

LETTERS TO THE EDITOR

Calcium Channel Blockers and Drug Interactions

Wayne (1) concluded that it may be preferable to use diltiazem in combination with beta-adrenergic blocking agents. In contrast, another study (2) of diltiazem with propranolol showed a deterioration in exercise performance compared with either drug alone. Further, the combination of diltiazem with a beta-blocker may have a synergistic action, prolonging AV conduction with resultant serious deleterious effects (3).

Diltiazem undergoes extensive hepatic metabolism, and interaction between the calcium channel blockers and drugs that alter hepatic flow are an important consideration. Therefore, diltiazem should be used with caution in patients with impaired renal or hepatic function. Any drug that affects hepatic flow will undoubtedly alter the half-life and pharmacokinetics of the calcium blockers. A classic example of a drug that decreases blood flow to the liver is cimetidine. Since both cimetidine and diltiazem are widely used, this drug interaction is important to remember.

Recently published studies have shown an interaction between calcium blockers and digitalis. Verapamil may displace digoxin at cellular receptor sites, thereby increasing plasma concentrations of digoxin and adding to the likelihood of digitalis toxicity. The same effect was found after administration of nifedipine, although to a lesser degree. The manufacturer warns that concomitant use of diltiazem with digitalis may result in additive effect on conduction. Hence, the dose of digoxin should be halved in patients taking calcium channel blockers.

Calcium channel blockers may also cause clinical problems in patients taking diuretic drugs, prazosin or hydralazine. These patients require a very cautious approach because of possible undue hypotension. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of disopyramide may result in negative interactions. It should be borne in mind that disopyramide level does not even have to be toxic. Combined verapamil and quinidine therapy should be avoided, as this combination has resulted in episodes of ventricular fibrillation and severe pulmonary edema.

Published reports (4) have revealed that interactions have occurred with barbiturates, phenytoin, methyldopa and procainamide. Potential applications for the use of the calcium blockers include hypertension control, treatment of Raynaud's phenomenon and treatment and prophylaxis of migraine. For physicians desiring proper patient management, a knowledge of the clinical manifestations of these interactions is essential.

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References

- Wayne VS. Interaction of calcium channel and beta-adrenergic blocking agents. *J Am Coll Cardiol* 1983;2:594-5.

- Hung J, Lamb I, Connolly S, et al. Effects of diltiazem and propranolol (abstr). *Circulation* 1982;66(suppl II):II-82.
- Hossack KF. Conduction abnormalities due to diltiazem. *N Engl J Med* 1982;307:953-4.
- Resenkov L. Antianginal agents: uses, drug interactions, and the complicating illnesses. In: *Symposium Proceedings on Antianginal Agents*, Boca Raton, Florida, December 3-5, 1982. Update on Angina Therapy. New York: Pfizer Laboratories, 1983:105-12.

Ventricular Ectopic Activity in Severe Heart Failure

Important observations not made explicitly by Wilson et al. (1) call into question some of their conclusions regarding the relative insignificance of ventricular ectopic rhythm. First, the exclusion of patients with "sustained ventricular tachycardia" (undefined by the authors, but presumably more than three successive premature ventricular contractions at a rate exceeding 100 beats/min) and those with syncope severely limits their conclusion that cardiac mortality in severe heart failure is without independent relation to ventricular ectopic activity. Second, if one presumes that those with five or more consecutive premature ventricular complexes or 39% of the 77 patients followed up by the authors are at greatest risk for sudden death, it becomes apparent that the 11 patients receiving procainamide and quinidine and constituting more than one-third of those at greatest risk may have been protected from sudden death if such therapy were efficacious, thereby reducing the apparent import of high levels of ventricular ectopic activity as an independent predictor of sudden death. This presumes, however, that the 11 receiving antiarrhythmic therapy were, in fact, those at highest risk and that their therapy significantly reduced the level of ventricular ectopic activity, two presumptions not assessable from the data presented by Wilson's group.

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Reference

- Wilson JR, Schwartz JS, St John Sutton M. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;2:403-10.

Holter-Monitored Sudden Death

Lewis et al. (1) appear to have overlooked the significance of changes in cycle length immediately preceding the tachyarrhythmia in at least 9 of their 12 patients. As in our patients (2), these changes typically consist of R on T phenomenon in the wake of a postectopic pause. This pause had most commonly been observed after multiform, repetitive ventricular ectopic activity. Both the pause and the mechanism of its production are theoretically important in the genesis of subsequent fatal arrhythmias. It may be somewhat misleading, therefore, to state that "no consistent re-

lation between the RR and the RR' interval initiating ventricular fibrillation or torsade de pointes was found."

Another detail that has escaped analysis is the patients' past status with respect to ventricular ectopic activity. The significance of either the arrhythmia density or the grade of ectopic activity before sudden death can only be assessed by comparing the data with past records. The "prodromal" nature of the "warning arrhythmias" was largely invalidated in our recent study (2) when we found that half of our patients had higher Lown scores in the past than on the day of their sudden death. Thus, while we know that malignant ventricular arrhythmias are a marker (independent or otherwise) of sudden death, we still do not know how soon the latter is supposed to happen.

Many readers probably regret that the authors' depth of analysis did not extend to data that are normally taken into account when

Holter tapes are interpreted: the patients' general status and activity, the standard 12 lead electrocardiogram, serum chemistry determinations and drug levels.

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References

1. Lewis BH, Antman EM, Graboyes TB. Detailed analysis of 24 hour ambulatory electrocardiographic recordings during ventricular fibrillation or torsade de pointes. *J Am Coll Cardiol* 1983;2:426-36.
2. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. *Circulation* 1982;66:218-25.

Correction

In the Education Update listing, "Adult Cardiovascular Training Programs in the United States" (*J Am Coll Cardiol* 1984;3:455-64), the University of California, San Diego was incorrectly categorized as having no accredited residency in internal medicine. It does have an accredited residency in internal medicine.