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Calcium antagonists: past, present and future – a personal view

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Calcium antagonists are now widely used in the management of patients with a variety of cardiovascular disorders, including angina pectoris and hypertension. The prototype of the group – the phenylalkylamine-based verapamil – lacked tissue specificity within the cardiovascular system. Its introduction triggered the search for other calcium antagonists with improved tissue selectivity and resulted in the introduction of a variety of dihydropyridine based compounds including nifedipine, nisoldipine, nitrendipine and felodipine. These drugs exhibited improved tissue selectivity relative to verapamil, but possessed unfavourable pharmacokinetic profiles resulting in short duration of action, short plasma half-lives and rapid onset of action. The resultant unfavourable side effects limited the efficacy of these compounds and although the introduction of slow release formulations attenuated some of the problems encountered during their use the search for a tissue selective calcium antagonist with an intrinsically favourable pharmacokinetic profile continued, resulting in the development of amlodipine.

Although a dihydropyridine, amlodipine differs from its predecessors in having a strongly ionized side-chain and an ability to insert directly into membranes lipid bilayers. This therefore provides the prototype of a third generation of calcium antagonists characterised by possessing a favourable pharmacokinetic profile (slow onset and prolonged duration of action coupled with a long plasma half-life) due to its own molecular structure. For purposes of classification verapamil can be regarded as the prototype of the first generation of calcium antagonists, nifedipine as the prototype of the second generation (improved tissue selectivity) whilst amlodipine is the prototype of a third generation (retained tissue selectivity with an intrinsically favourable pharmacokinetic profile).

Clinically amlodipine is an effective blood pressure lowering agent in hypertensives, where it also reverses left ventricular hypertrophy. Surprisingly amlodipine's safety extends to its long-term use in hypertensives with severely compromised left ventricular function – including chronic heart failure associated with non-ischaemic, dilated cardiomyopathy. *J Clin Basic Cardiol* 1999; 2: 155–61.

Key words: calcium antagonists, amlodipine, hypertension, non-ischaemic cardiomyopathy, left ventricular hypertrophy

There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy

Hamlet 1..4

Thirty years have elapsed since calcium antagonists were introduced into western medicine as agents with potential benefit in the management of patients with cardiovascular disorders [1]. With verapamil as the prototype, these compounds were designated initially for use in patients with symptoms caused by coronary insufficiency [2], making patients with angina pectoris a natural choice [3]. With experience gained from their increasing use, however, and as many other chemically different antagonists became available, it became apparent that the spectrum of cardiovascular disorders which might be relieved by their use extended well beyond that of coronary insufficiency-hypertension [4] and certain types of arrhythmias [5] being quickly recognised as suitable targets for some of these agents, with others to follow.

The original calcium antagonists were phenylalkylamine derivatives, the prototype, as already mentioned, being verapamil [2]. This particular antagonist lacks any appreciable tissue selectivity within the cardiovascular system, a factor which quickly prompted the search for other compounds which, whilst retaining calcium antagonistic properties, possessed some clinically relevant tissue selectivity. Diltiazem – a benzothiazepine derivative [6] – and nifedipine – a dihydropyridine derivative [7] – were therefore soon added to the list of clinically useful drugs of this type. Once the relevance of the relative vascular selectivity of nifedipine [7] was appreciated there was soon a plethora of dihydropyridine-based calcium antagonists undergoing development, including nitrendipine [8], nisoldipine [9], nimodipine [10], nicardipine [11], and felodipine [12]. The broad aim of this development was

to provide potent calcium antagonists with improved tissue selectivity relative to that of the parent dihydropyridine – nifedipine. However, whilst improved tissue selectivity was an important goal, what was apparently overlooked in the early stages of the development of these drugs was the need to improve their pharmacokinetic profile – or maybe the early attempts were unsuccessful. However, the continued search for calcium antagonists with all the desired properties – retained or enhanced potency, improved tissue selectivity and an acceptable pharmacokinetic profile – has now provided an array of active compounds, mostly dihydropyridine derivatives (Table 1), one of which – amlodipine [13] – exhibits a pharmacokinetic profile which sets it apart from the others to such an extent that for this reason alone it can be regarded [14] as providing the prototype of a “third” group or generation of these drugs (Table 1).

Table 1. Proposed classification of the calcium antagonists

Generations:	First	Second	Third
	Verapamil Diltiazem Nifedipine	Felodipine Isradipine Nicardipine Nimodipine Nisoldipine Nitrendipine	Amlodipine

The first generation calcium antagonists are the prototype drugs. As a group they have unfavourable pharmacokinetic profiles, unless used as slow release formulations.

