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Calcium Channel Blocking Drugs and Anesthetics: Is the Drug Interaction Beneficial or Detrimental?

ALTHOUGH CALCIUM CHANNEL BLOCKING drugs had been widely used in Europe and Japan before 1981, the first studies of the interaction between the prototype calcium channel blocking drug, verapamil, and anesthetics did not appear until that year.[1,2] My editorial accompanying the second report suggested that significant cardiovascular interaction was likely to occur because of the similarity in pharmacologic effects of calcium channel blocking drugs and, especially, inhalation anesthetics; and that considerable research activity in this area would be forthcoming.[3]

Certainly, the latter prediction has been fulfilled. To date, at least 20 publications document the pharmacologic interaction between anesthetics and calcium channel blocking drugs *in vitro*,[4-6] in open chest animals,[7-10] in closed chest animals,[11-20] and in humans.[21-25] The three calcium blocking drugs available for clinical use in the United States, verapamil, nifidepine, and diltiazem, have all been studied, as has nicardipine, a nifedipine derivative, in clinical trials in the U. S. at the moment.

There has also been additional evidence for the similarity between the pharmacologic effects of anesthetics and calcium channel blocking drugs. Bosnjak and Kampine showed depressant effects on sino-atrial node conduction by halothane, enflurane, and isoflurane to be similar to those of the cardioactive calcium blockers (verapamil and diltiazem).[26] Lynch demonstrated that halothane[27] and enflurane[28] appeared to have calcium channel blocking activity, while isoflurane appeared to affect intracellular calcium kinetics more.[29] The previously demonstrated negative inotropic and vasodilatory effects of the inhalation anesthetics are similar to those of the calcium channel blocking drugs.[30,31] In particular, isoflurane appears to more closely resemble the dihydroperidine blockers (nifedipine and nicardipine), while halothane and enflurane bear a closer relationship to the cardioactive calcium blockers, verapamil and diltiazem.[15-17] Nevertheless, the combination of the two classes of drugs had been shown to produce minimal hemodynamic effects when clinical concentrations of both were used in animals.[11,12,14-17] However, the most recent study on the interaction between calcium channel blocking drugs and inhalation anesthetics in this issue of the journal appears to contradict these observations. Priebe and Skarvan studied the effect of adding isoflurane to dogs basally anesthetized with fentanyl-droperidol and given an infusion of diltiazem.[10] They saw marked, dose-related depressant effects of isoflurane on all aspects of ventricular function, both right and left. In a slightly different protocol, Kapur and co-workers had looked at the effect of increasing plasma levels of diltiazem during steady state, low concentration (1 + MAC) isoflurane.[14] Plasma levels equivalent to those documented by Priebe and Skarvan produced minimal effects on ventricular function, with only slight depression of left ventricular dP/dt and elevation of pulmonary artery occluded pressures being seen. Of particular note, there was no change in heart rate, mean aortic pressure, or cardiac index. Another open-chest preparation was employed to look at the interaction between halothane (1% inspired) and verapamil in a similar preparation without measured plasma verapamil levels.[9] Low dose verapamil (320 μg/kg cumulative over a period of 60 min) produced marked depression of ventricular function with significant increases in left ventricular end-diastolic pressure and end-diastolic fiber length, and a 38% decrease in stroke volume, 32% decrease in cardiac output, 39% decrease in left ventricular dP/dt,

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Address reprint requests to Dr. Merin, Department of Anesthesiology, University of Texas Health Science Center at Houston, 6431 Fannin, Room 5020, Houston, TX 70030.

