#1372

NIFEDIPINE

Public Citizen

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Joan Claybrook, President

September 20, 1995

David A. Kessler, MD, JD
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

We write to urge that you immediately initiate an investigation into a clear violation of the labeling and advertising provisions of the Food, Drug, and Cosmetic Act by the pharmaceutical company Bayer. The company orchestrated and paid for the mailing of thousands of Dear Doctor letters defending its drug nifedipine (manufactured by Bayer under the trade names Adalat and Adalat CC) against a recent study that raised questions about the safety of nifedipine and other calcium channel blockers. However, the letters failed to disclose that Bayer had paid for the distribution of the letter, a flagrant violation of the law. This failure to disclose funding, along with the misleading nature of the letter itself, have the potential to seriously misinform prescribing physicians about recent research developments regarding calcium channel blockers, a class of drugs that was prescribed 87 million times to six million Americans in 1994. Twenty-seven million of these prescriptions were for nifedipine.

Two recent reports suggest that calcium channel blockers, which are prescribed for high blood pressure and coronary heart disease, may be associated with an increased risk of heart attack and death. In the first study, published in the Journal of the American Medical Association on August 23, 1995, the use of calcium channel blockers was associated with an increase in the risk of heart attack of approximately 60 percent among patients with high blood pressure.[1] The higher the dose of calcium channel blocker used, the more the risk of heart attack was increased. In the second study, published in the journal Circulation on September 1, 1995, the authors combined the findings of 16 randomized, placebo-controlled trials of nifedipine using a statistical technique called meta-analysis.[2] The use of nifedipine in these patients with known coronary heart disease was associated with a 16 percent increase in total mortality, with the risk of death increasing as the dose of nifedipine increased. Consequently, the National Heart, Lung and Blood Institute has warned recently that high doses of short-acting forms of nifedipine should be used "with great caution, if at all."

In a "Dear Doctor" letter dated August 22, 1995 (see attachment) and mailed on August 23, the day the first study was published, Dr. Norman Kaplan, an internationally-recognized expert in the treatment of high blood pressure at the University of Texas, Southwestern Medical Center at Dallas, downplayed the findings of the first study.[1] In a telephone conversation on September 11, 1995, Dr. Kaplan informed us that he had been approached by a public relations firm representing Bayer and asked to author a Dear Doctor letter defending nifedipine. He agreed to do so, but only after receiving assurances that the letter would clearly state that Bayer had paid for the distribution of the letter. (Dr. Kaplan stated that he received no honorarium for his efforts.) However, the letter that was mailed out made no mention of the company either on the envelope or on the letter itself, which was written on University of Texas stationery. The prescribing information was also not included as is customary in drug company sponsored mailings. When Dr. Kaplan complained about the lack of disclosure, he was informed that Bayer's name had been inadvertently left off. He agreed that the letter had been sent to thousands of physicians. (We have been told by four physicians in two states in internal medicine, cardiology and family practice that they received the letter.)

As Dear Doctor letters are considered "labeling" by the FDA and as such are required to include adequate directions for use (usually the prescribing information) and are precluded from making false and misleading statements. However, in addition to the failure to disclose its sponsorship, the letter is misleading in several respects:

• The letter completely omits the major finding of the study: that calcium channel blockers, of which nifedipine is one of the most frequently prescribed, were associated with an increased risk of heart attack.

• Although there are legitimate concerns about the possibility of systematic differences between the cases and the controls in the study (an issue raised in the letter), the letter fails to mention that the analysis controlled for age, pretreatment blood pressure, and duration of high blood pressure as well as a number of other factors associated with heart attacks.

• The letter does not mention an earlier meta-analysis,[3] which found a 17 percent increase in total mortality among patients receiving the subclass of calcium channel blockers that includes nifedipine, or several additional studies questioning the safety of the calcium channel blockers.[4,5,6,7,8]

This is not the first time that Bayer, the name adopted by Miles in April 1995, has stooped to inappropriate and or illegal practices in its efforts to promote Adalat CC. Miles is being criminally investigated by the Department of Health and Human Services for a 1993 scheme in which the company provided pharmacists with a $35 kickback for each new prescription of Adalat CC they filled.[9] This placed pharmacists in a conflict of interest, and some responded by either calling physicians requesting permission to switch from a competing brand of nifedipine to Miles' brand, or by simply conducting the switch without the physician's permission. On April 4, 1994, Miles entered into an Assurance with the Attorneys General of eleven states under which it agreed to not resume its program and to pay a fine of $605,000.[10]

More recently, the company used its influence to manipulate the roster of attendees at a press conference in Amsterdam. The press conference followed a presentation of the data from the most recent meta-analysis (the "second study"[2] described above). Bayer convinced the European Society of Cardiology to add to the press conference panel a researcher who disagreed with the findings of the meta-analysis.[11] In fact, it was not until several weeks later, only a few days before the meeting, that the author of the meta-analysis himself was invited to the press conference.

Over the last several years, Bayer has employed a variety of deceptive techniques in its attempts to bolster the sales of Adalat CC. The most recent addition to this ignominious tradition, the letter described herein, is not only illegal in that it fails to adequately disclose its sponsorship, it is also strikingly unbalanced. If American consumers are to be adequately protected from these reckless practices, you will ensure that Bayer is prosecuted to the fullest extent of the law.