The second generation of antagonists exhibit enhanced tissue selectivity relative to the parent prototype, but require slow release formulations to prevent large swings in plasma levels, and rapid onset of action.

The third generation contains antagonists which retain tissue selectivity and whose own chemistry confers on them a favourable pharmacokinetic profile.

Tissue Selectivity

An important property of the calcium antagonists is their differing tissue selectivity. For example, whereas verapamil for all practical purposes is equi-effective with respect to the myocardium, vasculature, conducting and nodal tissue, making it a broad spectrum calcium antagonist so far as the cardiovascular system is concerned (Table 2), nifedipine has no direct effect on the conducting and nodal tissues at concentrations which render it more effective as a vasodilator than either verapamil or diltiazem (Table 2). Unfortunately nifedipine retains an effect on the myocardium, although certainly the ratio between its effect on the vasculature relative to that on the myocardium favours the vascular effect (Table 2).

Nifedipine was quickly followed by a plethora of other dihydropyridine-based antagonists, developed because of their enhanced selectivity for the vasculature relative to the myocardium, whilst having no direct clinically relevant effect on either nodal or conducting tissues. Some of these more recently developed dihydropyridine-based antagonists have pharmacological profiles which render them potentially useful for the management of problems within specific vascular beds. Nimodipine, for example, with its relative selectivity for the cerebral vasculature (Table 3), was developed primarily for use in the management of patients with cerebral ischaemia [10]. Nisoldipine provides another example of a dihydropyridine-based antagonist which exhibits some selectivity within the vasculature – in this instance for the coronary blood vessels [9]. Thus, enhanced tissue selectivity became an important hall-mark of the “second generation” calcium antagonists and created great interest and enthusiasm, but despite this improvement one other highly significant requirement was still lacking, as indeed it was in the “first generation” antagonists. This deficiency centred around their unfavourable pharmacokinetic profiles. Perhaps unfavourable is too harsh a word to apply to this deficiency, but in terms of their clinical use it was a major limiting factor. It was the search for a potent, vascular-selective calcium antagonist with a slow onset of action and a pharmacokinetic profile which would provide prolonged effective therapy without the need for multiple dosing throughout the day which led to the development of yet another calcium antagonist, amlodipine [13]. Not surprisingly the improved pharmacokinetic profile of amlodipine was accompanied by a significant reduction [15] in the intensity and occurrence of side-effects.

The amlodipine molecule: its chemistry, pharmacology and pharmacokinetics

Taking amlodipine as the prototype of the third generation of calcium antagonists, and before considering why the pharmacokinetic profile of this particular antagonist is so advantageous, some consideration should be given to its chemistry, its interaction with cell membranes and its general pharmacology.

Chemistry

As far as the chemistry of amlodipine is concerned, whilst it is a 1,4-dihydropyridine-based calcium antagonist it differs from other members of this group, including the prototype nifedipine, by the presence at the 2-position of the dihydropyridine ring of a side-chain which carries a basic amino group [13]. According to Burges and his colleagues [16] who developed this compound, it is the presence of this side-chain with its basic amino group which is primarily responsible for setting this particular dihydropyridine-based antagonist

Table 2. Tissue selectivity of some commonly used calcium antagonists

Calcium antagonist	Myocardium	Vasculature	Conducting & nodal tissue
Amlodipine	+	++++	-
Diltiazem	+	+	+
Felodipine	+	++++	-
Nifedipine	+	++	-
Nimodipine	+	++++	-
Nisoldipine	+	++++	-
Nitrendipine	+	+++	-
Verapamil	+	+	+

+ denotes relative selectivity; - denotes lack of effect

Note that amlodipine (a third generation antagonist) and felodipine (a second generation antagonist) have the same degree of selectivity for the vasculature. Their selectivity, however, exceeds that of nifedipine. Felodipine and amlodipine can be distinguished between on the basis of their intrinsic pharmacokinetic profiles. For example, felodipine has an elimination half-life of 15 hours, even when used in the extended release formulation. In comparison, the elimination half-life of amlodipine is 35–50 hours – see ref. [14] for details.

Table 3. The comparative vascular selectivity of some dihydropyridine-based calcium antagonists

Calcium antagonist	Coronary	Vascular Selectivity Cerebral	Peripheral
Amlodipine	+	+	+
Nifedipine	+	+	+
Felodipine	+	+	+
Nisoldipine	+++	+	+
Nimodipine	+	+++	+

+ denotes relative selectivity

apart from other chemically similar antagonists developed so far.

