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LETTER TO THE EDITOR

THERE ARE MANY BENZO-PYRONES FOR LYMPHEDEMA

In an Editorial Comment (1) it was stated that increasing reports of hepatotoxicity from benzo-pyrones have prompted dosage restrictions, warnings, and removal of the oral formulation. Whereas this statement is true for oral coumarin (although a number of appeals in Australia are in progress), it is absolutely incorrect for all other benzo-pyrones, including topical coumarin. None of these has ever been documented as causing liver damage or having any other serious side effect. In addition, even oral coumarin has not been with certainty shown to cause this problem. Its "possible" plus "probable" rate is about 3 per 1,000 (2).

Some 3,500 benzo-pyrones are known (3,4). Of these about 50 have been tested in high-protein edemas and 25 in experimental lymphedemas. All reduced the edema in these conditions (3,4). Three kinds of benzo-pyrones (or very similar drugs) have been shown to improve lymphedema in humans, in randomized double-blind placebo-controlled trials (5-10). These are available in some 50 countries of the world. Various (bio)flavonoids are available in even more.

It was singularly unfortunate that the generic term (benzo-pyrones) was used when referring only to coumarin, and indeed only to oral coumarin.

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J.R. Casley-Smith, D.Sc., M.B.B.S, M.D. (h.c.m.)
Henry Thomas Laboratory
University of Adelaide
S.A. 5005, AUSTRALIA

Editorial Response: Whereas technically J.R. Casley-Smith is correct in pointing out the current status of Lodema (brand of coumarin tablets) in Australia, the issues are nonetheless more complicated. According to "Health Watch" on the internet (http://www.interlog.com/~mcpherc/watch.htm), Lodema was marketed in Australia before the current Therapeutic Goods Act took effect in 1991. For this reason, the drug was automatically included (i.e., "grandfathered") in the Australian registry of therapeutic goods with sponsorship by the Lymphoedema Association of Australia. Because of reports of hepatotoxicity (2 deaths, abnormal chemical tests of liver function and other serious liver cell dysfunction), the Australian Department of Health and Family Services voiced concerns about the pharmaceutical aspects of Lodema. After receiving responses from the sponsor to their queries, the Secretary of the Australian Department of Health and Family Services canceled the registration of Lodema "*on the grounds that the safety of this product is unacceptable and the quality of the product is unacceptable*". (italics added)

Citing the minutes of the 178th Meeting of the Australian Drug Evaluation Committee (ADEC):

The Committee ... resolved to advise the Minister and the Secretary that: "The ADEC has reviewed the data submitted by the Lymphoedema Association of Australia Incorporated in response to a request from the TGA (Therapeutic Goods Administration) for evidence of efficacy of Lodema tablets for the "grandfathered" indications and has determined that coumarin tablets appear to have a positive risk-to-benefit ratio in the treatment of post-surgical lymphoedema and lymphoedema associated with filariasis at the recommended dose of 200mg twice daily. However, the risk-to-benefit ratio for oedema due to sports injuries, infection and chronic venous insufficiency would preclude approval of coumarin tablets for these indications. *There are insufficient data to support the efficacy of topical coumarin preparations (powder or ointment) in the treatment of lymphoedema due to any cause.* (italics added)

Since then, the Medical Post in Canada reports cancellation of a large clinical trial on the effectiveness of Lodema being conducted at Princess Margaret Hospital in Toronto for the treatment of lymphedema *as a result of deaths and liver damage associated with use of the drug [in Australia]* (italics added). Dr. Charles Godfrey, Professor Emeritus at the University of Toronto involved in the trial has voiced his safety concerns to individuals who may be obtaining Lodema themselves through mail order and self-medicating. Professor Godfrey has written to the *New England Journal of Medicine* requesting that the publication print an addendum to an article it published three years earlier on the results of a study which reported the drug as safe for use in the treatment of lymphedema. He would like the publication to point out the current status of the drug (its removal from the market in Australia and its potential dangers). He is also concerned that information on the Internet about post-mastectomy use of the drug Lodema does not carry any cautionary information.

As these bulletins suggest, the matter of Lodema and by implication the benzopyrones in general is coming under closer scrutiny especially the issue of quality control in its preparation, its short- and long-term toxicity as well as its efficacy.