ventricular cavity muscle mass during the 1st year after an index myocardial infarction occur in a nonparallel fashion. The observations, in fact, are vindicated by prior experimental studies.

JOHN A. RUMBERGER, PHD, MD
Department of Cardiology
Mayo Clinic and Foundation
200 First Street Southwest
Rochester, Minnesota 55902

BERNARD J. GERSH, MB, DPHIL
Department of Cardiology
Georgetown University
Washington, D.C. 20007

References

1. Shu NH, Hirose K, Reed JE, Gersh BJ, Behrenbeck T, Rumberger JA. Ventricular shape and orthogonal wall stress adaptations during the first year after anterior wall myocardial infarction [abstract]. J Am Coll Cardiol 1993;21 Suppl A:403A.
2. Ginzton LE, Conant R, Rodrigues DM, Laks MM. Functional significance of hypertrophy of the noninfarcted myocardium after myocardial infarction in humans. Circulation 1989;80:816–22.
3. McDonald KM, Francis GS, Carlyle PF, Hauer K, Matthews J, Hunter DW, Cohn JN. Hemodynamic, left ventricular structural and hormonal changes after discrete myocardial damage in the dog. J Am Coll Cardiol 1992;19:460–7.
4. McDonald KM, Carlyle PF, Francis GS, Cohn JN. The comparative effects of beta-adrenoceptor blockade and angiotensin converting enzyme inhibitor therapy on established ventricular remodeling in the dog [abstract]. Am J Hypertens 1993;6(5):14A.
5. McDonald KM, Francis GS, Matthews J, Hunter D, Cohn JN. Long-term oral nitrate therapy prevents chronic ventricular remodeling in the dog. J Am Coll Cardiol 1993;21:514–22.

Interaction of Propafenone and Mexiletine

We congratulate Yeung-Lai-Wah and colleagues (1) for their interesting report concerning combination drug therapy using propafenone (a class IC antiarrhythmic agent) and mexiletine (a class IB agent) in patients with a history of sustained ventricular tachycardia that had not responded to propafenone or procainamide alone or in combination.

Undoubtedly, the electrophysiologic properties of these antiarrhythmic drugs are partially due to specific interactions with sodium channels, as described in the modulated receptor model proposed by Hondeghem and Katzung (2). We disagree, however, that "little is known about pharmacokinetic interaction between propafenone and mexiletine" (1). The metabolism of propafenone (as well as that of encainide and flecainide) is genetically mediated, following the same oxidation pathway as that of debrisoquine and sparteine through the P450 2 D6 cytochrome (also known as P450 dbi or CYPED6). It follows then that, like debrisoquine, these drugs exhibit genetic polymorphism in patients who are either "extensive" or "poor" metabolizers (3–6). It has also been demonstrated (7–9) that mexiletine metabolism, both in vitro and in vivo, is probably linked to the debrisoquine/sparteine pathway, with similar genetic polymorphism.

Therefore a combination of the two tested drugs could have a synergistic effect not only because of specific electrophysiologic properties, but also because of an alteration of the metabolism of one or both drugs, which could lead to a dramatic increase in the plasma levels of the parent drug and a decrease in the levels of its metabolites. The absence of blood level determinations in this study makes it impossible for the authors to make any statement concerning such drug interactions.

We agree with the authors (1) that " . . . blood levels of propafenone do not correlate well with clinical efficacy . . . " However, two of the main metabolites of propafenone (5OH propafenone and ND propyl propafenone) have type IC electrophysiologic effects, and study of a correlation between blood levels and clinical efficacy has to take these considerations into account.

Furthermore, because multiple studies have reported that mexiletine only significantly prolongs the cycle length of the induced ventricular tachycardia, it could be argued that the improvement in antiarrhythmic efficacy of the tested drugs used in combination might mainly be linked to an increase in the plasma levels of propafenone as a consequence of mexiletine competition for the same metabolic pathway.

As a result of these pharmacokinetic alterations, one might observe an increase in either the electrophysiologic effects or in the side effects of the drug, or both, with all the attendant consequences.

To avoid unexpected and untoward consequences, the choice of antiarrhythmic combinations and the choice of dosage should be made with great care, especially when the drugs in question have a common metabolic pathway.

C. LIBERSA, MD, PHD
J. CARON, MD
F. BROLY, MD, PHD
D. LACROIX, MD
M. LHERMITTE, PHD
Services de Cardio Pharmacologie and
Laboratoire de Toxicologie du Département de Biochimie
CHU de Lille, Faculté de Médecine
1 Place de Verdun
59045 Lille Cedex, France

References

1. Yeung-Lai-Wah JA, Murdock CJ, Boone J, Kerr CR. Propafenone-mexiletine combination for the treatment of sustained ventricular tachycardia. J Am Coll Cardiol 1992;20:547–51.
2. Hondeghem LM, Katzung BG. Time- and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. Biochim Biophys Acta 1977;472:373–98.
3. Libersa C, Caron J, Bechtel P, et al. Interest and limitations of phenotype determination of hydroxylation ability in patients treated with propafenone. J Electrophysiol 1987;1:5:466–74.
4. Funck-Brentano C, Turgeon J, Woosley RL, Roden DM. Effect of low dose quinidine on encainide pharmacokinetics and pharmacodynamics: influence of genetic polymorphism. J Pharmacol Exp Ther 1989;249:134–42.
5. Mikus G, Gross AS, Beckmann J, Hertrampf R, Gundert-Remy U, Eichebaum M. The influence of the sparteine/debrisoquine phenotype on the disposition of flecainide. Clin Pharmacol Ther 1989;45:562–7.
6. Haefeli WE, Bargetzi MJ, Follath F, Meyer UA. Potent inhibition of cytochrome P450IID6 (debrisoquin 4-hydroxylase) by flecainide in vitro and in vivo. J Cardiovasc Pharmacol 1990;15:776–9.
7. Broly F, Libersa C, Lhermitte M. Mexiletine metabolism in vitro by human liver. Drug Metab Dispos 1990;18:362–9.
8. Broly F, Libersa C, Lhermitte M, Dupuis B. Inhibitory studies of mexiletine and dextromethorphan oxider in human liver microsomes. Biochem Pharmacol 1990;39:1045–53.
9. Broly F, VanDamme N, Libersa C, Lhermitte M. The metabolism of mexiletine in relation to the debrisoquine/sparteine-type polymorphism of drug oxidation. Br J Clin Pharmacol 1991;32:459–66.

Reply

We thank Libersa and colleagues for their thoughtful comments. The additional information regarding the metabolism of mexiletine may be very important to the understanding of the propafenone-mexiletine interaction. The potential competition for metabolism