LETTERS TO THE EDITOR

Letters to the Editor will be published, if suitable, and as space permits. They should not exceed 1,000 words (typed double spaced) in length, and may be subject to editing or abridgment.

Erratum

To the Editor:

Dr. L. S. Gettes has alerted me of the fact that three figures appearing in our review article devoted to the subject of ventricular tachycardia (Circulation 47: 1364, 1973) appear to be adaptations of figures which he had published earlier (Am J Cardiol 28: 526, 1971). These figures (in our article Nos. 1, 7 and 8) were diagrammatic simplifications of certain electrophysiologic concepts.

One might rationalize that these figures were based on what is now a commonly held viewpoint and furthermore, that they do not represent anyone's painfully acquired data. Of course, such attempts at justification are mere frivolous sophistry. It is best to hasten and apologize to Dr. Gettes for inexcusable oversights which were exclusively my fault. If there is any comfort to be gained from this transgression, perhaps it resides in the realization that next to promulgation of truth, there is some virtue in the public recantation of error.

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Treatment of Angina Pectoris

To the Editor:

Certain arguments, such as those concerning religion, politics, and long-acting nitrates, remain sufficiently moot to prohibit immediate definitive solution: hence, our interest in the editorial by Goldstein and Epstein entitled "Nitrates in the Prophylactic Treatment of Angina Pectoris." In that editorial, the authors cast doubt on the value of the long-acting nitrates in the prevention of angina, suggest that nitroglycerin ointment might be superior and warn against the potential dangers of nitrate tolerance. Several points were raised in the editorial requiring discussion.

Goldstein and Epstein maintain that studies measuring nitrate effect on blood pressure and other hemodynamic alterations would be of questionable value, were a concomitant increase in the patient’s ability to exercise not demonstrated. The main problem with this point of view is that, although bringing about a decrease in the number of anginal episodes is undeniably the principal aim when using nitrates, it must further be appreciated that measuring exercise capacity — electrocardiographic ischemic changes, duration of exercise, etc. — provides a relatively insensitive index of drug effect. Coronary ischemia commonly occurs in the absence of angina or segmental ST segment depression, underscoring the difficulties of using these variables as reflectors of drug efficacy. Also relevant to this point is the report of Giannelli et al. where it was shown that propranolol improved angina without significantly influencing magnitude of ST segment depressions during treadmill testing.

Notwithstanding the difficulties inherent in assessing nitrate activity, many groups have reported a lasting effect of sublingual nitrates, more prolonged, in several instances, than that obtained with nitroglycerin. Such studies indicate that the sublingual long-acting nitrates are effective for at least 45 to 60 minutes. In our study we chose to monitor the hemodynamic alterations brought about by the nitrates because of the objective nature of their parameters and, therefore, less likely of their being influenced by the aforementioned problems, patient or investigator bias or by spontaneous variation in the patient’s symptoms. This investigation showed that isosorbide dinitrate given sublingually evoked a significant hemodynamic action lasting for at least one hour, an effect more prolonged than that produced by nitroglycerin. The nitrate-induced hemodynamic changes, by decreasing cardiac work, would likely reduce myocardial oxygen requirements. Thus, these hemodynamic changes most likely mediate the clinically germane action of the drug — relief of ischemic pain — and are pertinent to its use in angina. It should be further pointed out that even the study of Goldstein et al. showed 4 of 11 patients with improved exercise capacity one hour after administration of sublingual isosorbide dinitrate.

Goldstein and Epstein cast doubt on whether equivalent doses of nitroglycerin and isosorbide dinitrate have been used in the various studies, clearly a valid and important issue. This question, however, becomes especially difficult to answer when one considers that the onset and duration of the action of the two drugs may differ. When such is the case, does one compare drug dosage immediately after administration, at the peak of drug effect, one hour later? The question is clearly a semantic one. We noted that 10 mg of sublingual isosorbide dinitrate had the same hemodynamic effect 5 or 10 minutes after administration as 0.4 mg of nitroglycerin. Moreover, patients receiving a double dose of nitroglycerin, 0.8 mg, manifested no hemodynamic effect after one hour. Thus, it appeared that the differences noted between isosorbide dinitrate and nitroglycerin could not be explained by an imbalance of drug dosage.

Goldstein and Epstein also expressed concern about the possibility of nitrate tolerance developing, blunting subsequent acute nitrate effects. Subtle evidence of nitrate tolerance has been demonstrated using plethysmography, but these slight changes may have little clinical import. Both our and Goldstein et al.’s previous studies revealed no evidence that chronic nitrate treatment prevented the clinical or physiological effects of isosorbide dinitrate from taking place.

