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Hypertension in the elderly and calcium antagonists

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Safety concerns have largely focused around observational studies. One such study, that of Pahor is of better design than several of the others and highlights the dangers of inappropriate use of nifedipine capsules in the very elderly especially if there is only borderline hypertension. Emergency BP reduction is seldom required, especially not in the elderly. Such patients need to be examined and individually assessed. Chronic therapy of systolic hypertension in the elderly can be by either initial diuretic as in the SHEP study, or by initial calcium antagonist, as in the SystEur study. Long or medium acting preparations of calcium antagonists are preferred. From the point of view of cost-effectiveness, diuretics are cheaper than calcium antagonists and probably easier to manage. In the middle aged, there are few or no outcome studies with calcium antagonists, and only a few with beta-blockers. When diuretics do not work, or can not be expected to work, combination of a diuretic with a beta-blocker or an ACE inhibitor or switching to calcium antagonist-based therapy may safely be considered. *J Clin Basic Cardiol* 1999; 2: 167–8.

Key words: calcium antagonists, hypertension, elderly

Hypertension and stroke are common causes of disability and death throughout the world. World wide, cerebrovascular disease is second in the rank order of deaths. Bearing in mind the World Health Organization-Harvard School of Public Health projection that in the year 2020 deaths from cardiovascular disease in developing countries will greatly exceed those from AIDS, we in South Africa are especially aware of the risks of leaving hypertension untreated. To achieve improved mortality in hypertension trials has been difficult because in the middle-aged subjects commonly tested, there are few complications. In elderly subjects, however, a number of convincing trials have shown the benefits of diuretic-based treatment of hypertension and, more specifically, treatment of systolic hypertension. Logically, the closer the patient is to the end of life, the more will improvement in one single important risk factor such as hypertension delay the end. A recent metaanalysis suggests that to prevent one stroke, 22 elderly patients would have to be treated for 5 years, compared with 113 younger patients [1].

In the elderly, it is recognized that middle-aged patients with essential hypertension will in all probability and in due course become elderly, thus creating the condition of essential hypertension occurring in the elderly. Here both the systolic and the diastolic levels are typically elevated. Second, there is a different condition, the specific result of the ageing process and loss of aortic and arterial elasticity, namely systolic hypertension with, however, a normal diastolic value. In either case, there are good reasons for reducing the afterload against which the heart works, and calcium antagonists are among the drugs theoretically most attractive. Recently, however, emphasis has fallen on the potentially adverse effects of these agents and on the lack of outcome studies.

Is there any mortality risk with calcium antagonists?

Almost all of the potentially adverse effects have been described in case control or cohort studies which are of nature observational, and therefore potentially defective in their conclusions. One of the best of such studies is the report by Pahor et al. [2] which is a prospective cohort study of good design with only a few defects. In essence, all individuals living in three American communities were incorporated into the study and then the diagnosis of hypertension made by a variety of methods including direct observation. The blood pressure over the time of the study observation was not followed, nor was compliance with drug therapy. The major finding in this observational study on the very elderly with mean age 78 years, was that short-acting

nifedipine (capsules) was associated with an increased all-cause mortality when compared with beta-blocker use, whereas verapamil had a mortality profile similar to that of beta-blockade. Diltiazem lay between nifedipine and verapamil. When corrected for confounders, only the effect of nifedipine was significantly adverse. The mechanism involved is suggested by the observation that the harm could be localized to those patients with an initial blood pressure reading of less than 160/90 mmHg and with “high” doses defined as more than 20 mg nifedipine capsules per day, in which the relative risk for mortality was 3.1, (ie, mortality increased by 310 %) with confidence intervals of 1.7–5.8.

It must be emphasized that this was an observational study and that it is impossible fully to correct for confounders such as treatment bias. An example could be as follows. The prescribing doctor, believing nifedipine capsules to be “most powerful” antihypertensive, deliberately chooses this drug for those thought to be more severely ill and requiring more rapid reduction of BP. Not surprisingly, because they are more ill to start with, those treated by nifedipine fare worse.

Nonetheless the issue of the use of nifedipine capsules in the elderly does raise potential concerns.

