More News About Calcium Antagonists

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If this keeps up, calcium antagonists are going to get a very bad reputation. Already, in some circles, reports of adverse cardiovascular, gastrointestinal, and now neoplastic consequences have generated a strong avoidance reaction. How justified is such a response? How solid are the data upon which the reaction is based? What is a reasonable posture for the responsible physician? Specifically, for those whose primary interest has been hypertension, how should this new information influence our decisions? What must patients be told? Where do we go from here?

Calcium antagonists are powerful agents with multiple effects. The short acting variety have long been used in the management of a variety of vascular conditions in pursuit of therapeutic as well as preventive benefit. Much, if not all of the early justification for their use derived from a combination of preclinical and clinical studies employing surrogate endpoints. These studies appropriately focused upon physiological or pathological features of the vascular system. In many cases, the desired effect was achieved. For example, blood pressure reduction has been readily achieved with a minimum of side effects. Effects on symptoms and pathological expressions of vascular disease have also sometimes been quite favorable. Presumably, in view of these findings, calcium channel blockers have achieved enormous popularity in the treatment of coronary artery disease states and, by extrapolation, in the control of high blood pressure.

WHAT SHOULD WE KNOW?

Were physicians justified in building a treatment strategy based on this kind of data? The ideal and widely accepted gold standard for determining the value of therapeutic interventions is the prospective randomized controlled trial. Calcium antagonists have generally not been subjected to such rigorous analysis. The reason, of course, for demanding this level of evidence is that although we may select drugs to accomplish a health goal because of a demonstrated effect on a single physiological parameter or pathological process, what we really care about is the overall health effect of the drug. Drugs invariably have effects that go beyond those sought or anticipated. Indeed, they frequently have wholly unanticipated consequences. Thus, a full scale prospective trial, having morbidity and mortality as endpoints, may yield results contrary to those anticipated based on surrogate endpoint studies. Antiarrhythmic agents are only one case in point.

WHAT HAVE WE LEARNED?

Regrettably, the report from Pahor et al, in this issue of the American Journal of Hypertension, is but one more in a growing list of disturbing findings that bring into question the safety of immediate release calcium antagonists. Multiple bits of trial data in the treatment of coronary artery related disease has suggested that cardiovascular mortality may be increased in those treated with calcium antagonists. Observational data in hypertensive patients found the incidence of myocardial infarction to be increased in patients receiving calcium antagonists in comparison to other antihypertensive agents. Then, in a study recently published in Lancet, the suggestion has surfaced that gastrointestinal bleeding may also be a problem for calcium antagonist treated patients. None of these studies, by themselves, are conclusive. All involve, almost exclusively, the short acting variety of calcium antagonist. The results seen with the short acting forms cannot automatically be extrapolated to apply to the more recently introduced long acting calcium antagonists.

What then can we make of the available data? First of all, it seems reasonable to admit that the enormous popularity achieved by calcium antagonists over the
past decade was based more on promise than performance. Physicians treating coronary artery disease turned to these agents in advance of confirmatory clinical trial data on hope generated by intermediate evidence. That is always a gamble, and in this case, it was not a winning one. The disturbing data from Psaty, Furberg, and others should be a cautionary note. The physician's primary responsibility is to do no harm. Almost certainly, some harm was done by virtue of the exuberant acceptance of claims for calcium antagonists.

**SHORT ACTING CALCIUM ANTAGONISTS**

From the vantage point of 1996, it seems reasonable to conclude that the enthusiasm for short acting calcium antagonists was premature. Suspension of the demanding rules for proving benefit and ensuring safety has produced unfortunate consequences. Doctors acted in advance of the data that ought to be required before replacing traditional therapies with promising, but unproven nostrums. The case in regard to antihypertensive therapy is particularly stark. Short acting drugs (save verapamil) did not gain Food and Drug Administration approval for the treatment of high blood pressure. That they continue to be used and even recommended for this purpose is a matter of considerable concern. There is simply no data to justify the use of any short acting calcium antagonist in the treatment of high blood pressure.

