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Discussing: L. H. Opie (Cape Town), Th. Stefenelli (Vienna), R. Gasser (Graz)

Calcium antagonists have always been a controversial issue. Recently developed, newer compounds have given rise to new questions. And, with every new answer we find, like with the outcome study SYSTEUR, new questions arise. Laboratory data and clinical studies have brought about conflicting results, and dissenting voices of experts make it difficult for the physician to decide which drug to use in which patient.

In the old Vinery of Prof. Gasser in Southern Styria, a small group of experts discussed recent developments and open questions on this subject in a relaxed atmosphere. The following pages will give a brief outline of the discussion led by Prof. Gasser (G), Graz, and Prof. Stefenelli (S), Vienna, with Prof. Opie (O), Cape Town. All three of them have worked substantially on calcium metabolism and Ca-channel blockers. J Clin Basic Cardiol 1999; 2: 153–4.

G: Newer dihydropyridines have a longer biological availability in the patient, which leads to less side effects. Does that make these drugs superior to earlier, short acting Ca-antagonists?

O: This would be the same as with a slow release form of nifedipine. Are newer dihydropyridines therefore superior to earlier, short acting dihydropyridines? In hypertension, the only calcium antagonist that had a positive outcome study is nitrendipine given twice a day and it had a very good effect in the SYSTEUR study. Other studies with positive outcome we have are on short acting verapamil and longer acting amlodipine.

G: Dementia and hypertension – a recently discussed issue. Do you see primary prevention of dementia as a strategic goal for antihypertensive treatment?

O: To me it is common sense that high blood pressure could be one of the factors promoting dementia, because the brain is soft, the pressure inside the arteries is very high and damages the arteries, little areas of necrosis may occur and so on. I don’t find this very difficult to accept. As far as I know, concerning Ca-antagonists there is only one good study, the nitrendipine study – as part of the SYSTEUR study, which is a prospective study. And they got results, which I don’t think are astounding, but they got results. You slow down the development of dementia using nitrendipine which is a twice daily Ca-antagonist, not really a long acting one.

G: What, in your view, would be the main argument for using Ca-antagonists in hypertension?

O: I suppose that the main argument for Ca-antagonists is that they generally work. They generally bring down the blood pressure and that is what people want. And the main argument against them is that they haven’t got outcome studies except for the SYSTEUR study, which is on elderly patients with systolic hypertension and there they work well – in the diabetic subgroup they were brilliant: total mortality was reduced.

G: Do you think that results from the outcome studies can be extrapolated to other dihydropyridines – or is that somewhat daring?

O: Well, the first issue is whether systolic hypertension is the same as ordinary hypertension. By definition, systolic hypertension occurs in the elderly, so it is a high risk group. The best results were found in diabetics, again a high risk group. Then, if you take the HOT study with felodipine, also a long acting once a day preparation, that had good results in the diabetics. In others, the results with HOT were not so outstanding. I don’t think that this reflects the Ca-antagonist use. I think that any agent would have been better in diabetics, because they are at higher risk.

G: Would you still treat any patient with nifedipine capsules for hypertension nowadays?

O: For standard hypertension, you would never use the short acting Adalat anymore. We still use it in South Africa for severe hypertension which theoretically one should hospitalise and treat intravenously – but that is rather difficult for a doctor far away from a hospital and working in the bush.

There are, however, various other indications for Adalat capsules, which one very rarely hears about nowadays: that is Raynaud’s phenomenon and coronary artery spasm.

S: What, in your opinion, is a subgroup of patients that you would treat with calcium antagonists as a first line drug?

O: Patients that come in with severe hypertension, and where I want a quick result and where I want a drug that is very likely to work. For me, in these cases, a calcium antagonist would be a good first choice. If you are talking about mild hypertension, no myocardial or coronary disease, no Raynaud’s phenomenon etc. than I think one has to go for the evidence based story of the use of diuretics.
S: And what about the combination hypertension and coronary artery disease?

O: You know that is an open question because, if you look at the β-blocker data, they are not so impressive in that condition. β-blockers do not actually prevent clinical coronary artery disease in hypertensives with coronary heart disease according to the metaanalysis.

S: Indeed, there is no primary prevention by β-blockers.

