

LETTER TO THE EDITOR

BENZOPYRONES AND THE PLACEBO "ARM"

The editorial (1) on the comparative study of coumarin 135mg versus 90mg in the same issue (2) states that it was a serious omission that a placebo "arm" was not included in the trial. I disagree. Until the recent publication of the first negative randomized controlled trial of benzopyrones in lymphoedema (3), there had been six trials comparing either coumarin or oxerutins with placebo; all six demonstrated significant benefit with the active drugs and no benefit or deterioration on placebo (*Table 1*). This in itself is significant ($p < 0.05$).

Because the results are not presented uniformly, meta-analysis is impossible. Trials 1 and 3 give percentage change in arm volume whereas trials 2, 4 and 6 give absolute changes, and in trial 5 the results are given as changes in the *ratio* of arm volumes (swollen/normal). It is possible, however, to compare increases versus decreases in arm volume. When the six trials are analyzed in this way, it can be seen that a decrease in arm volume was never achieved with a placebo group or during a placebo period. However, in the first trial to show no benefit with benzopyrones (3), there appears to be a decrease in arm volume with placebo. Regrettably, the report does not provide an integrated analysis of the results in the 93 patients who completed the whole of the 12-month trial, again making comparison difficult.

In the trial of 2 doses of coumarin (2), the volume reduction in the arm was 13% and 15%, respectively. As patients were not receiving other forms of conservative treatment, these results can reasonably be

ascribed to the drug regimen. In contrast, in the negative trial of coumarin, half of the patients were found to have a decrease of 3% in arm volume over the 6-month period (but the other half had a small increase, 0.8%) (3). In other words, it beggars belief to interpret volume reductions of 13% and 15% as placebo responses.

Although the data in several of the trials in the Table relate to only small numbers of patients, I was surprised to learn from the editorial that some of the positive trials were carried out in "underdeveloped areas (e.g. China, India)." Of the six positive trials summarized in the Table, two were conducted in France, two in Australia and two in the United Kingdom.

Laboratory studies have demonstrated that benzopyrones increase the hydraulic resistance of the capillary membrane (10) and that they have a proteolytic effect in lymphoedema which is blocked by the destruction of the macrophages (11). Benzopyrones convert a slowly worsening condition into a slowly improving one. Thus it seems naive, indeed misleading, to say that "No actual quantification of such proteolysis and direct bloodstream absorption has been provided nor has urinary excretion or catabolism of these so-called amino acid byproducts been documented." Given the slow rate of proteolysis and the nature of the breakdown products, it would be pointless to pursue such measurements.

The time has surely come to review thoroughly the benefits of benzopyrones in lymphoedema, possibly by setting up an

TABLE 1
Changes in Arm Volume in Randomized Placebo-Controlled
Trials of Benzopyrones

Authors	Duration Trial (months)	No. of patients Evaluated	Placebo	Active Drug
1. Desprez-Curely et al 1985 ⁴	6	91 ^a	↑	↓
2. Piller et al 1988 ⁵	12	40	↑	↓
3. Pecking & Cluzan 1989 ⁶	6	78 ^a	↑	↓
4. Casley-Smith et al 1993 ⁷	12	52	↑	↓
5. Taylor et al 1993 ⁸	12	22 ^b	↑	↓
6. Mortimer et al 1995 ⁹	6	19 ^{a,b}	↑	↓

a. Group comparisons with approximately half in each of 2 groups (benzopyrone, placebo); other trials were crossover design (6 months on benzopyrone, 6 months on placebo in random order).
b. Compression garments worn throughout the trial period.

Expert Committee to review the evidence from both laboratory and clinical studies. This is now urgent given the fact that several countries have withdrawn the marketing licence for oral coumarin. If coumarin goes, will the pharmaceutical industry be willing to market oxerutins instead?

I am concerned that many people, particularly those with primary, chronic posttraumatic or chronic postoperative lymphoedema, will be denied a treatment of proven benefit because the fickle tide of popular opinion is presently against it.

