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The rationale of using calcium antagonists in the treatment of ischaemic heart disease

E. Kickenweiz, H. Köppel, B. Moosbrugger, R. Gasser

Calcium antagonists were discovered in the late 60s by Albrecht Fleckenstein and co-workers, who also solved the question of the action of calcium antagonists on the slow calcium channel. Since then, enormous developments have taken place and calcium antagonists have found a broad application in the treatment of hypertension as well as coronary heart disease. Drugs such as verapamil and nifedipine have proven useful in the long-term treatment of coronary heart disease. In particular, these drugs did not show any development of tolerance as, for example, nitrates did.

Many studies have shown that calcium antagonists have a solid place in the treatment of ischaemic heart disease. They dilate coronary arteries and decrease oxygen consumption. Newer compounds in second and third generation dihydropyridines such as amlodipine, lercanidipine and lacidipine have revolutionized calcium antagonist treatment. These newer drugs do not show an effect on the cardiovascular system like early dihydropyridines did (tachycardia etc.). This article explains the rationale of using calcium antagonists in the treatment of ischaemic heart disease and the mechanisms of the principle underlying this type of treatment. *J Clin Basic Cardiol* 1999; 2: 181–6.

Key words: calcium antagonists, ischaemic heart disease

Calcium antagonists (Ca-antagonists) have been used for more than two decades in the treatment of coronary heart disease. Their use was initially promoted for variant angina, but soon expanded to all forms of coronary heart disease entailing stable and unstable angina. On the basis of promising experimental findings, these drugs were also given in the treatment of myocardial infarction, however with disappointing results. The same was true for secondary prevention. The basic principle underlying Ca-antagonist therapy of ischaemic heart disease is the improvement of myocardial oxygen balance. On the one hand, Ca-antagonists (in particular verapamil and diltiazem) reduce myocardial oxygen demand via negative inotropic and chronotropic action – on the other hand, the afterload is reduced by peripheral vasodilatation. In addition, coronary dilation improves oxygen delivery, especially during exercise. Ca-antagonists inhibit trans-sarcolemmal calcium influx, thus preventing deleterious myocardial calcium overload, as seen during ischaemia and in atherosclerosis. Indeed, recent human studies have proven a preventive effect of calcium blockers against atherosclerosis.

The discovery of Ca-antagonists and their principle of action has revolutionized cardiovascular therapy in the course of more than twenty years. Since their discovery, the therapeutic spectrum of these drugs has constantly increased. It covers certain forms of arrhythmias as well as hypertension and coronary heart disease. In this context important developments have taken place. The positive effect of Ca-antagonists is attributed to the reduction of afterload via a decrease of peripheral resistance, the lowering of myocardial oxygen demand and the inhibition of calcium overload in cardiac and vascular tissue. The anti-atherosclerotic effect of these drugs has also been discussed. The latter has been evidenced in numerous animal experiments and by a number of multicenter trials in patients [1].

Ca-antagonists can be effectively used in the treatment of the following conditions: stable as well as unstable angina, hypertensive heart disease and transient ischaemia as well as myocardial “stunning”. The specific Ca-channel blocker diltiazem has been used effectively in order to treat acute non-transmural infarction. Other studies, however, point out that the use of

Ca-antagonists during acute myocardial infarction is problematic, in particular in patients with left ventricular dysfunction.

In secondary prevention, Ca-antagonists have failed and it has been generally accepted that they should not be used. Ca-antagonists of the dihydropyridine-group increase heart rate and can be effectively combined with betablockers [2]. The uses of different types of Ca-antagonists require a differentiation of patient classes as well as substance classes.

Recent research has been directed to the development of highly specific and more selective subgroups of Ca-antagonists: For example, dihydropyridines show little negative effect on inotropy and tend to decrease reactive neuro-humoral activation which, in turn, is favourable for the treatment of ischaemic cardiomyopathy. This article gives an overview of the various types of Ca-antagonists and their use in the treatment of coronary heart disease.

Historical review

In 1882 Sydney Ringer changed his laboratory assistant. The result was that his isolated perfused Langendorff hearts stopped beating. It took some time until Ringer found out that his former laboratory assistant used the dirty water of the Thames, while his new assistant used distilled water in order to produce the solutions for the perfusate. The dirty river Thames contained enough soluble calcium to allow contractility. From this laboratory accident results our knowledge that calcium is needed for electromechanical coupling [3]. Thirty years later, Cow investigated the effect of calcium on isolated smooth muscle. Ebashi later described the interdependence between actin, myosin, troponin and ATP-activity together with calcium [4].

