JACC Vol. 8, No. 3
September 1986:739–40

LETTERS TO THE EDITOR

Nifedipine Versus Isosorbide Dinitrate in Patients With Exertional Angina Receiving Propranolol

Morse and Nesto (1) have reported that the combination of nifedipine and propranolol is more effective than the combination of isosorbide dinitrate and propranolol in reducing the incidence of angina and improving exercise performance. It would be unfortunate if these unwarranted conclusions were to go unchallenged.

Their study clearly demonstrates that when a serious flaw exists in the basic design, "double-blind crossover comparison" may afford little justification for drawing sweeping conclusions. In reality, what Morse and Nesto appear to have shown is that maximal doses of nifedipine to the limits of tolerance are superior to minimal or relatively low doses of isosorbide dinitrate when these agents are used in combination with propranolol. The disparity in the dosage range chosen for the respective drugs is unwittingly made clear by the authors in their statement that "although only 4 patients could tolerate the maximal dose of 120 mg/day of nifedipine, 14 tolerated the maximal dose of 120 mg/day of isosorbide dinitrate." Thus, of the 27 patients with exertional angina in the study, 13 received four daily doses of isosorbide amounting to 20 mg or less per dose and of these, 7 actually received only 10 mg of the drug with the same frequency. In three cases, the lowest dose of isosorbide dinitrate (10 mg, four times daily) caused intolerable headaches so that premature termination of treatment or crossover to nifedipine therapy was the final resort. Obviously, such hypersensitivity to the nitrates should have eliminated these subjects from the study at the outset because their inclusion only served to bias the results in favor of nifedipine.

The data therefore indicate that only 14 patients of the 27 in the series received isosorbide dinitrate orally in a dosage of 30 mg four times daily. By today's standards even this represents only a modest amount of the drug, inadequate for optimal therapeutic response. For many years the dosage of oral nitrates was set by arbitrary means and not by careful observation and titration in human subjects. Through experience, older clinicians recognized that when nitrates are administered by the *oral* route there is an attenuation of effect as compared with the responses following *sublingual* administration. This loss in potency was known to encompass all orally administered nitrate compounds and is now attributed to enzymatic degradation in the liver before drug action at cardiovascular target sites. To overcome this nullifying influence and to approach responses possible with sublingual nitrates, inordinately high doses were found to be essential by the oral route. The long use of "homeopathic" and other ineffectual doses of oral nitrates has had a "carryover" effect in retarding wide recognition of therapeutic benefits to be derived from dosage levels extending to the limits of tolerance.

Despite these considerations, *sublingual* nitrates are far more potent than *oral* nitrates even in massive dosage for the treatment of stable angina pectoris. Moreover, the additive and often synergistic response observed when *sublingual* isosorbide dinitrate is used in conjunction with a beta-blocker (2) is a unique phenomenon that has not been matched to date by any combination of beta-blocker and calcium channel blocker (3). Until this is fully recognized, many patients with stable angina are destined to be deprived of optimal therapy for this disorder.

A final comment appears indicated concerning the cost of drug therapy. Nifedipine alone in the dosage range employed by Morse and Nesto would require an expenditure by the patient of $650 to $1,000 a year. Isosorbide dinitrate orally (Tembids, 40 mg, four times daily) or sustained release nitroglycerin (6.5 mg, four times daily) would cost the patient $100 to $128 for 1 year's supply. For the same period of time, sublingual isosorbide dinitrate (5 mg, four times daily) would cost $56 and a beta-blocker about $152. In other words, the outlay for nifedipine alone for 1 year would amount to two to three times the combined cost of a beta-blocker, *oral* nitrate and *sublingual* isosorbide dinitrate for the same interval ($650 to $1,000 versus $336). From the evidence, the increased expenditure for nifedipine does not at this time appear warranted for the treatment of stable angina pectoris responsive to standard therapy.

HENRY I. RUSSEK, MD, FACC
1 North Ocean Road
Boca Raton, Florida 33432

References

1. Morse JR, Nesto RW. Double-blind crossover comparison of the antianginal effects of nifedipine and isosorbide dinitrate in patients with exertional angina receiving propranolol. J Am Coll Cardiol 1985;6:1395–401.
2. Russek HI. Propranolol and isosorbide dinitrate synergism in angina pectoris. Am J Cardiol 1968;21:44 54.
3. Russek HI. Comparison of nifedipine versus nitrates in combination with propranolol in patients with angina pectoris. Presented at 16th Annual Cardiovascular Symposium, American College of Cardiology, New York, NY, December 1983.

Reply

We clearly recognize that nearly half the patients in our study group probably did not receive what is commonly regarded as "maximal" nitrate therapy and that those who were advanced to maximal therapy, as defined in our protocol, may very well have tolerated even higher dosages. It is for exactly these reasons that the dosage schedules for individual patients were painstakingly displayed.

Those patients who received "minimal or relatively low dosages" of isosorbide dinitrate were given those low dosages because of reported side effects that prevented further upward dose titration. In a study that is rigidly double-blinded, the investigator (unlike the experienced clinician) does not have the luxury to interpret as well as monitor adverse effects and thereby may not confidently reassure patients that these (adverse effects) will likely subside with higher doses. For the same reasons, the three patients who were prematurely crossed over or terminated were allowed to do so because they simply would not take the drug. We would be subject to enormous criticism had we, in such a blinded setting,