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Reply:

It is ironic that Twycross should question the need for a placebo (control) arm in the study of Burgos et al (1) based on the conviction that prior surveys had already validated (presumably incontrovertibly) the benefit of benzopyrones in treatment of lymphedema. Yet, the recent careful study by Loprinzi et al (2), which casts serious doubt on two commonly expressed shibboleths, namely, the putative effectiveness of benzopyrone therapy and the invariable worsening of lymphedema if left untreated over a relatively short time period, should be a sufficient rebuttal to the notion that a placebo arm is unethical and unnecessary.

In a larger context, influence of clinical trials on the daily practice of medicine has an instructive but variegated history. In 1835, the French physician Pierre Louis demonstrated in a large randomized carefully controlled clinical trial that "blood-letting" was ineffective in the treatment of

inflammatory diseases (3). Indeed, it has been claimed that after this study, the lancet disappeared from most hospitals in Europe and America (4). In the wake of this experience, many 19th century physicians were quick to embrace, despite limited biological insight, a statistical approach (termed numerism) to decide treatment regimens for recognized ailments. This initial enthusiasm of the medical community led two illustrious French physicians (the renowned physiologist Claude Bernard and famed clinician Armand Trousseau) to dramatize the shortcomings of this attitude. In his classic treatise, "An Introduction to the Study of Experimental Medicine" (5), Bernard rejected the idea that physiochemical phenomena and their expression in sick patients could be reduced to mere mathematics. Bernard recognized that the response of the average patient to therapy is not necessarily the response of the patient being treated. In effect, if all patients shared identical characteristics and equivalent risks, the overall analysis of a clinical trial would be sufficient to provide medical practitioners with an unambiguous guide to treatment. Trousseau even more emphatically expressed the view, "I do not reproach the numerical method because it numerates, but reproach it because it only numerates. I reproach it for counting too much, counting too long, counting always, and for declining to put any mind into the facts. This method is the scourge of intellect; it transforms the physician into a calculating machine, making him the passive slave of the figures which he has amassed. The greatest reproach which I cast upon it is that it stifles medical intellect." (6).

For the next 100 years, uncovering fundamental mechanisms and basic principles dominated research efforts in experimental animals and man and, as a result, a pathophysiologic understanding of most disease processes took a quantum leap forward. Nonetheless, with the explosion of pharmaceutical agents and treatment options during the past 30 years, a grass-roots

movement emerged for large clinical comparisons for determining which of various treatment modalities were efficacious. The effect has been a rising dominance of so-called “evidence-based medicine,” a sharp decline in the physician-investigator uncovering new basic clinical phenomena (7), and ever greater reliance on protocol comparisons in huge multicenter trials to determine “proper” therapy for an individual patient. Despite greater dependence on statistical analysis, many experienced physicians remain cautious about embracing carte-blanche wholesale recommendations of supposedly well-done clinical trials when the outcomes fly in the face of empirical observations and well-reasoned deductions. As renowned biochemist Erwin Chargaff expressed it, “reason and judgment should not abdicate when faced with dogma” (8). Perhaps we have forgotten the intricacies of natural phenomena and that medical texts are organized according to diseases and organ systems, but sick patients are “mongrels” with comorbid conditions with wide age and gender differences. To cite Chargaff once again, “The force which seems to condemn our life is statistics” (9).

Aside from these pragmatic considerations, there is also the disturbing specter of Gresham’s Law whereby large amounts of dubious data, as in metanalysis, tend to preempt good data. Thus, it is entirely possible that prior trials of benzopyrones, because of the enthusiasm of the investigators, have given the illusion of success based on superficially favorable outcomes. If so, a placebo arm in the clinical trial of Burgos et

al was not only ethical but, as earlier suggested (10), may have led to a vastly different conclusion regarding the value or lack thereof of benzopyrones.

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