Ca-antagonists have been used for a long time in order to treat coronary heart disease. More than three thousand years ago, the Chinese started to use tea from a plant called Dan Shen, that contains a naturally available Ca-antagonist called “Tanshinone”. The drug was used in Chinese medicine in order to treat angina pectoris [5].

In 1963 Albrecht Fleckenstein was asked to investigate a substance called “iproveratril” (later verapamil) and “prenyl-

amin". Fleckenstein and co-workers found that these substances affect myocardial contractility as well as smooth muscle tone. This effect could be compared to the effect of calcium withdrawal: When calcium was added to the solution, contractility recovered [6]. Fleckenstein was the first to postulate the principle of calcium antagonist action [7]. Only ten years later, Lewis and co-workers [8] began to use these drugs in the treatment of hypertension. Around the same time, the first dihydropyridine Ca-antagonist was discovered. It was a substance called "Bay a 1040", which was used earlier as a yellow colouring pigment. Fleckenstein and co-workers then [9] showed that the substance has a highly specific vasodilator effect. In 1975 Nikajima and co-workers [10] found that there was another class of highly specific Ca-antagonists related to benzothiazepines: diltiazem. The blockade of slow calcium channels as a fundamental principle of calcium antagonism was first postulated by Kohlhart and Fleckenstein in 1972 [11]. Their work confirmed the earlier concept of calcium antagonist action as a slow channel blocker. Livsley and co-workers were the first to introduce Ca-antagonists for the treatment of angina pectoris [12]. Glossman and associates described receptor binding at the calcium channel for these substances in 1984 [13]. Several authors later described calcium antagonist myocardial protection, mainly Bourdellion, Henry, Clark and Fleckenstein [14–17].

Classification of Ca-antagonists

There are two major groups of Ca-antagonists: Group A (highly specific Ca-antagonists), and group B (less specific Ca-antagonists) [16, 18, 19].

Group A

This group of highly specific Ca-antagonists consists of 3 subgroups:

1. Dihydropyridine Ca-antagonists (nifedipine, nicardipine, nisoldipine, niludipine, isradipine, nitrendipine, amlodipine, flordipine, silvadipine, darodipine and others)
2. Verapamil-type Ca-antagonists (verapamil, gallopamil, anipamil, romipamil, tiapamil and others) and
3. Benzothiazepine-type Ca-antagonists (diltiazem and derivatives)

All Ca-antagonists have one thing in common: they inhibit the slow trans-sarcolemmal calcium influx without influencing sodium flow. Moreover, these Ca-antagonists are able to suppress "calcium dependent" action potentials without influencing "magnesium dependent" membrane phenomena [16]. These substances allow the suppression of calcium dependent electromechanical coupling in the ventricular myocardium up to 100 % without influencing sodium influx at these concentrations. The drugs bind stereo-specifically to characteristic receptor subunits of calcium transport proteins which act as slow calcium channels [16].

The subdivision of this class A of Ca-antagonists in subgroup 1 (verapamil), subgroup 2 (nifedipine) and subgroup 3 (benzothiazepine) is based on the WHO classification [18]. A simplified model allows the understanding of the distinctive actions of Ca-antagonists [20]: dihydropyridine Ca-antagonists mainly act on vascular smooth muscle cells and have vasodilatory effect. Verapamil-type Ca-antagonists also tend to dilate vessels, but reduce conduction velocity as well as pacing rate. Hence, they lead to a negative inotropic and chronotropic effect. Dihydropyridine Ca-antagonists may cause tachycardia as a result of a quick decrease in blood pressure via the baroreceptor reflex. Such a "reflective tachycardia" may cause an attack of angina pectoris. Another group of Ca-antagonists

has properties between group 1 and group 2: the so-called benzothiazepine Ca-antagonists and their derivatives. Diltiazem is not only cardiodepressive but also a strong vasodilator.

Group B

This group represents the less specific Ca-antagonists. Among these are prenylamine, fendiline, terodiline, caroverine, perhexiline, cinnarizine, flunarizine and bepridil [16, 20]. These substances have a lower affinity to the calcium channels and the calcium antagonist activity is less pronounced than in group A. They also affect the fast sodium current. Various papers have shown that this group of Ca-antagonists also affects magnesium-dependent bioelectrical membrane phenomena. Fleckenstein used this criterion as the second important principle of this differentiation between group A and group B of Ca-antagonists [16, 20]. Group B of Ca-antagonists is only rarely used in clinical treatment today.

