

LETTER TO THE EDITOR

LYMPHEDEMA, THE POOR AND BENZO-PYRONES: PROPOSED AMENDMENTS TO THE CONSENSUS DOCUMENT

The ISL Consensus Document on the Diagnosis and Treatment of Peripheral Lymphedema (1) continues the thrust of a similar document formulated ten years earlier (2). The new Consensus contains many excellent pronouncements with which most would agree. It provides a unified overview of lymphedema and should be invaluable for guidance for diagnosis and treatment. The document should also assist many in their ongoing discussions with governmental officials, social security, health funds, and hospital administrators in the proper care of patients with lymphedema.

Nonetheless, the Consensus has two major shortcomings. These have been discussed at the recent XVth International Congress of Lymphology in São Paulo (September 1995) and again at the Executive Committee meeting in Tucson (April 1996). This letter gives these ideas written expression.

Lymphedema, A Disease For The Rich?

The Consensus Document primarily applies to relatively affluent patients or countries with excellent health services. It was formulated largely in terms of what resources are available in parts of Europe and of the United States. It is not, however, readily applicable to poor countries, nor to poor patients without access to good health services in any country. Even in the more wealthy nations, knowledge of lymphedema and skills in its treatment are often lacking over wide regions. The Consensus, moreover, fails to take into account that treatment

regimens which depend on compression garments are extremely difficult to maintain in hot, humid, and dirty conditions. In one sense, such considerations are irrelevant to the Consensus because it addresses the essentials for good diagnosis and treatment. However at present good treatment is possible for only *some* patients in *some* regions of *some* countries.

The Consensus failed to distinguish among various possible treatments under less-than-ideal economic, social, or geographical conditions, or to indicate what are the best possible treatments in such adverse situations. Yet these conditions are the ones present in most parts of the world, especially in regions where lymphedema is most prevalent. Even in affluent countries, there are many patients who, for a number of reasons, are unable to benefit from the best treatments currently available.

It is necessary, therefore, to consider the best of "second-best treatments." This outlook does not presume that second-best is desirable; very much to the contrary! Yet often this is all that is possible. Accordingly, various alternative therapies should be considered and, if possible, graded for their effectiveness and their cost (e.g., in terms of money, effort-time, effect on the patient's way of life).

We have begun to attempt such "grading" (3,4), but we are only too aware how efficacy varies with the skills available and the socio-economic conditions, and of how much treatment cost varies from country to country. The task may prove too complex for anything

useful to emerge. However, if not attempted, it will not happen. In the meantime, we propose that the Consensus should at the very least recognize that the best treatment is not always possible, and further that a variety of alternative treatments may be better under varying circumstances.

The Benzo-Pyrones

The preceding raises another drawback of the current Consensus Document. Oral benzo-pyrones were largely dismissed and its topical application was not even mentioned. Yet benzo-pyrones are safe, cheap, and effective. Considering lymphedema in the context of a world-wide problem, benzo-pyrones are often the only treatment that can be usefully offered to a patient with lymphedema. Edema reduction with benzo-pyrones is by no means as rapid as with the best treatments (when these are performed properly), but they do reduce lymphedema and elephantiasis (5).

Indeed, the slow action of the benzo-pyrones can be beneficial, because lymphedema is reduced without use of compression garments. The latter are essential for therapies which give rapid edema reduction and for its maintenance. Yet compression garments are difficult or impossible to wear in hot, humid, or dirty conditions. (Whether compression garments would improve the results from benzo-pyrones is unknown.)

It seems unfortunate that despite well-designed clinical trials, the usefulness of many benzo-pyrones is not better recognized. These drugs have been tested by over 37 authors in 8 countries, in (effectively) 51 clinical trials (personal review). Note the word “effectively” is used because different grades of lymphedema were counted separately if they were evaluated separately. The benzo-pyrones studies included coumarin, coumarin plus troxerutin, oxerutins (O-(β -hydroxyethyl)-rutosides, HR) and diosmin.

There have been 39 trials of oral and 12 of topical preparations (11 and 6, respec-

tively, were combined with other therapies). Oral or topical benzo-pyrones all reduced lymphedema (usually to a clinically notable extent). In almost all the trials, patient symptoms were also decreased including episodes of secondary acute inflammation (SAI). Combining all 25 trials of oral benzo-pyrones alone in which the reduction of peripheral edema could be estimated (1,225 patients *in toto*) provided a mean reduction of edema of $36 \pm 6\%$ (mean \pm SE) per year. There were no differences between arms and legs. Elephantine legs were less reduced ($15 \pm 6\%$) than Grades 1 and 2 ($57 \pm 9\%$; $p=0.002$) but the edema was much greater initially.

Nor are these benzo-pyrone drugs merely useful by themselves. Both oral and topical forms, and these combined, materially augmented reduction of lymphedema by various physical and surgical techniques. They often also reduce the incidence of SAI in these.

Statements About Benzo-pyrones in the Consensus Document

The Consensus Document (1) claims that the “exact role of the benzo-pyrones ... is still to be definitively determined including the appropriate formulations and dose regimens.” Whereas this statement is undoubtedly true, it is also equally true of almost every aspect of medicine! There are never enough good clinical trials to resolve all uncertainties. It is, therefore, unfortunate that benzo-pyrones were singled out in this way; most other treatment protocols recommended have equally uncertain background information. Even for the quickest and best, namely Complex Physical Therapy (CPT), there are manifold uncertainties about optimal details for its use. Thus,

1. CPT is usually continued for 1-2 weeks after an edema plateau is reached. Is this essential, helpful, useless? The first is usually advocated, but how strong is the evidence?
2. How vital is skin care? It almost certainly is important but no controlled trial has been carried out to prove this.