Radioligand binding studies [17] have clearly established that the primary site of action of amlodipine is within the dihydropyridine binding domain of the Ca^{2+} -channel complex, where it slowly associates with one particular region of the channel complex. This relatively slow rate of association – or “binding” – to the channel complex is clinically relevant because it explains, in part (Figure 1), why the onset of action of amlodipine is so slow relevant to that of other drugs of this type [13].

Radioligand binding studies also showed that amlodipine dissociates from its specific binding sites extraordinarily slowly [17] – a factor which must contribute to its prolonged effectiveness [18]. In this respect amlodipine differs from all of its predecessors, including felodipine and isradipine even when these are used as slow-release formulations.

There is one other peculiarity relating to the chemistry of amlodipine which warrants mention at this stage and it relates to the fact that the presence of the basic amino group on

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Figure 1. Schematic representation of the mechanisms which contribute to the slow onset and long duration of action of amlodipine [14]

the side-chain of its dihydropyridine ring renders the molecule highly ionized at physiological pH [13]. This is not just an erudite piece of information, since the presence of this ionized side-chain facilitates the insertion of the molecule into the lipid bilayer of cell membranes [19]. According to Tulenko and his colleagues [20] it is this ability of amlodipine to interact not only with the Ca^{2+} -channel complex itself but also with the lipid bilayer of the cell membrane which determines its overall pharmacological profile. Included in this profile is an ability to "reorder" cholesterol overloaded smooth muscle cell membranes, thereby rendering them less leaky with respect to Ca^{2+} . Tulenko and his colleagues [20] have shown quite convincingly that this ability to "reorder" leaky membranes would contribute quite substantially to such antiatherosclerotic effectiveness as amlodipine may have [21, 22].

In summary, then, as far as the chemistry of amlodipine is concerned it is more than just a curiosity. Indeed, it is highly relevant to the whole field of calcium antagonism, because for the first time it establishes that the inclusion of an ionized side-chain on the dihydropyridine ring of a dihydropyridine-based compound profoundly affects its profile, without either diminishing its efficacy as a calcium antagonist, destroying its tissue selectivity or providing it with an unfavourable pharmacokinetic profile [23].

Pharmacology

The pharmacological profile of amlodipine is now well documented [18]. Like nifedipine it potently inhibits Ca^{2+} induced contractions in vascular smooth muscle preparations but whereas nifedipine achieves its maximum effect within thirty minutes amlodipine requires many hours despite being approximately twice as potent as nifedipine [24]. This slow onset of action of amlodipine is not peculiar to vascular smooth muscle – it also applies to its effect on the myocardium where, although its depressant effect is at least five times less than that of nifedipine [24], it still takes several hours to develop. Thus amlodipine can be described, quite accurately, as a *slow acting, vascular-selective antagonist*.

The slow onset of action of amlodipine was not predicted when the compound was initially chosen for further study – indeed the drug was nearly abandoned when, after its initial injection into an anaesthetized dog no fall in blood pressure was evident within the first thirty minutes, at a time when the maximum dilator response to other currently available calcium antagonists would have been present or already passed its peak [Burgess, personal communication]. Now it is one of the key properties which sets this antagonist apart from all other currently available drugs of this type, because its slow onset of action is an inherent physicochemical property of the molecule and not dependent upon delivery by way of a slow release device – as is the case with all the other currently available calcium antagonists.

The slow onset of action of amlodipine in itself is a complex phenomenon. As already mentioned this is due in part to an abnormally slow rate of association with its binding site in the Ca^{2+} -channel complex [17]. This is only part of the explanation, however, because when given orally the drug has an usually long hepatic transfer time resulting in as many as twelve hours [23] being required before peak plasma levels are achieved. To put this in perspective felodipine even when used in the extended release form (ER), requires between two and eight hours [25], nitrendipine needs only two hours [26] and isradipine less than 90 minutes [27] to reach peak plasma levels after oral administration.

In summary, therefore, one of the novel pharmacological characteristics of the recently developed, dihydropyridine-

based calcium antagonist amlodipine is its slow onset of action, a property which sets it apart from any of its predecessors. Most of the calcium antagonists which preceded amlodipine are now available as slow or "extended" release formulations. Thus felodipine ER, nifedipine SR, diltiazem SR and verapamil SR are the commonly used formulations of these antagonists, but whilst this practice avoids the rapid-onset phenomenon encountered with the earlier formulations of these compounds and attenuates the large differences between peak and trough plasma levels which accompanied their use, it still does not achieve the relatively small variations in plasma levels obtained for amlodipine [23]. Obviously the absence of large differences in peak to trough plasma concentrations is important for any drug, if only because it facilitates the maintenance of a stable effect over the entire dosage interval. The importance of this becomes apparent when considered in terms of the higher risk of serious cardiovascular events occurring during the early morning hours, at a time when plasma levels of other calcium antagonists are often too low to be effective.