O: Yes, it does not appear that they do it. We don’t have many data that calcium antagonists do prevent CHD, but we have one study, the PREVENT study with amlodipine, which did reduce a variety of end points, but the patients were not actually hypertensives with angina. So, I think we do not have sufficient information. I guess, I might be quite interested in using verapamil for angina plus hypertension – but there are no data – just on first principles: it is a good antianginal drug, it does not cause tachycardia, it does not put up catecholamines … what would you say?

S: Coronary heart disease is the main disease that leads to myocardial infarction. Hypertension per se may intensify the progression of coronary heart disease or increase the risk of stroke. Hence, I believe that one should choose a drug which is a first line antianginal drug and preferably, at the same time, shows an antihypertensive capability.

G: I quote L. H. Opie from Cape Town: “… from these data, it would appear, that the long acting agents as a group do not have the adverse mortality effects that short acting nifedipine had.” Quote end. Is that still valid?

O: It is true that they don’t have the adverse effects. That does not say that they all have the wanted good effects.

G: If you could design a new Ca-antagonist, what specific properties would you look for? Which particular advantages should it have compared to the drugs we know?

O: It should have the properties of mibefradil, because this was vasoselective, antianginal, because it had verapamil-like properties – it is a sort of cross between verapamil and nifedipine – what it did not do, as far as I can see, is bring down neuro-humoral stimulation. An ideal Ca-antagonist should bring down neuro-humoral stimulation as well. It should reduce circulating noradrenaline.

S: And, of course, it should not have the drug side effects in terms of drug interactions that mibefradil had.

G: Is there any Ca-antagonist you know of which has all of these properties?

O: No, but verapamil has several of these properties.

S: Does the presence of pronounced left ventricular hypertrophy influence your decision of which drug to use – either an ACE-inhibitor, a Ca-antagonist a β-blocker or another drug?

O: The drug you choose must bring down the blood pressure.

S: But it takes 2–3 years to reduce LV hypertrophy with diuretics, whereas it takes a few months with ACE-inhibitors.

O: I am not sure that you are fully entitled to say that. There is a study in the American Journal of Hypertension (1998; 11: 631) in which it required 24 months to 3 years to induce regression with the ACE inhibitor as primary treatment. The interesting recent development is that there have been a few studies which show that diuretics do reduce LV-hypertrophy over time. There are now studies comparing ACE-inhibitors, Ca-antagonists and diuretics in this context. I believe that the major factor is blood pressure reduction.

G: Isradipine did not so very well in the MIDAS trial. Why do you think that happened?

O: I have a different interpretation from the authors – they say that at equivalent blood pressure reductions isradipine was less good than diuretics. In my opinion, they were not actually comparing exactly similar blood pressures. With blood pressure, just a few mm of Mercury may influence the outcome. If you look at the blood pressures achieved, the systolic blood pressure was higher with isradipine than with the diuretic. There are, however, a number of other studies which have suggested that diuretics actually reduce systolic pressure better than Ca-blockers.

S: There are dissenting voices concerning the use of Ca-antagonists in acute coronary syndromes …

O: There are no studies on long acting DHP Ca-antagonists such as amlodipine in unstable angina or acute myocardial infarction. And I don’t know of any studies being planned. But there are studies planned with verapamil and diltiazem.

G: Thomas, the long acting Ca-antagonists, which have half times of up to 50 hours, maintain stable blood pressure values over time. Do you think that this is important in the context of compliance?

S: If you take the drug once, instead of in the morning and at night, sure, the compliance will be better.

G: I remember, when I worked in Prof. Fleckenstein’s laboratories, in Freiburg, it was the time when amlodipine was discovered and we received the drug to test it and we saw that it had a very long action in our salt-sensitive hypertensive rats. We thought that this drug would most certainly never be used in humans because of this possible accumulative effect, but seemingly, it does not occur.

S: We have never seen such an accumulative effect. In this aspect, the drug appears safe. Even over weeks, giving higher doses of the drug, we did not see a further drop in blood pressure.

G: Did UKPDS change your view on treating hypertensive patients?

O: UKPDS, the HOT study and SYSTEUR happened all around the same time. All these studies changed one’s point of view and it is very clear that diabetes is a major risk factor for hypertension and it is also very clear that if you treat diabetics, you get a better result than when you treat non-diabetics. The UK study showed that, in diabetics, it seems more important to treat hypertension vigorously than to treat high blood sugar.
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