3. Is it better to have daily CPT treatments for 4 weeks than every third day for 12 weeks? Whereas there is evidence for this recommendation, it has not been properly established.

4. Do two daily sessions of CPT give twice the reduction of one? It is unlikely but unknown.

Some of these are unlikely ever to be completely substantiated. After all, who would withhold skin care from a random 50% of patients just to establish statistical verification? Yet it could equally be argued that unless such an unbiased trial is done, valuable resources may be squandered.

Similarly, there are many unanswered questions about use of antibiotic drugs and lymphedema — their importance, need, and in which patient? There are hardly any published reports of even the short-term effectiveness of external compression (pneumatic) pumps let alone after (even) 2 or 5 years (3). Many maintain that pumps often cause serious complications yet convincing numerical documentation is rarely described. Several surgical techniques and treatment of lymphedema are mentioned in the Consensus; yet (6) detailed numerical data about these operations are seldom available (3).

Undoubtedly one would like to know more about each of these therapies. However, it is a disservice to patients and their advisors to single out one kind of therapy for criticism (albeit correct) but to neglect others. This attitude is especially unfortunate when there have been far more randomized and controlled trials (let alone double-blind ones) of benzopyrones than of pumps, operations, antibiotics, CPT, and even all combined for treatment of lymphedema (3) and personal review.

CONCLUSIONS

We suggest that the Consensus Document be amended as follows:

1. A section should be included that: The most appropriate treatment for an individual patient depends on:

a) Which therapies are available, including the necessary training and skills of those who provide them.

b) The patient's socio/economic condition and what financial aid is available.

c) The patient's way of life and whether changes in this way of life, which are essential for therapy, are possible and whether the patient will comply with them.

2. The section relating to benzo-pyrones should be replaced with:

a) **Oral benzopyrones.** These drugs are believed to increase extralymphatic removal of tissue plasma proteins by augmenting proteolysis and also stimulating contraction of lymphatic collectors. Benzopyrones are neither an alternative nor a substitute for CPT but they offer slower, but effective, reduction in the volume of lymphedema and associated symptoms and sequelae (including acute infections/ lymphangitis) when CPT is unavailable or not possible. The drugs also improve outcome of many other treatment regimens.

The exact role for benzopyrones, as with most therapies of lymphedema, is still to be definitively determined including appropriate formulations and dose regimens. Rarely coumarin, one form of benzopyrone, causes idiosyncratic hepatitis; this complication has not as yet been reported for other benzopyrones, or for topically applied coumarin.

b) **Topical Benzopyrones.** Although there are few clinical trials for topical application, the results in treatment of peripheral lymphedema are similar to those of oral benzopyrones. Combining both oral and topical application may improve edema reduction further, especially when used with other treatments. No side effects have been reported to date for topical benzopyrones.

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Editorial Comment (CLW):

In this lengthy Letter to the Editor, the Casley-Smiths raise several cogent issues regarding the role of benzo-pyrones in the management of lymphedema and stipulate, based on available information, that a "Consensus Document" previously published in *Lymphology* (28:1995, 113-117) needs correction and updating.

In drafting the Consensus Document, the members of the Executive Committee recognized at the outset that the guidelines were recommendations only and were not intended to be overly restrictive. In short, they well understood that "optimal" and "desirable" is not always "practical" or "feasible." Indeed, in a Prologue to the Document, the Editors and Secretary General of the ISL, commented, "*The document is not meant to override individual clinical*

considerations for problematic patients nor is it meant to be a legal formulation that if varied from signifies medical malpractice."

In other words, it was realized that local, regional, and national conditions or patient circumstances might preclude what was advocated or even desirable. The intended purpose was nonetheless to submit a studied, reasonable, and generally sound approach to patients with lymphedema based on a global perspective and review of current attitudes and treatment modalities.

In this setting, the Casley-Smiths have now proposed a "position paper" in which they summarize their dissatisfaction with the Document as it now exists, their perceived lack of greater recognition of the value of benzo-pyrones particularly as it relates to impoverished communities and hot and humid climates, and further request that the putative value of drug treatment and particularly the benzo-pyrones be given greater exposure and emphasis. Unfortunately, like the Casley-Smiths with their boundless enthusiasm for benzo-pyrones, other advocates have equal zeal for thermotherapy and microsurgical lymphatic reconstructive operations, which though mentioned in the Consensus are felt by their protagonists to have been given insufficient recognition. Whereas all these clinician/investigators may have a legitimate "complaint," the published Document seems even in retrospect to reflect the general consensus throughout the world that, at least at this point in time, the preferred treatment approach for peripheral lymphedema is multimodal combined physiotherapy along the lines advocated by the Földis, Vodder, and others.

In the particular case of benzo-pyrones, it also should be noted that increasing reports of hepatotoxicity from their usage have prompted drug dosage restrictions in Germany and other parts of Europe, cautionaries in its use in Brazil, and voluntary removal of the oral formulation from the marketplace by the benzo-pyrone manufacturer in compliance with governmental regulations in Australia.