The treatment of coronary artery related syndromes is nevertheless far short of its goal. Tools to relieve symptoms, retard disease progression, and extend healthy life are far from optimal. The reduction in coronary artery disease morbidity and mortality predicted for antihypertensive therapy has not been achieved. The pharmaceutical industry appropriately strives to identify and develop new means to overcome these deficits. In short, although effective and beneficial drugs are available to treat these cardiovascular conditions, therapeutic gaps still need filling. It is not that medicine is naked before its cardiovascular enemies, but that it lusts after more powerful weapons. In these circumstances, the conservative will discard the useful tools of the present only in the face of certainty that the replacements will be better.

**LONG ACTING CALCIUM ANTAGONISTS**

That, of course, brings us to the current issue. What is the proper role for the longer acting stablemates of the calcium antagonists? The claims that such agents differ sharply and meaningfully from their short acting predecessors are justified. The effects of these agents on important measurable physiological phenomena are demonstrably different from the short acting types. They do not generate the reflex increase in sympathetic activity, marked hypotension, or effect cardiac rhythm as do their short acting predecessors. But, the critical question remains. What patients care about is not isolated, individual effects, but rather the sum total of all the actions of these agents. In short, they, and presumably their physicians, want to know, first and foremost, how these agents effect the quality and duration of their lives. Prospective randomized clinical trials can provide the answer to those questions. Unfortunately, despite their wide use, no such evidence exists for short or long acting calcium antagonists.

**CURRENT OPTIONS**

What should we do pending arrival of the gold standard information? One option is to repeat the sorry experience of short acting calcium antagonists. Good theoretical evidence supports the clinical application of the long acting drugs. Well designed and executed comparative trials have shown sustained release calcium antagonists to perform at least as well as other antihypertensive agents and, in some subgroups, with even greater success. We can take the chance and prescribe these very expensive drugs in the hope that effects on surrogate endpoints will translate into genuine health benefits. The dangers described here by Pahor, and elsewhere by others, derive from studies of short acting agents, are primarily based on observational study, and tell us nothing of the overall risk-benefit relationship associated with their use. Long acting agents may be very different and produce benefits so far in excess of any hazards that they could become the antihypertensive agents of choice. But that is based on hope (or hype) and not evidence. The best we know for sure is that long acting agents are not short acting.

**THE PRUDENT PHYSICIAN**

In view of what we know, how should the prudent physician, and particularly those treating hypertension, behave? What do their patients deserve to know? While sustained release calcium antagonists control blood pressure and reduce ventricular mass, they possess no uniquely desirable effects in terms of performance or cost. At the same time, there are particular cases when the sought for goal cannot be produced by any other agent. That seems to be a situation in which to turn to calcium antagonists.

Prudence therefore dictates that first choice should be reserved for agents whose value and safety have been demonstrated. When calcium antagonists are chosen, physicians should be aware of the facts and share them with their patients. Controlling blood pressure prevents morbidity and reduces mortality. This has been consistently demonstrated in many clinical trials, in different populations, with different characteristics, when diuretics and β-blockers were
the main therapeutic agents. Our first antihypertensive choice should therefore be one of these two. When they are unacceptable or unsuccessful, a long acting calcium antagonist is sometimes the next best available choice. Thus, we take a chance in the hope that the known health benefits associated with a lowered blood pressure, demonstrated for other agents, will transfer to these unproven drugs. JNC V had it right. Diuretics and β-blockers first—others when necessary or specifically indicated.

Where do we go from here? As always, more data and less talk would be helpful. Prospective, randomized trials—particularly the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) comparing diuretics, angiotensin converting enzyme inhibitors, α-blockers, and a long acting calcium antagonist—are underway. We who treat hypertension can confidently rely on proven strategies, eschewing any course correction until compelling positive evidence appears.

REFERENCES