

THE USE OF 5,6 BENZO-[α]-PYRONE (COUMARIN) AND HEATING BY MICROWAVES IN THE TREATMENT OF CHRONIC LYMPHEDEMA OF THE LEGS

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ABSTRACT

Sixty patients with leg lymphedema from a variety of etiologies were divided into randomized two groups, matched by Grade, duration, age, sex, and cause of lymphedema. Using a double-blind format, one group received 5,6 benzo-[α]-pyrone (coumarin 1,2 benzopyrone, 400 mg/day) for six months; the other received a placebo. For the next six months, both groups received a standardized regimen of heat (using microwaves) coupled with compression garments.

Benzopyrone produced approximately 20% reduction in the volume ($p=10^{-4}$) and improvement in circumferences and tonometry ($p=10^{-5}$ and 10^{-7}). Symptoms (feelings of swelling, pain, heaviness and loss of mobility) were also significantly improved ($p=0.03$ to 10^{-7}).

During the second six months, when microwave heat therapy was added to drug therapy, the patients who had previously received the placebo showed significant improvement ($p=0.03$ to 10^{-9}) in signs and symptoms of lymphedema. Some, but not all, of the group that was receiving benzopyrones were also significantly improved by heat therapy ($p=0.8$ to 0.002). Taking benzopyrones for 12 months plus heat treatment for six months was significantly better, for some criteria, than the placebo plus heat therapy ($p=0.7$ to 0.04). On the other hand, heat plus

either placebo or benzopyrone was often significantly better than either the active or inactive drug without heat ($p=0.8$ to 10^{-9}).

Chronic lymphedema is a common form of high protein edema (1). It has been estimated that there are nearly 140 million patients worldwide (including 20 million after treatment for breast cancer). In China, there are approximately 2-3 million patients with lymphedema from filariasis who have not received effective treatment. With so many affected patients, we sought a simple, safe, effective and inexpensive remedy. At the present time, the benzopyrones are the only known oral medication which seemingly removes excess protein from edematous tissues and reduces lymphedema (1-8).

Benzopyrones act to increase the numbers of macrophages at the site of high protein edema and accelerate normal proteolytic activity (1). When the excess protein undergoes proteolysis and amino acids can be resorbed directly into the bloodstream, edema fluid regresses. The tendency towards chronic inflammation and excess fibrosis in the affected limb is also reduced (1). Whereas many animal studies have been performed (1) and some clinical trials (1-3), at the time this patient trial was begun there was no experience about their use in China (although a successful trial in filaritic lymphedema and elephantiasis has since been reported) (6).

For many years our group has used topical heat and compression bandaging to reduce lymphedema (9-11). Although successful, we wished to determine whether benzopyrones would render heat treatment of lymphedema even more effective, and also independently to examine the effect of administration of benzopyrones alone. Hence, we studied the effect of benzopyrones alone (as a randomized, double-blind, placebo-control trial) in matched groups for six months and then added our standard heat and compression treatment while continuing the benzopyrone or a placebo for another six months.

PATIENTS AND METHODS

Only patients with unilateral leg lymphedema were examined so that the contralateral (normal) leg could act as a control. Using the I.S.L. Classification (12), there were 20 Grade 1, 32 Grade 2, and 8 patients with elephantiasis (Grade 3). Thirty seven were women and 23 were men. Five had primary lymphedema; the rest were caused by: infection (mainly tinea) 33, filariasis 13, trauma 4, surgery for carcinoma 3, resection of lipoma 1, and pregnancy 1. The 60 patients were randomized (by Grade, age, sex, and duration and cause) into two matched groups. None of these factors made significant difference in the outcome and accordingly they are not treated separated. Mean age was 34.8 ± 13.6 years (SD) for the benzopyrone group and 38.6 ± 15.8 for the placebo group.

Double-blind procedures were followed for the administration of the drugs and recording of the results. For six months one group received two 200 mg tablets a day of 5,6 benzo- α -pyrone (1,2 benzopyrone, coumarin); the other received a placebo. No compression garments were used at this stage. Compliance was monitored by tablet counting. All tablets were taken.

For the next six months, each group continued with the "active" drug or the placebo but in addition each underwent two

courses of topical leg heating and compression bandaging. The heating was done using a microwave oven as previously described (11), for an hour a day for 40 days.

Although evaluations were done monthly, only the initial and the final results for each period are reported here. Leg volume was measured by water-displacement to the hip. Two measurements were made and the average value recorded. Leg circumferences were measured at six standard points, every 10 cm above the heel. The sum is reported. (Whereas it is slightly more accurate to calculate limb volume from the truncated-cone formula, the correlation between the two is close especially when there is a normal limb for comparison so that just a degree of edema can be compared) (13). Skin tonometry was performed as previously described (7) which uses a simple measuring device (14). The "arbitrary" values increase as the skin and subcutaneous tissue softens.