Coronary artery disease and Ca-antagonists

The therapeutic spectrum of drugs that is available in order to treat coronary heart disease has various options. Not only interventional cardiology and bypass surgery, but also pharmacotherapy is used. The latter consists of nitrates, betablockers and Ca-antagonists. The multifaceted genesis of angina pectoris requires different strategies and a differentiated use of Ca-antagonists.

Basic pathophysiological principles of coronary artery disease

In this context we would like to point out the different pathogenic principles of coronary artery disease. The basic principle is an imbalance between oxygen delivery and oxygen demand. This can be rooted in an increased oxygen demand of the myocardium on the one hand, on the other hand, it can occur secondary to a decreased coronary blood supply. In most cases, we find a mixed form where reduced coronary flow is unable to provide the substrate and oxygen desired by the myocardium [21–24]. Decreased coronary delivery can have various reasons: vasospasm, concentric and eccentric coronary stenosis as well as partial or complete coronary occlusion. The different forms of coronary insufficiency named can also be mixed. In most cases it remains unclear which components are predominant. What remains is a strategy of trial and error, which, however, underlie certain principles, of course.

Ca-antagonists in the treatment of coronary artery disease

Albrecht Fleckenstein was the first who alluded to the possibility of a therapeutic use of Ca-antagonists in the treatment of coronary artery disease [7]. Later work by Maseri and co-workers has constantly indicated coronary spasm as one of the important causes of myocardial ischaemia. In this context, Ca-antagonists have become an important tool in the strategy of treating coronary artery disease [25]. Moreover, certain limitations of other coronary therapeutics, for example, tolerance development in nitrate therapy demand therapeutics such as Ca-antagonists. In particular, Ca-antagonists with a negative chronotropic and inotropic effect which at the same time enact a vasodilative effect (verapamil) seem to be excellent therapeutics for the treatment of coronary artery disease [26, 27]. In this context, we also would like to mention the combination of dihydropyridines and betablockers.

The anticalcinotic and antiatherosclerotic effect of Ca-antagonists (Fleckenstein) have opened a new era of calcium antagonist therapy in coronary artery disease. Numerous animal experiments, as well as a couple of larger clinical trials, have underlined this effect of calcium antagonist drugs [1, 20, 28–33].

Mechanisms of action and indications for Ca-antagonists in patients with coronary heart disease

The detailed mode of action of various subtypes of Ca-antagonists will not be discussed in this context, but can be found in the references [eg, 1, 20, 34, 35]. In brief:

1. In principle, Ca-antagonists act via a relaxation of epicardial as well as intramyocardial coronary arteries and lead to an increase of oxygen delivery as well as to an inhibition of coronary spasm. The latter plays an important role in the genesis of angina pectoris [20, 36].
2. Ca-antagonists also cause vascular relaxation by acting directly on the smooth muscle cell in the peripheral artery. Thereby, peripheral resistance is decreased and so is afterload. This, in turn, leads to a reduction of myocardial oxygen demand and improves myocardial oxygen balance. The intensity and frequency of angina pectoris attacks will hence be decreased [20, 36, 37].
3. The blockade of calcium influx in myocytes of the working myocardium will decrease ATP consumption, which leads to a decrease in oxygen- and substrate demand. In clinical terms, this leads to a decrease in angina [20, 36].
4. The prolongation of conduction velocity leads to a negative chronotropy of Ca-antagonists, which prolongs the duration of diastole and leads to an improved cardiac output as a result of an improvement in the Franck-Starling mechanism. In this context, the oxygen consumption is decreased also [20, 38].

The clinical efficacy of Ca-antagonists in the treatment of coronary heart disease is evidenced by:

1. Subjective decrease in the frequency of angina attacks [24, 36, 39, 40] as well as in a decreased use of nitrates [24, 36].
2. Decrease of heart rate and blood pressure under therapy (heart rate may not be decreased in the presence of dihydropyridines, this phenomenon was described and discussed first by Loaldi [32] – the lack of decrease of heart rate is prominent during exercise [24, 36–38].
3. Increased exercise tolerance, which improves life quality for the patient [24, 36–40].
4. Reduction in exercise induced ST-depression [39, 40].