It also needs emphasis that the nifedipine used in the study of Pahor et al. was of the short-acting variety. Long-acting and slow onset of action calcium antagonists cannot be implicated on the basis of this study, and a recent retrospective cohort study suggests that harmful outcomes in the therapy of hypertension are more likely to be associated with short than with long-acting calcium antagonists [3].

Because there are no outcome studies in “emergency hypertension”, all recommendations are pragmatic. Thus the attending doctor has to “play it by ear”. But, it should be stressed, the administration of a powerful and rapidly acting drug such as nifedipine capsules in relatively high doses to very elderly patients who only have borderline hypertension is bad judgment and probably culpable clinical practice, with inevitably bad results.

Is there risk of myocardial infarction?

Any powerfully hypotensive drug can cause coronary underperfusion. It is not clear why the prescribing doctors chose a calcium antagonist in the observational study of Psaty [4] that claimed to link use of short acting formulations of these drugs to increased myocardial infarction. Other studies both observational [5, 6] and prospective [7] have shown that myocardial infarction is not a risk with correctly used calcium antagonist therapy.

Is there a cancer risk with calcium antagonists?

It has also been averred that cancer is a side-effect of calcium antagonist use in studies by Pahor on the same population as found the adverse effects of nifedipine [8]. Allegedly, all the calcium antagonists were to blame, although the numbers were extremely small. In my view, the Pahor study has been superseded and supplanted by another, bigger, more reliable study by Olsen et al. [9] in a Danish cohort of approximately 18,000 users. The introduction in Denmark in 1968 of a Central Population Register and each citizen's unique 10-digit personal identification number basically eliminates loss to follow up and allows specific identification of the calcium antagonist use. The number of cancer cases observed in these individuals, of which 68 % were aged 60 or over at the first entry of the three-year study, was compared with the rates from the Danish Cancer Registry. There was no difference in cancer incidence between those taking calcium antagonists and those in the cancer registry. Furthermore, in two prospective studies in the elderly (STONE and Syst-Eur) the incidence of cancer tended to fall rather than to rise in the group treated by the calcium antagonist. Therefore, in my view, the cancer risk is largely discounted.

Do calcium antagonists have outcome studies in the therapy of hypertension?

Although diuretics as first line therapy in the elderly are well established on the basis of a number of trials [10], beta-blocker monotherapy is not [11], the latter being associated with no improvement in outcome and (by subgroup analysis) an increase in cardiovascular mortality. Indirect evidence is that combined diuretic plus beta-blocker treatment is beneficial [12]. Two commonly used alternate therapies are ACE inhibitors and calcium antagonists. Currently there are no outcome studies available with ACE inhibitors. Recently, outcome studies have appeared in which a calcium antagonist was used as initial therapy. In the single-blind STONE study, nifedipine tablets (not capsules) were given twice a day to elderly subjects with initial BP levels of about 168/96–100 mmHg [13]. Compared with placebo, stroke and heart failure were both reduced by over half with significant confidence intervals. The trial has been criticized for its design, and the very low cholesterol Chinese population is not typical for the Western societies.

Hence the Syst-Eur (Systolic European) study on systolic hypertension in the elderly becomes relevant. The study was presented by Dr Staessen, the chief investigator, at the European Society of Hypertension meeting in Milan (June, 1997). The calcium antagonist nitrendipine, a seldom used drug of the nifedipine family, was given twice a day to elderly patients with systolic hypertension (mean initial BP 174/86 mmHg). Additional therapy by an ACE inhibitor and/or a diuretic was allowed to reduce the blood pressure adequately, to mean values of about 153/78 mmHg. Of 2390 subjects given active treatment, 1758 were followed for one year, 1285 for two years, 979 for 3 and 705 for four. Corresponding figures for the placebo group were 2297, 1683, 12235, 928 and 682. The results, published in detail in [7], show a large reduction in stroke without any increase in adverse events such as cancer, myocardial infarction, or bleeding; rather, in every case there was a downward trend in the incidence. However, it should be noted that a significant portion of the patients – possibly about one-third – were on co-therapy with the ACE inhibitor and/or a diuretic. Nonetheless, the SystEur study does much to show that, when correctly used, calcium antagonists of the medium acting nifedipine-like family can be used with benefit and safety in systolic hypertension.