Each measurement of the lymphedematous leg was expressed as a percentage compared with the nonedematous contralateral leg. This way of expressing the extent of the edema, while taking account of the normal leg, is least prone to error (13). Differences between the start and the end of a measuring period were obtained by subtracting the relevant ratios for each individual. Significance of the differences between the various means of these measurements were estimated using 2-tailed paired t-tests.

Symptoms were recorded as "improved," "the same," or "worse" over each six-month period. (In fact, none were worse in either the benzopyrone or the placebo groups and so this last designation was omitted.) Differences in symptoms were estimated using X²-tests (with Yates correction, if necessary).

RESULTS

Effects of Benzopyrone Alone

Over the first six months, there were

TABLE 1
Values for Volume, Circumference and Tonometry
(Lymphedema/Normal)

| No. = 30 per Group | PLACEBO | | <i>p-value</i> <i>Plac. vs. Benz.</i> | BENZOPYRONE | |
|---|-----------|------|--|-------------|------|
| | Mean (%) | S.E. | | Mean (%) | S.E. |
| VOLUME | | | | | |
| Initial | 120.1 | 3.56 | | 122.6 | 4.00 |
| End Benzo alone | 120.0 | 3.59 | 10^{-4} | 117.9 | 3.71 |
| End Benzo + Heat | 114.5 | 3.18 | 0.013 | 112.8 | 2.80 |
| <i>p-value Benzo vs. (Benzo + Heat)</i> | 10^{-6} | | | 0.77 | |
| <i>p-value (Benzo + Heat) vs. (Plac. + Heat)</i> | | 0.73 | | | |
| CIRCUMFERENCE | | | | | |
| Initial | 107.5 | 0.98 | | 108.7 | 1.47 |
| End Benzo alone | 107.8 | 1.00 | 10^{-7} | 106.8 | 1.36 |
| End Benzo + Heat | 105.0 | 0.92 | 0.14 | 105.3 | 1.16 |
| <i>p-value Benzo vs. (Benzo + Heat)</i> | 10^{-9} | | | 0.47 | |
| <i>p-value (Benzo + Heat) vs. (Plac. + Heat)</i> | | | 0.042 | | |
| TONOMETRY (<i>n.b. increased ratios indicate softening of tissues</i>) | | | | | |
| Initial | 69.8 | 3.95 | | 59.6 | 3.11 |
| End Benzo alone | 73.0 | 3.49 | 10^{-5} | 77.5 | 2.51 |
| End Benzo + Heat | 83.8 | 1.71 | 0.002 | 86.6 | 2.52 |
| <i>p-value Benzo vs. (Benzo + Heat)</i> | 0.028 | | | | |
| <i>p-value (Benzo + Heat) vs. (Plac. + Heat)</i> | | | 0.60 | | |
| The p-values were calculated from the individual differences between the initial and the final values for the various periods. Benzo—benzopyrones; Plac—placebo | | | | | |

highly significant improvements in the volume, circumference, and tonometric findings in the benzopyrone group compared with the placebo (Table 1). The reductions in leg volume were not large (4.7% in an excess of 22.6%, i.e., about 20% of the edema), but the softness of the tissue (tonometry) increased significantly (18% of the original 40% less than normal).

The symptoms (Table 2) also improved

significantly during this period in the benzopyrone group compared with the placebo. Particularly notable were the improvements in the feeling of swelling and of restricted mobility. The feelings of burning pain and/or heaviness also significantly improved.