Our contention is not that the debate about long-acting nitrates is settled, but rather that the complexities of evaluating antianginal agents are great and that the subject of efficacy of the long-acting nitrates remains a viable one. Several studies employing well-designed exercise protocols and blinding techniques have demonstrated an effect of sub-
lingual long-acting nitrates more prolonged than that achieved by nitroglycerin. It is likely that the duration of action of the sublingual nitrates is not as long as would be ideal, merely more prolonged than that achieved by nitroglycerin: a 1-2½ hour duration of action seems most likely. Evidence that oral "long-acting" nitrates have a prolonged duration of action is, we agree, lacking. Although the information that nitroglycerin ointment may be superior is potentially exciting, its preliminary nature deserves reconfirmation before its acceptance to the exclusion of the sublingual mode of administration.

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References

The authors reply:

Dr. Cohn's thoughtful letter raises some interesting and important points. We agree that the complexities of evaluating antianginal agents and the resultant lack of precise information are a major reason for continuing uncertainty concerning the relative therapeutic merits of the various nitrate esters. Rather than resolving conflicting opinions, we hoped that our editorial3 would clarify certain therapeutic concepts and focus attention upon important gaps in factual information that is presently available.

Dr. Cohn is certainly entitled to his doubts concerning the role of exercise testing. Nevertheless, exercise evaluation remains uniquely related to therapeutic choice simply because it represents a systematic way of studying symptomatic response. We have emphasized previously that testing techniques must be selected carefully to optimize their discriminative potential. In our hands, exercise testing has readily documented the efficacy of several modes of therapy for angina — including isosorbide dinitrate. We do not mean to detract from the importance of physiologic and pharmacodynamic investigations of the nitrates. Indeed, these studies provide information that is essential in arriving at an integrated concept of nitrate therapy for angina. However, we anticipate that the findings of these more basic studies would ultimately receive confirmation in studies related immediately to the therapeutic goal, i.e., relief of ischemia and its symptomatic sequelae. Dr. Cohn has very astutely identified the central dilemma involved in comparing nitrate esters: What dose should be selected for each drug? Clearly, it is not satisfactory to presume that a single, arbitrarily chosen dose will be representative of the actions of all possible doses of each agent. Yet this arbitrary choice beclouds comparative studies purported to demonstrate the advantages of sublingual "long-acting" nitrates. To document unequivocal superiority of a "long-acting" nitrate, one must show that pretoxic doses can achieve greater efficacy and/or duration of action than any pretoxic dose of the rival nitrate. The repeated testing needed to support such a claim is arduous and (since one is dealing with the borderlines of toxicity) potentially hazardous. Nonetheless, if definitive supporting evidence cannot be produced, unqualified claims of superiority should be muted.

An alternative to arbitrary dosage choice can be achieved by a technique matching physiologic action of nitrates. Such a technique has been used by us3 and, in a slightly different context, by Dr. Cohn and associates.7 We thought it of some interest that doses of sublingual nitroglycerin and sublingual isosorbide dinitrate producing equal physiologic change and equal increment of exercise capacity showed equally rapid disappearance of clinical benefit. As Dr. Cohn points out, however, the nature of matching is, itself, an arbitrary choice. What if our criteria for matching had been entirely different? Would we have achieved the same result? Moreover, what if large doses of sublingual isosorbide dinitrate were better tolerated than matched (or less-than-matched) doses of nitroglycerin? Wouldn't this supersede the therapeutic implications of our previous study. Obviously, we are no more capable of finally resolving the nitrate controversy than we are of resolving the religious and political questions mentioned in Dr. Cohn's letter. We assert that we looked for evidence of a longer action for sublingual isosorbide dinitrate (within a commonly employed dosage range) and failed to find such evidence. We remain open-minded about the possibility that future testing using different techniques may document improvement in ischemic symptoms resulting from sublingual isosorbide dinitrate that cannot be achieved by any pretoxic dose of sublingual nitroglycerin. We might add that the same open-minded attitude should logically be extended to oral nitrate esters. Studies of these agents also suffer because of the difficulties involved in studying many different doses. Impressively claimed prolonged hemodynamic efficacy have been advanced regarding agents such as oral nitroglycerin. Perhaps more complete testing with a wide range of doses will succeed in identifying a practical and uniformly effective regimen for oral nitrates. We should not solidify our current skepticism in rigid orthodoxy.
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