioning lymphatics and on the interstitial pressure. The interstitial pressure in turn, depends on the elasticity of the skin. The more the skin is elastic, the more the arm can expand. Figure 3 shows that for every cm in circumference that the lymphoedematous limb is above the normal one, the tissues become more resistant to compression by .96 mm.

However, what of benzopyrones treatment? How does this bring about a restoration of the tissue compressability? Firstly, its mode of action must be examined. Venalot® has two components, coumarin and troxerutin, both of which are benzopyrones. It is now well documented that the benzopyrones are very useful in the treatment of high protein oedemas especially those which are of lymph or thermal origin (1, 4, 8, 9). They are both drugs of many actions (1, 10). However their main action is to facilitate the removal of excess protein by causing its lysis (1, 11). Because of their size, high diffusion coefficients and their little molecular seiving, the resulting fragments can rapidly leave the tissues the way the protein originally entered – by the vascular system (1).

Since the benzopyrones remove this excess protein, the tendency for the formation of further fibrotic tissue is reduced (1). The initial removal of the stagnant tissue fluids also allows the various cells of the tissue system to have a better chance of surviving, since the conditions of metabolic acidosis so common in stagnant tissue fluids are removed (9).

What of the existing fibrotic tissue? Like some other anti-inflammatory drugs, the benzopyrones are also capable of facilitating its removal by causing it to be lysed (12). The cells involved in this action, in lymphoedematous cases at least, seem to be the fibroblasts, neutrophils and macrophages. The results presented here confirm this lysing ability. There is also the possibility that by removing the excess protein (which is the stimulus causing the excess collagen deposition) the normal remodelling process of the body can remove the excess collagen. Firstly an examination of the length of Venalot® treatment: at less than eight months treatment, the tissue compressability is less than normal, but thereafter becomes much more compressable. In fact the tissue compressability improves by 16.4 mm for every month's treatment. Of course, the removal of all that fibrotic tissue leaves the remaining tissues in a rather flaccid state especially since their elasticity has been lost. This explains the very low resistance to compression of the patients who received more than 10 months treatment. Upon examination of patients treated for 20 months or more it was found that their compressability differed little from normal. At this stage, we believe, the elasticity of the tissues has been restored to normal levels.

Previous results with benzopyrones in lymphoedema have not been very encouraging, however, this has been due to the rather short treatment times and the low doses used. We have previously shown that at least eight months treatment is necessary before many of the patients show objective improvement and that at least 24 months treatment is necessary before more than 50% show objective improvement (4). The criteria used in these cases was a reduction of 2 cm or more in the circumference compared to the normal arm (4). However, objective improvements are far out-weighed by reports of subjective improvements. We believe these are very important because a person who feels better, has less bursting pains, fewer cramps and a reduced feeling of heaviness can certainly enjoy life more. In this respect in the above report, even at the end of eight months treatment 60% of the patients reported subjective improvements such as those listed above (4).

Certainly then, by using the tissue tonometer, it has confirmed that the lymphoedematous tissues become more resistant to compression with time, more importantly it gives an estimate of the rate of increase. Also it gives an indication of the effectiveness of a therapy and, unlike other objective measures of the state of lymphoedematous limbs, approximates very closely with the patient's subjective claims.

It is noteworthy that the benzopyrones are the only medical therapy for lymphoedema; also these are cheap, safe and can be taken by mouth!

References

1 *Casley-Smith, J.R.:* The actions of the benzopyrones on the blood-tissue-lymph system. Folia Angiologica 1976 (in press)

2 *Clodius, L., L. Deak, N.B. Piller:* A new instrument for the evaluation of tissue tonicity in lymphoedema Lymphology 9 (1976) 1–5

3 *Olszewski, W.:* On the pathomechanism of development of post surgical lymphoedema. Lymphology 9 (1976) 1–5

4 *Piller, N.B., L. Clodius:* The clinical effectiveness of Venalot® on primary and secondary lymphoedema. Europ. J. Clin. Invest. 1976 (submitted for publication)
5 *Stillwell, G.K.:* Treatment of postmastectomy Lymphoedema. Modern Treatment 6 (1969) 396
6 *Clodius, L.:* Secondary arm lymphoedema. In: Lymphoedam ed. L. Clodius, Thieme, Stuttgart 1976 (in press)
7 *Drinker, CK., M.E. Field, J. Homans:* The experimental production of oedema and elephantiasis as a result of lymphatic obstruction. Amer. J. Physiol. 108 (1934) 509
8 *Piller, N.B.:* Drug induced proteolysis: A correlation with oedema reducing ability. Brit. J. Exp. Pathol. 57 (1976) 263
9 *Piller, N.B.:* A conservative means of reducing the intensity and duration of thermally induced oedema. Burns 2 (1976) 143
10 *Piller, N.B.:* An integration of the many modes of action of coumarin: An explanation of its effectiveness as a therapy for thermally injured tissue. Vasa 1976 (submitted for publication).
11 *Piller, N.B., J.R. Casley-Smith:* The effect of coumarin on protein and PVP clearance from rat legs with various high protein oedemas. Brit. J. Exp. Pathol. 56 (1975) 439
12 *Houck, J., V. Sharma:* Induction of collagenolytic and proteolytic activities in rat and human fibroblasts by anti-inflammatory drugs. Science 161 (1968) 1361.

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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