Effects of Heat Alone

The effect of topical heat can be seen in

TABLE 2
Alterations in Symptoms

| | PLACEBO | | | BENZOPYRONE | | | <i>p-value</i> <i>Plac. vs. Benzo</i> |
|--|---------|-----------|------|-------------|-----------|------|--|
| | No. | Improved | Same | No. | Improved | Same | |
| First Six Months (Placebo or Benzopyrone, no Heat) | | | | | | | |
| Feeling of Swelling | 29 | 5 | 24 | 30 | 25 | 5 | 10^{-7} |
| Burning Pain | 14 | 3 | 11 | 11 | 8 | 3 | 0.03 |
| Feeling of Heaviness | 26 | 10 | 16 | 28 | 24 | 4 | 0.0009 |
| Restricted Mobility | 24 | 4 | 20 | 25 | 23 | 2 | 10^{-6} |
| Second Six Months (Placebo or Benzopyrone, plus Heat) | | | | | | | |
| Feeling of Swelling | 29 | 22 | 7 | 30 | 4 | 26 | 10^{-6} |
| Burning Pain | 14 | 5 | 9 | 11 | 3 | 8 | 1 |
| Feeling of Heaviness | 26 | 14 | 12 | 28 | 3 | 25 | 0.002 |
| Restricted Mobility | 24 | 19 | 5 | 25 | 2 | 23 | 10^{-6} |
| <i>p-values for differences between First Six Months and Second Six Months</i> | | | | | | | |
| Feeling of Swelling | | 10^{-5} | | | 10^{-7} | | |
| Burning Pain | | 0.4 | | | 0.03 | | |
| Feeling of Heaviness | | 0.3 | | | 10^{-8} | | |
| Restricted Mobility | | 10^{-4} | | | 10^{-9} | | |
| Whole Year (Placebo or Benzopyrone, plus Heat for second six months) | | | | | | | |
| Feeling of Swelling | 29 | 27 | 2 | 30 | 29 | 1 | 0.4 |
| Burning Pain | 14 | 8 | 6 | 11 | 11 | 0 | 0.04 |
| Feeling of Heaviness | 26 | 24 | 2 | 28 | 27 | 1 | 0.5 |
| Restricted Mobility | 24 | 23 | 1 | 25 | 25 | 0 | 0.3 |
| No patient became worse during any time period | | | | | | | |

the placebo group, where the improvements were significant. The reduction in leg volume was 5.5% and in excess of 20% (i.e., about 30% of the edema) and the tonometry also improved significantly (10.8% of the original 20% less than normal). The feelings of swelling and of restricted mobility were

significantly improved, but those of pain or heaviness were not.

Effects of Benzopyrone Plus Heat

The volume and the tonometry (but not the circumference) showed significant

improvement after heat therapy in patients who also received benzopyrone ($p=0.013$, 0.002 , 0.14 , respectively). The reduction in volume was 9.8% in 22.6% (i.e., ~45% of the initial edema). Tonometry improved by 27% of the original 40% below normal.

In the benzopyrone group, only the tonometry showed a significant difference ($p=0.002$, in favor of the benzopyrone) between improvement with benzopyrone alone and of benzopyrone plus heat. In the placebo group, such differences were also significant in favor of heat therapy.

Circumference (but not volume nor tonometry) showed a significant ($p=0.04$) difference between benzopyrone plus heat and the placebo plus heat (i.e., only in the final six months). Only one of the symptoms (burning pain) was significantly different at the end of the year between the two groups. The difference was in favor of use of benzopyrone.

DISCUSSION

The data suggest that 5,6 benzo- α -pyrone (1,2 benzo- α -pyrone, coumarin) reduces lymphedema when used alone. This finding independently confirms previous studies with benzopyrones (1-8). As before, improvement is not rapid (here, one-fifth of the edema in six months). On the other hand, no compression garments were worn, the side effects of the drug was minimal and it was relatively cheap and easy to take. Moreover, the tonometric data showed that the leg softened considerably when compared with the placebo so that further improvement was likely if benzopyrones continued to be taken.

These results also confirm our previous studies and those of others (17) showing that topical heat therapy reduces lymphedema (9-11). The reduction by two courses of heat alone was nearly one-third of the edema (in the placebo group).

It is of no little interest that benzopyrones significantly improved both the final volume and the final tonometry values after the

courses of heat therapy. The reduction by the two regimens was nearly half of the initial edema. The effect of benzopyrone has also been shown when patients are treated by complex physical therapy both improving edema reduction and helping to maintain it (15). As shown again by this study, benzopyrones improved the softening of the tissues (1,3,7), a finding that appears to be the end result of decreasing both edema and the amount of excess fibrosis (1). This last effect is particularly helpful for other treatment regimens because easier transport of fluid and protein through the peripheral tissues would permit easier removal by remaining functional lymphatics.

Other workers have confirmed the benefits of heat on lymphedema reduction (17). How thermal therapy works is not known, although several possibilities have been addressed (9-11,16). Clearance of radio-labeled large molecule tracers is enhanced (9,10), but the mechanism is unclear. A diminution of fibrosis after heat therapy seems likely. Because placebo treatment showed a reduction in limb circumference only in the final six months, it suggests that earlier reduction with use of benzopyrones in the first six months precluded further reduction of edema later on with heat treatment. Similarly, the limited alleviation of signs and symptoms in the second six months with benzopyrones (opposed to the notable improvement in the first six months) suggests that after six months of benzopyrone, there were only a few patients remaining who still could be improved with further treatment.

ACKNOWLEDGMENTS

We are grateful to Hamilton Laboratories (G.P.O. Box 7, Adelaide, S.A. 5001, Australia) and to The Lymphoedema Association of Australia for the supplies of 5,6 benzo- α -pyrone (coumarin) and its placebo, and to Dr. J.R. Casley-Smith (University of Adelaide) for assistance in the preparation of this paper for publication.

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