The Calcium Channel Blocker Controversy - A Caution to Physicians and Pharmacists

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Recently I attended a presentation that implied that the use of calcium channel blockers after myocardial infarction was detrimental. It was suggested that physicians and pharmacists should avoid prescribing and dispensing of calcium channel blockers in this population.

The two year controversy over the efficacy and/or harmful effects of calcium channel blockers began with a meta-analysis by Furberg et al (1) and continued with many more meta-analyses (2), case-control studies (3) and clinical trials. The conclusions of these studies have led many physicians and pharmacists to believe that calcium channel blockers are hazardous not only in post-infarction patients, (4) but also in stable angina and hypertensive patients (3).

It is now obvious that the results of those studies should have been approached with greater care and caution as many authors have described the failure or limitations of these studies. For example, the meta-analyses have been highly criticized in the literature for reasons such as: classifying and including the calcium channel blockers as a single class rather than three separate classes (5), inclusion of short-acting immediate release calcium channel blockers which has the potential to skew the data towards negative effects, (6) and the failure to separate trials which used treatment in acute vs chronic stages (3). One author suggests that Furberg's attempts to deem short-acting calcium channel blockers as “detrimental” in chronic stable angina is questionable (3). Nonetheless, it is well known that long-acting or sustained release calcium antagonists should be used in preference to short-acting immediate release calcium antagonists (7) in hypertension and chronic stable angina. The case-control retrospective studies (3) have been criticized for suffering from “indication bias”. The first lesson to learn from these examples is that studies using immediate release calcium channel blockers should not be analyzed to critically evaluate the use of sustained release calcium channel blockers. As Furberg quoted, “if the intermittent reflex increases in sympathetic activity associated with these short-acting formulations are responsible for the increased risk of mortality, then it is possible that the long-acting versions may be entirely safe” (2). Recently, clinical trials have shown that sustained release calcium channel blockers, nifedipine and verapamil (7), (8) and (9) reduces the number of coronary events in patients with chronic stable angina. In two studies (7, 8) they compared the use of a beta-blocker to the calcium channel blocker and concluded that the two classes of the drugs produce the same outcomes with regards to mortality and serious cardiovascular morbidity (7). Further the calcium channel blockers should be divided into three separate classes rather than one. Furberg, stated that, “the principal mechanism of action of calcium channel blocking agents are peripheral and coronary vasodilatation. The relative potency of the pharmacological actions varies among calcium antagonist; thus, their clinical effects may be different. These differences, however, are likely to be differences of degree rather than kind” (2). I think most will agree that the increase in potency brings about a difference in pharmacological activity i.e., sympathetic reflex.

The safety of calcium channel blockers after myocardial infarction is questioned. Since previous studies, SPRINT I (10), II (11) and INTACT (12) have included short-acting calcium channel blockers (5), allowing the data once again to be skewed, and rendering proper interpretation of data impossible. The question asked by many physicians is still unanswered, however the World Health Organization and the International Society of Hypertension states that there is no need for revisions in most existing guidelines (hypertension and stable angina) and to proceed with caution in other instances (13). Shortly after these recommendations, Psaty and Furberg criticized the WHO-ISH for errors of omission, selective use of evidence and epidemiological principles and narrow application of the viewpoint of mega-trials (14).

To resolve this controversy, the limitations, which have been pointed out, should be addressed and avoided in future meta-analyses and clinical studies. Researchers, physicians and pharmacists should become aware of

the limitations of these studies and interpret literature carefully before alarming the millions of patients and prescribing doctors. Unfortunately, this controversy has already skewed the minds of many physicians and pharmacists.

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