COMMENTARY

Is it safe to use calcium channel blockers in hypertension?

Calcium channel blockers are commonly prescribed for the treatment of hypertension. They lower blood pressure effectively and possess certain theoretical advantages, such as their neutral effect on lipids and ability to reverse left ventricular hypertrophy. Hitherto, they have been considered very safe because serious adverse effects are uncommon, and they can be prescribed in patients with diabetes, gout, peripheral vascular disease, and renal impairment. However, there are no data on their efficacy in reducing cardiovascular events and mortality. Recently, doubts have been raised about the safety of calcium channel blockers and there is currently a heated debate in medical journals, conferences, and the media.[1]

It has been known for some time that calcium channel blockers may not improve the prognosis in unstable angina and acute 'Q-wave' myocardial infarction. Indeed, Furberg et al recently concluded that high doses of short-acting nifedipine cause increased mortality in patients with coronary heart disease, although their meta-analysis has been strongly criticised.[2] Nevertheless, it is generally accepted that calcium channel blockers are useful to many patients for control of blood pressure and anginal symptoms. However, the recent case control study by Psaty et al suggested that the use of calcium channel blockers in hypertensive patients was associated with an increased risk of myocardial infarction compared with the use of diuretics or ß-blockers, and raised new doubts about this class of drugs.[3]

Three points need to be stressed. Firstly, case control studies are retrospective and are generally inferior to randomised controlled prospective studies. Secondly, it is easy to confuse association with causation—as an example, you are more likely to see a doctor when you are ill but seeing a doctor does not make you ill. Thirdly, 'risk' is a statistical jargon that does not imply causation, and is therefore highly misleading in this context.

Psaty et al set out to investigate if there is any association between antihypertensive drugs and myocardial infarction (MI). Patients with MI were the subjects and hypertensive patients with no history of MI were the controls. By examining medical records, the pharmacy database and speaking to surviving patients, demographic data, medical information, and risk factors were documented. Although the methodology was sound, there were flaws.

In an ideal case control study, subjects and controls should be closely matched in all respects. However, in this study, the subjects were more likely to be male, had significantly higher blood pressure, longer duration of hypertension, higher cholesterol, higher incidence of diabetes, higher incidence of smoking, were less physically active, and had twice the incidence of angina and claudication compared to the controls. If anything, the study confirmed that these are indeed potent risk factors for MI. Since there was an excess of risk factors in the MI group, the occurrence of MI was explained to a large extent. Relevant information that was not available to the researchers included obesity, stress and renal disease. Although there were systemic differences between subjects and controls, analysis did not need to be abandoned because the figures could be 'adjusted' using statistical methods. Needless to say, this process, though valid, is arbitrary. Indeed, the risk ratios reported were calculated after up to 17 adjustments (for 17 covariates). Randomisation is the best way of ensuring that the groups under comparison are matched, and this is the single most important reason for conducting randomised trials.

The authors were, of course, aware that calcium channel blockers are prescribed for angina and therefore the prescription of these drugs may simply indicate that the patient had coronary artery disease. They have allowed for this in their analysis. What is uncontrollable is the possibility that, with many antihypertensive drugs available, physicians choose a particular drug based on complex reasons, taking into account severity of hypertension, coexisting diseases and contraindications. These complex reasons may not be stated in the notes, nor may they be conveyed to the patients. For instance, a patient with mild uncomplicated hypertension may be prescribed a diuretic or ß-

blocker, whereas a patient with difficult-to-control hypertension, diabetes, gout, claudication, or angina may be given a calcium channel blocker, perhaps in addition to another agent. In other words, patients with angina, more severe hypertension, and contraindications for diuretics and ß-blockers (e.g. diabetes, gout, peripheral vascular disease) may be more likely to receive a calcium channel blocker. This is not mere conjecture but was actually the case in this study. The controls, i.e. patients who had not had a MI but were at risk, were significantly more likely to receive calcium channel blockers if they had diabetes or clinical cardiovascular disease.[3] Conclusions drawn from a case control study rests on there being more MI patients taking calcium channel blockers than would occur by chance. There were clear reasons why the MI patients were more likely to be taking calcium channel blockers. The authors were commendably circumspect in their conclusions and did not advocate any change in prescribing practice, whilst raising the possibility that high-dose calcium channel blockers may be harmful.

The complexity of the statistical analysis precludes a general debate on the validity of Psaty's conclusions. However, the study aroused a secondary controversy concerning the manipulation of medical opinion by drug companies.[1] Interested readers may follow this debate in The Lancet.[4] There is nothing unethical about a drug company defending the reputation of their products by legitimate means. If they wish to call on the services of renowned doctors sympathetic to their products, why not? I am confident that these doctors do not compromise their integrity when they appear to be endorsing certain drugs. I am equally confident that medical practitioners are not easily fooled by false propaganda. However, there is another side to this—rival drug manufacturers might "twist the knife" for their own gain. Some of them will preach that not all calcium channel blockers are equal and that second generation drugs may be safer. Since nearly all new calcium channel blockers are of the dihydropyridine group, I cannot see how these would not be tainted if first generation calcium channel blockers are found guilty.

The case against calcium channel blockers is far from proven. Large prospective trials (ALLHAT, HOT, INSIGHT and SYST-EUR) evaluating the impact of calcium channel blockers on cardiovascular events and mortality in hypertensive patients are in progress and the results will be known in the next few years. Until then, there is no need to depart from standard practice. Low-dose diuretics and ß-blockers are first-line agents in the treatment of essential hypertension in the absence of contraindications as their effects on reduction of cardiovascular events and mortality are proven.[5-7] Other agents, including calcium channel blockers, are useful second-line drugs to achieve good blood pressure control.

BMY Cheung, MA, MB BChir, MRCP, PhD
Lecturer in Clinical Pharmacology and Therapeutics
Department of Medicine
The University of Hong Kong
Pokfulam Road
Hong Kong

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