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and a 50% decrease in peak aortic blood flow acceleration. At comparable halothane concentrations and probable verapamil plasma levels, Kapur *et al.*[12] and Chelly *et al.*[15] again saw minimal effect of the combination of low-dose halothane and verapamil on hemodynamic performance. The only other previously published study of the interaction between anesthetics and calcium channel blockers which reported a marked interaction in depression of ventricular function was that of Kates *et al.*[7] Using a left heart bypass preparation in the dog, these authors showed marked depression of ventricular function by very low plasma concentrations of verapamil and subanesthetic concentrations of isoflurane. Subsequent studies by Kapur and co-workers[12] and Rogers *et al.*[16] showed minimal effects on ventricular function at considerably higher isoflurane and verapamil doses in both acute and chronic closed-chest preparations. A pattern now emerges which serves to explain the discrepancies among the studies of anesthetics and calcium channel blocking drugs. In closed-chest animals, including swine[11] and dogs in both acute[12-14,20] and chronic models,[15-19] only with high doses of anesthetics (greater than 1.5 MAC) and/or high plasma levels of the calcium blockers were clinically significant hemodynamic interactions observed. In fact, the major detrimental interaction in both the acute and chronic studies was related to severely depressed atrioventricular conduction and sinus arrest, which resulted in severe bradycardia (less than 30 min^{-1}) resistant to treatment unless the inhalation anesthetic was discontinued. The studies in humans conducted with low-dose calcium blockers and low concentrations of the anesthetics[21-25] also showed minimal hemodynamic interaction. On the other hand, all experiments conducted in open-chest, heavily instrumented animals have shown marked depression of ventricular function produced by the interaction of both diltiazem and verapamil, and halothane and isoflurane. The only exception studied the response of the open-chest dog to one bolus dose of nifedipine during 1 and 2% halothane.[8] This predominant vasodilator calcium blocker produced minimal hemodynamic effect, even with 2% halothane, suggesting that the dihydroperidine calcium blockers may be better tolerated, even by the open-chest animal. Another dihydroperidine calcium blocker, nicardipine, also produced only vasodilation and arterial hypotension, even during deep isoflurane anesthesia in the chronically instrumented closed-chest dog.[17]

In retrospect, these observations are predictable. It has been shown that verapamil is much more depressant to ventricular function in patients whose ventricular function is already compromised by disease.[32] Consequently, it would be expected that high concentrations of inhalation anesthetics, which do depress ventricular function, would produce more interaction with even low concentrations of the cardioactive calcium blocking drugs. In like manner, the addition of beta adrenergic blocking drugs given intravenously to intravenous calcium channel blocking drugs also produced significant depression of ventricular function, especially in the presence of the potent inhalation anesthetic, halothane.[20] It has also been well demonstrated that the open-chest, instrumented animal is a very different physiologic preparation than even acutely anesthetized, closed-chest animals, and certainly than chronically instrumented, closed-chest animals.[33,34] The fact that subtherapeutic concentrations of verapamil and subanesthetic concentrations of isoflurane produce such marked hemodynamic depression in the open-chest animal[7,10] is graphic demonstration of this observation.

Although the calcium channel blocking drugs may be of some use given intravenously during anesthesia, the more common clinical problem is the management of patients who have been chronically treated with these drugs. It is probably not warranted to extrapolate interactions from intravenously administered calcium blockers, even with steady-state plasma levels, to patients chronically treated with oral drugs. Bonow and co-workers have shown that the effect of intravenous versus chronic verapamil is different in patients with hypertrophic cardiomyopathies.[35] Our laboratory has recently studied the effect of chronically administered verapamil and the three inhalation anesthetics, and have found that, even at higher plasma verapamil levels than those measured in our acute experiments, the hemodynamic effects of the inhalation anesthetics were quantitatively less.[19] In addition, Kapur and co-workers have shown that patients treated with a combination of beta blockers and nifedipine tolerated high-dose fentanyl anesthesia for coronary artery revascularization without difficulty, and even showed no undue depression of ventricular function when verapamil was infused intravenously during anesthesia.[25] Finally, patients taking calcium channel blockers preoperatively were not observed to have any conduction block in the perioperative period, even when concurrent beta adrenergic blocking drugs were also being taken.[36]

Consequently, it would appear that, in patients with reasonable ventricular function for most surgery (possibly excepting open chest), clinical concentrations of the inhalation anesthetics and reasonable doses of calcium channel blocking drugs are well tolerated. In fact, the use of calcium channel blocking drugs during anesthesia may be beneficial for the treatment of supraventricular tachycardias, hypertension, or coronary spasm. However, the administration of intravenous verapamil or diltiazem during open chest surgery in patients with depressed ventricular function anesthetized with potent inhalation anesthetics may well be associated with further decreases in ventricular function. These drugs should be administered cautiously, if at all, under these circumstances. There is no evidence to date that the patient chronically taking calcium channel blocking drugs represents a significantly increased risk for anesthesia and surgery without other complicating factors. In general, then, the drug interaction between general anesthetics and calcium blocking

drugs, when both are used properly, is beneficial rather than detrimental.

ROBERT G. MERIN, M.D.
Professor of Anesthesiology
Department of Anesthesiology
University of Texas Health Science Center at Houston
Houston, Texas

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