This study does not show the superiority of the calcium antagonist over other therapy, largely diuretic based, which is also very effective in stroke reduction [1]. Rather, the SystEur study supports the proposal that when correctly used, with

full knowledge of their pharmacological effects, the calcium antagonists are useful antihypertensives with outcome benefit.

A remaining problem: Should nifedipine capsules be used for the acute therapy of very severe hypertension?

First it is important firmly to distinguish between a true hypertensive crisis and a pseudo-emergency, such as the doctor on call wishing to be home for supper. A true emergency needs full examination and assessment of the patient. There can be very few occasions in which acute BP reduction is really required in patients without malignant hypertension, itself a rare condition. In general, the aim remains to bring down blood pressure slowly. Occasionally there is a true emergency that does require acute BP reduction by an oral agent, for example in primary care and especially in the rural setting in countries such as South Africa.

The guide-lines of the South African Hypertension Society are that a patient with very severe hypertension, thought to be life-threatening, should be admitted to hospital urgently. As this procedure might take some time or even days in the rural areas, the recommendation is for nifedipine 5 mg (not 10 mg) orally every 6 hours while the patient is referred and hospitalized the same day. This situation, a true emergency, does not correspond to the overall situation highlighted by Grossman and Messerli [14] in which nifedipine capsules (10 mg) were carelessly used and led to adverse side effects. Our extensive experience with carefully given and monitored nifedipine capsules has been documented [15]. Theoretically there should also be initial co-administration of longer acting therapy for example by a diuretic plus beta-blocker (especially if there is myocardial ischaemia) or ACE inhibitor (especially if there is heart failure). Initial use of a truly long acting calcium antagonist such as amlodipine or nifedipine GITS in severe/emergency hypertension is untested but should work well. According to present opinion, it is the long-acting calcium antagonists with slow onset of action that are, in general, much safer [3] so that the use of amlodipine or nisoldipine or long acting preparations of nifedipine or of felodipine or of isradipine might all be acceptable, although untried.

References

- Sanderson S. Hypertension in the elderly: pressure to treat? *Health Trends* 1996; 28:71–5.
- Pahor M, Guralnik JM, Corti M et al. Long term survival and use of anti-hypertensive medications in older persons. *J Am Geriatr Soc* 1995; 43: 1191–7.
- Alderman MH, Cohen H, Roque R, Medhagen S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet* 1997; 349: 594–8.
- Psaty BM, Heckbert SR, Koepsell TD et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; 274: 620–5.
- Jick H, Derby L, Gurewich V, Vasilakis K. The risk of myocardial infarction associated with antihypertensive drug treatment in persons with uncomplicated essential hypertension. *Pharmacotherapy* 1996; 16: 321–6.
- Braun S, Boyko V, Behar S et al. Calcium antagonists and mortality in patients with coronary artery disease: A cohort study of 11,575 patients. *J Am Coll Cardiol* 1996; 28: 7–11.
- Staessen JA, et al. for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; 350: 757–64.
- Pahor M, Guralnik JM, Ferrucci L et al. Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1997; 348: 493–7.
- Olsen JH, Sorensen HT, Friis S, et al. Cancer risk in users of calcium channel blockers. *Hypertension* 1997; 29: 1091–4.
- SHEP Study. Implications of the systolic hypertension in the elderly program. *Hypertension* 1993; 21: 335–43.
- MRC Study. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; 304: 405–12.
- STOP Study. Dahlöf B, Lindholm LH et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; 338: 1281–5.
- STONE Study, Gong L, Zhang W, Zhu Y, Zhu J. Shanghai Trial of Nifedipine in the Elderly. *J Hypertens* 1996; 14: 1237–45.
- Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies. *JAMA* 1996; 276:1328–31.
- Jennings A, Jee LD, Smith JA, et al. Acute effect of nifedipine on blood pressure and left ventricular ejection fraction in severely hypertensive outpatients. Predictive effects of acute therapy and prolonged efficacy. *Am Heart J* 1986; 111: 557–63.

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