The delivery of other calcium antagonists as slow or extended release formulations certainly does have some merit in that it attenuates the large swings in plasma levels already referred to. However this does not mean that they share the advantages of amlodipine which, because of its own chemistry, is inherently long acting and has a smooth plasma profile. Its long plasma half-life involves a relatively slow rate of hepatic metabolism [23]. As a consequence of this the bioavailability of amlodipine is high – sixty to eighty percent after oral administration compared with only twenty two percent for felodipine ER, as an example [25].

Amlodipine has other advantages including a slow rate of elimination (Figure 2) [23] and a slow rate of dissociation from its binding sites in the Ca^{2+} -channel complex [22]. These are characteristics which, once again, are inherent properties of the molecule, thereby reinforcing the argument in favour of placing amlodipine in a category apart from any of the earlier antagonists which were developed and allowing it to serve as the prototype of a "third generation" (Table 1) of these drugs.

Returning to the pharmacology of amlodipine some mention should be made of its tissue selectivity, because if the molecule did not retain selectivity for the vasculature its use would be limited. Fortunately, at clinically relevant dose levels, it lacks any direct effect on nodal or conducting tissues [28], and is relatively selective for the vasculature [18] – including a dilator effect on the coronary arterial vessels at concentrations which have little or no effect (Figure 3) on the myocardium [24].

As far as the pharmacology of this recently developed dihydropyridine based calcium antagonist is concerned, there-

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Figure 2. Elimination half-lives (mean values) of a spectrum of first, second and third generation calcium antagonists, felodipine, nisoldipine and isradipine, being used in their SR formulations [14]

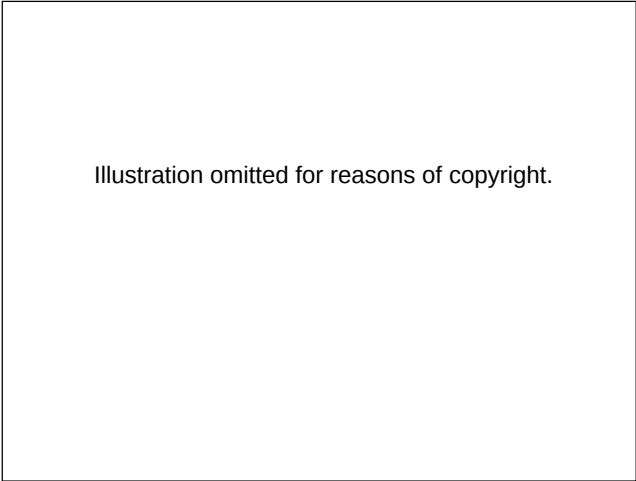


Illustration omitted for reasons of copyright.

Figure 3. Data relating to the inhibitory effect of amlodipine on tension development in isolated strips of human coronary artery and papillary muscle [24]

fore, it is a potent, vascular-selective agent with an inherently long plasma half-life, slow onset of and prolonged duration of action. These properties are an intrinsic property of the molecule and therefore should not be confused with the conditions which occur when relatively short-acting antagonists with a short plasma half-life are delivered by way of slow release formulations, because once these latter drugs appear in the circulation they naturally behave in accordance with their own chemistry. Slow release formulations of the earlier dihydropyridines therefore, whilst they certainly are advantageous relative to their own initial formulations, cannot be equated with amlodipine when considered in terms of its unusual but desirable pharmacokinetic profile because here it is the molecule itself which dictates that profile (Figure 1).

Pharmacokinetics

Mention has already been made of the unusual pharmacokinetic profile of amlodipine, a profile which allows it to be used on a "once a day" basis for the treatment of angina pectoris, hypertension and other cardiovascular disorders without inducing side effects caused by a rapidly developing vasodilator response or fluctuations in plasma concentrations. This unusual pharmacokinetic profile is characterised by a slow onset but long duration of action and a high bioavailability (Figure 1).

As already mentioned the slow onset of action involves both a slow rate of absorption due to a prolonged hepatic transfer time [23] and a slow rate of association with the Ca^{2+} calcium complex [22]. Its relatively high bioavailability is largely due to a slow rate of degradation by the liver [29] resulting, in turn, in a slow rate of elimination [25]. Some calcium antagonists, it should be recalled, undergo extensive first pass hepatic metabolism, resulting in a relatively low bioavailability. Other factors which contribute to the high bioavailability of amlodipine include an unusually large volume of distribution [18]. This is due to widespread tissue binding which in turn provides an *in situ* reservoir of the drug [18]. Some drug companies actually discarded amlodipine from their development programme, thinking that this large volume of distribution would be detrimental. To the contrary, it contributes to the long duration of the action which is so characteristic of this particular dihydropyridine.