Yours sincerely,

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Endnotes

1. Psaty BM, Heckbert SR, Koepsell, TD et al. The risk of myocardial infarction associated with antihypertensive drug therapies. Journal of the American Medical Association 1995; 274:620-625.

2. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. Circulation 1995; 92:1326-1331.

3. Held PH, Yusuf S. Impact of calcium channel blockers on mortality in survivors of acute myocardial infarction. In: Singh BH, Wellens HJJ, Hiraoka M, eds. Electropharmacological Control of Cardiac Arrythmias. Mount Kisco, NY:Futura Publishing Co., Inc.; 1994:399-411.

4. Holland Interuniversity Nifedipine/Metoprolol (HINT) Research Group. Early treatment of unstable angina in the coronary care unit: a randomized, double blind, placebo controlled comparison of recurrent ischemia in patients treated with nifedipine or metoprolol or both. British Heart Journal. 1986; 56:400-413.

5. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy with that of isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990; 82:1954-1961.

6. The Israeli SPRINT Study Group. Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT): a randomized intervention trial of nifedipine in patients with acute myocardial infarction. European Heart Journal 1988; 9:354-364.

7. Goldbourt R, Behar S, Reicher-Reiss H, Zion M, Mandelzweig L, Kaplinsky E, for the SPRINT Study Group. Early administration of nifedipine in suspected acute myocardial infarction: the Secondary Prevention Reinfarction Israeli Nifedipine Trial 2 Study. Archives of Internal Medicine 1993; 153:354-353.

8. Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of angiographic progression of coronary artery disease by nifedipine: results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). Lancet 1990; 335:1109-1113.

9. Tanouye E. Miles under probe for paying druggists to advise patients about its product. Wall Street Journal, May 31, 1995, p.A3.

10. In the Matter of Miles, Inc. Order approving Assurance of Discontinuance, State of Minnesota District Court, Second Judicial District, April 4, 1994.

11. Horton R. Spinning the risks and benefits of calcium antagonists. Lancet 1995; 346:586.

THE UNIVERSITY OF TEXAS
SOUTHWESTERN MEDICAL CENTER
AT DALLAS

Department of Internal Medicine **Hypertension Division**

August 22, 1995

Dear Doctor:

You may have heard about presentations that have raised concerns about the use of calcium channel blockers in the treatment of hypertension and coronary heart disease. One of these reports will be published in *JAMA* on August 23, 1995. The paper is accompanied by an editorial that allows you to judge the data in their proper context and to draw your own conclusions as to their relevance to clinical practice.

One of the calcium channel blockers under attack is nifedipine.

I wish to point out that nifedipine has been used worldwide for the treatment of hypertension for more than 20 years. Nifedipine, and indeed the whole class of drugs, is the most popular for the treatment of hypertension in the US today. This reflects the fact that they are effective and that clinicians find them safe for the treatment of hypertension.

Specifically, the extended release formulations of nifedipine provide a smooth control of arterial pressure throughout a 24-hour period after once-daily administration.[1,2] Numerous trials have proven that nifedipine, when given in the extended release formulations, does not increase heart rate at the recommended doses of up to 90 mg per day.[1-3]

In looking at the Psaty study closely, several facts are evident:

- The use of nifedipine was not associated with a statistically significant increase in risk of myocardial infarction.
- Even if risk had been shown, case-control studies cannot prove a cause-effect relationship.
- The nifedipine formulation used in the study is an older short-acting compound never marketed for the treatment of hypertension.
- Typically, patients receiving CCBs like those selected for the study are older and sicker, and more likely have underlying CHD, which can affect their risk of myocardial infarction.

In conclusion, we should not fault the long-acting formulations of nifedipine for the possible sins of short-acting nifedipine — which was never intended for use in hypertension.

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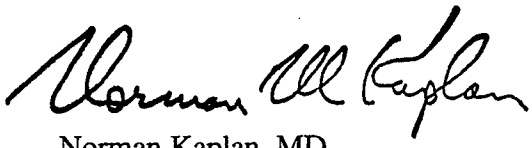
Studies such as these can be useful tools to researchers, and can help identify new areas for further study. Their applicability to clinical practice, however, is highly questionable. Only randomized prospective trials (as are now being performed) can document the benefits and hazards of drugs for the treatment of hypertension. We should recall that similar case-control studies claimed that reserpine caused cancer, claims that were proven wrong because of biases in selection of cases and controls. It is my opinion that the known risks of hypertension are the enemy, not the unproved hazards of calcium channel blockers. That's why I remain confident that sustained release formulations of calcium channel blockers, including nifedipine, remain a good choice for the treatment of hypertension.

Sincerely,

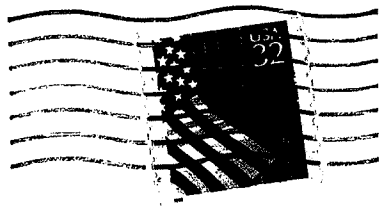


Norman Kaplan, MD

References:

1. Zanchetti, et al. *High Blood Pressure.* 1994; 3:45-56.
2. Glasser, et al. *Clin Ther.* 1995; 17 (1):12-29.
3. Parmley, et al. *J Am Coll Cardiol.* 1992; 19 (7):1380-1389

Norman Kaplan, MD



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