Do Calcium Antagonists Increase the Risk for Malignancies?*

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Calcium antagonists have been used for the treatment of cardiovascular disorders for more than a quarter of a century. Until very recently, physicians were under the impression that these drugs were efficient, well tolerated and safe. Over the past 3 years, calcium antagonists have been accused of increasing the risk of heart attacks, arrhythmias, strokes, gastrointestinal and intraoperative bleeding, Parkinson’s disease, systemic lupus, acquired immune deficiency syndrome (AIDS), malignancies, cognitive dysfunction and suicide. The sheer multitude and heterogeneity of these accusations are puzzling. Perhaps even more puzzling is the fact that most papers bringing these adverse events to our attention stem from the pen of the same few investigators. Most puzzling, however, is the unparalleled new media coverage that accompanied these retrospective studies, causing much unnecessary anxiety and even panic among our patients.

Cardiovascular disorders, such as hypertension, hyperlipidemia and arrhythmias, commonly require treatment for years and even decades. Because morbidity and mortality of these disorders (particularly when mild) are relatively low, the benefits from treatment are comparatively small. Thus, the British Medical Research Council (MRC) study (1) allows us to calculate that almost 1,000 patients need to be exposed to antihypertensive therapy with a diuretic drug for 1 year to prevent one single stroke. Diuretic drugs are comparatively powerful drugs to prevent stroke, and benefits are easy to demonstrate. In contrast, the effects of beta-adrenergic blocking agents on strokes, and the benefits of beta-blockers and diuretic drugs on coronary artery disease, are considerably smaller. This means that numerous patients will be exposed to the adverse effects and cost of these drugs without ever harvesting any real benefit. Given this scenario of small benefits and longterm exposure, any potential risk of malignancy associated with drugs to treat chronic cardiovascular disorders has to be taken very seriously.

Chemical agents can increase the risk for malignancy either by being directly carcinogenic or by impeding the immunoresponse or apoptosis, or both. Direct carcinogenicity usually requires many years and even decades of exposure and is specific for certain malignancies only. In contrast, the effects of immunosuppression or inhibition of apoptosis can manifest themselves within a much shorter time frame and affect a much larger spectrum of malignancies. It is this latter mechanism (apoptosis) that is purported to be affected by calcium antagonists. In this regard, the report of Braun et al. (2) in the current issue of the Journal provides some reassurance. In a cohort of >11,000 patients, half of whom were receiving a calcium antagonist, no increase in malignancy was observed. Of note, most patients were receiving the short-acting forms of nifedipine, diltiazem and verapamil—the very same drugs that in much smaller studies were accused of carcinogenicity. Several other studies from powerful data bases also have refused the hypothesis of calcium antagonists increasing the risk of malignancies. Thus, in >4,000 patients of the West of Scotland Cancer Surveillance Unit (3), a retrospective analysis showed no increased malignancy risk. Similarly, a Danish cohort study (4) of >17,000 patients showed no excessive malignancy risk in those taking a calcium antagonist. In all four prospective, randomized trials assessing morbidity and mortality, the malignancy risk was lower in patients receiving calcium antagonists than in those receiving either placebo or diuretic drugs (Fig. 1) (5–8). Perhaps the most powerful set of data providing evidence against the possibility of calcium antagonists meddling with apoptosis stems from the Mayo Clinic. In 621 posttransplant patients with immunosuppression by cyclosporin, Tejtor et al. (9) found that there was no excess malignancy risk in those receiving calcium antagonists (despite comparable immunosuppression) compared with those who were not.

Do the data of Braun et al. (2) and other similar studies allow us to firmly refute the possibility that calcium antagonists are carcinogenic? Certainly not. Low grade direct carcinogenicity is a known entity (10). Clearly, further studies are needed in order to clarify these issues.
nicity may take decades to surface and cannot be ruled out by short-term (up to 5 years) trials however thoroughly they were designed. By the same token, the available data do not allow us to rule out that other drugs used to treat cardiovascular disorders, such as angiotensin-converting enzyme inhibitors, beta-blockers, antiarrhythmic agents or lipid-lowering or diuretic drugs, would not ultimately turn out to be low grade carcinogens. However, the above data set makes it extremely unlikely that calcium antagonists increase the risk of malignancy by affecting apoptosis or immunosuppression, or both. Thus, although we can be reassured to a great extent by existing data, we will have to continue to be vigilant with regard to carcinogenicity of all drugs that are used to treat cardiovascular disorders for years and decades.

References