How, when and which Ca-antagonist to use in the treatment of coronary artery disease

Vasospastic angina

The importance of vasospasm in the genesis of coronary heart disease was already described in 1959 by Prinzmetal. Time and again we find patients with angina pectoris and a normal coronary angiogram. In many of these cases, the vasospastic form of angina is the predominant cause. However, the pathophysiology of vasospastic angina has not yet been elucidated completely. The importance of vasospasm in the context of the development of myocardial infarction has been discussed by numerous authors [22, 25, 41–46]. In this context, it could be shown that, in many cases, sudden cardiac death as a result of myocardial infarction did not occur together with occlusive thrombosis in any of the coronary arteries [47, 48].

Coronary spasm can be induced by cold, stress and various unknown factors. It is likely that also endothelial factors as well as platelet borne substances play a role in this context [49, 50].

Neurogenic mechanisms have also been suggested as causal for coronary artery spasm [51–53]. Dihydropyridines constitute an excellent means in order to thwart vasospastic angina.

Rafflenbeul has clearly shown the effect of intravenous nifedipine in coronary spasm [54]. Numerous other authors have confirmed the data and the use of dihydropyridines in the treatment of coronary artery spasm, which nowadays is an established concept [55–57]. However, there are also data that show that verapamil as well as diltiazem show positive effects upon coronary artery spasm [56]. On the other hand, there are also hints that nifedipine and diltiazem are more effective than verapamil [58]. In summary, we can say that Ca-antagonists, in particular dihydropyridines, constitute an excellent means for the treatment of vasospastic angina. In serious cases of vasospastic angina, the intravenous use of dihydropyridines has also been described [59].

The advantage of Ca-antagonism lies in the lack of tolerance development (unlike nitrates).

Numerous papers allude to the superiority of dihydropyridines over nitrates [eg, 55].

Silent ischaemia

The pathophysiology of silent ischaemia has not been elucidated so far. The spontaneous occurrence in the presence of physical and psychological stress suggests a vasospastic component. Hence, Ca-antagonists are highly effective in the treatment of such episodes.

Betablockers, however, have proved superior to Ca-antagonists in this concern. Rizzon and co-workers have shown that such silent episodes of ischaemia can well be managed with nifedipine (120 mg/day) or verapamil (480 mg/day) both being superior to nitrates [60]. Repetitive ischaemic episodes may lead to “myocardial stunning”, which can be also treated very well by Ca-antagonists.

Stable and exercise induced angina

A. Eccentric coronary arteriosclerosis

Stable angina based on eccentric coronary artery disease is well suited for treatment with dihydropyridine Ca-antagonists. The reason for this observation is that eccentric atherosclerosis still has contractile sections of the arterial wall, which can be dilated when Ca-antagonists are used. Since this can lead only to a partial vasodilation, the combination with a negative inotropic or chronotropic substance like betablockers seems prudent and has various advantages. Therefore, the combination of betablockers and Ca-antagonists has been recommended because the betablocker component will prevent an increase in heart rate, secondary to a reduction in blood pressure and, at the same time, will reduce oxygen demand [61]. It has also been shown that the combination of dihydropyridines with betablockers is superior to a combination of nitrates with betablockers. This combination exerts a favourable influence upon the left ventricular function during exercise [62]. Diltiazem has also been used effectively in this context for therapy of coronary heart disease. Extensive work in this field has been performed by Subramanian [36].

B. Concentric coronary arteriosclerosis

In the case of concentric coronary artery sclerosis, Ca-antagonists may have a negative effect [5, 32, 36, 37]: In particular, Ca-antagonists of the dihydropyridine class may lead to a peripheral vasodilatation and, via the baroreceptor reflex, to an

increase of heart rate and, more importantly, to the so-called steal phenomenon:

The vascular bed in other sections of the coronary artery that are not affected by atherosclerosis is dilated – as a result, blood is “stolen” from the areas that are situated distally from the concentric atherosclerotic lesion. The latter is stiff and can not be dilated [63, 64]. Hence, Ca-antagonists are less likely to be successful in the treatment of this type of coronary artery disease. However, in combination with beta-blockers, dihydropyridines can be given as well as diltiazem [61, 62].

Ca-antagonists of the benzothiazepine-type as well as verapamil are well suited for this type of coronary artery disease in stable angina [36, 38–40, 65]. The following drugs have been shown as ideally suited compounds: gallopamil, verapamil and diltiazem.

However, the main effect of these drugs in this particular subtype of coronary artery disease is the decrease in oxygen consumption of the myocardium as a result of negative chronotropic and negative inotropic effects. More than 10 years ago, the combined use of verapamil and propranolol was propagated [66, 67], however, this combination seems dangerous, because it can lead to AV-block III and asystole [68, 69].

It should also be noted that during physical exercise, the relative tension of the arterial wall can be increased (possibly a result of increased catecholamines) [70] and, as a result, coronary artery dilation via Ca-antagonists could be even more effective under exercise than at rest [70, 71]. This results in improved oxygen delivery and could be the main source of the antianginal effect of nifedipine [2, 71]. Another important patho-mechanism in ischaemic heart disease is increased “diastolic stiffness” of the myocardium, which is an early manifestation of ischaemia [2, 72]. Verapamil improves left ventricular filling, but does not affect diastolic ventricular function to the same extent [72–74].

Unstable angina

Unstable angina may be very different from stable angina as far as its pathophysiology is concerned. It is largely rooted in vasospastic forms of angina and in intermittent coronary thrombus formation [75–77]. Clinically, it appears as angina at rest and requires hospitalization of the patient with intravenous therapy in order to avoid progression to myocardial infarction. Dependent upon the possibilities and the severity of unstable angina, the intracoronary and the intravenous administration of Ca-antagonists have proven useful [54, 55]. In a “cross-over study” with intravenous nifedipine the results were better than those with intravenous nitroglycerine. It was shown that ischaemic episodes can be better controlled [78].

Previtali and co-workers have treated patients with a tendency to spastic angina using oral nifedipine, diltiazem and verapamil as well as in unstable forms of angina. All 3 types of Ca-antagonists have been shown as highly effective in the prevention of ischaemic attacks, whereby diltiazem and nifedipine have been more effective than verapamil [79].

However, verapamil has still shown a better antianginal effect than propranolol [80].

Ischaemic cardiomyopathy

Most Ca-antagonists with negative inotropy should be avoided in this condition. They will further decrease the already deficient left ventricular function. Especially the negative humoral effects in dilated cardiomyopathy can be potentiated by short

acting dihydropyridines, benzothiazepines and verapamil type of Ca-antagonists. Here, one would prefer nitrates and ACE inhibitors.

Often such patients suffer from an adrenergic overdrive that leads to tachycardia. Betablockers have been used effectively to counteract this adrenergic overdrive. This results in an improved diastolic filling and thus in an improved haemodynamic situation of the heart. Some studies using newer generations of Ca-antagonists are on the way and results are not yet available. As far as secondary prevention of myocardial infarction is concerned, Yusuf and Fuhrberg published a meta-analysis of long and short term investigations and showed an increased mortality (6 %) in patients who have been treated with Ca-antagonists after myocardial infarction. This analysis shows no favourable effects of Ca-antagonists in secondary prevention. Currently, the evidence for positive effects in certain subgroups of Ca-antagonists is scant and therefore we would currently not recommend those drugs in the treatment of myocardial infarction.

Primary prevention

Larger primary prevention studies for Ca-antagonists are rare. Lichtlen [31] looked at normotensive patients with coronary artery disease after 3 year's treatment with nifedipine and could show a certain degree of prevention of atherosclerotic plaque development. A number of experimental studies alluded to the antiatherosclerotic effect of Ca-antagonists. The link between arterial wall cholesterol and Ca^{++} is, however, still missing. Cardiovascular events such as myocardial infarction or sudden cardiac death were not reduced in this study, progression of coronary artery disease was also not affected. These results have been supported by a Canadian study using nicardipine [81]. Klein [29] and co-workers as well as Kober and co-workers (personal communication) have found certain indications that diltiazem and verapamil would cause a regression of atherosclerotic plaques. However, these were retrospective analyses.

The recently published follow up data of the INTACT trial show a remarkable retardation of progression of coronary artery disease while, however, no favourable clinical effects of long term dihydropyridine administration have been seen in these patients and the number of cardiac deaths and non-fatal cardiac events was equal in both groups (patients with and without nifedipine). The vision of primary prevention of coronary heart disease using Ca antagonists will certainly take much more time to manifest itself in the real world of day to day practice. A lot of further clinical trials will be needed in order to allow a solid final statement on primary prevention with Ca-antagonists.

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