Slow onset of action and high bioavailability are only two of the unusual pharmacokinetic characteristics of amlodipine.

The third is its long duration of action [18]. This is a complex characteristic, due, in part, to an abnormally slow rate of dissociation from its specific binding sites [17], its large volume of distribution and extraordinarily long elimination half-life, up to fifty hours for amlodipine, compared with fifteen hours for felodipine ER [25], for example.

The question which needs to be answered now is whether this unusual pharmacokinetic profile of amlodipine is clinically relevant. Alternatively, should this particular calcium antagonist be regarded as just another vascular-selective dihydropyridine based antagonist to be added to the ever increasing list of second generation calcium antagonists of this type?

The answer to this question is not difficult to find, given that the drug is effective when used on a "once a day" treatment basis, that it is well tolerated and provokes little if any bothersome side-effects [30]. The absence of troublesome side-effects is linked to its slow onset of action, such that the attendant reduction in arterial pressure develops slowly [13, 16] and therefore without triggering the reflex tachycardia, increases in cardiac output and raised plasma catecholamine levels and renin activity triggered by the more rapidly acting dihydropyridines [31, 32]. The benefit of the longer duration of action – whether it be due to a prolonged binding to the channel complex, increased bioavailability or enhanced volume of distribution –, is equally easy to establish, particularly when it is realised that major fluctuations in blood pressure persist when drugs and formulations that are short acting are used [33].

The classification of amlodipine as the prototype of a third generation of calcium antagonists – Is it justified?

Before considering some of the clinical data relating to the usefulness of this third generation calcium antagonist in the management of patients with certain types of cardiovascular disorders it is probably appropriate to consider precisely why amlodipine is being regarded as the prototype of a third generation of calcium antagonists (Table 1). Since it is a dihydropyridine it might have been imagined that it would be classed together with other vascular selective dihydropyridines – such as nitrendipine, isradipine or felodipine. However there are properties which set this drug quite apart from the other chemically related compounds. These properties involve:

(a) firstly, its unusual pharmacokinetic profile (slow onset and prolonged duration of action, as already discussed) and the fact that this profile is an inherent property of amlodipine's own molecular structure [16, 18, 23] and

(b) secondly, its ability to enter and re-order cholesterol-distorted membrane lipid bilayers and in so doing restore their normal function with respect to the control of membrane permeability, particularly with respect to Ca^{2+} [19, 20].

This almost certainly means that there are two ways in which amlodipine can ameliorate the Ca^{2+} overloading which is such an unfortunate feature of pathologically-injured tissues [34]. Firstly it can, by virtue of its ability to restrict Ca^{2+} entry by way of the L-type channels [13, 16], limit Ca^{2+} entry via this route – a property which it shares with other calcium antagonists. In addition, however, it can, by re-ordering the lipid bilayer of the membranes concerned, restrict their permeability with respect to Ca^{2+} [20].

Why, then, does amlodipine possess the properties described above (a, b) when they are absent from other dihydropyridine-based antagonists? Almost certainly what sets amlodipine apart from the other antagonists developed so far is the presence of

the side-chain on the 2-position of the dihydropyridine ring which carries a basic amino acid group, rendering the molecule charged at physiological pH. Is this the pattern for all future third generation calcium antagonists, one wonders?

Calcium antagonists and the treatment of hypertension

A wide variety of therapeutic agents are now available for use in the management of patients with essential hypertension. Ideally these agents should lower systolic and diastolic blood pressure, should not produce orthostatic hypertension, should lack undesirable side effects, have a favourable metabolic profile and should be long-acting and therefore available for use on a once-daily basis. In addition, their blood pressure lowering effect should be due to relaxation of the peripheral vasculature and not to a reduction in cardiac output, their continued use over long periods of time should not result in the development of tachyphylaxis and if possible they should attenuate some of the secondary consequences of hypertension, including atherosclerosis and cardiac hypertrophy. The question to be answered here, then, is whether the longer-acting calcium antagonists fulfil these criteria.

The recent HOT study [35] in which felodipine ER was used at a dose of 5 mg on a daily basis as part of a large study aimed primarily at establishing whether there is any correlation between the reduction in either systolic or diastolic blood pressure achieved and the occurrence of major cardiovascular events (non-fatal myocardial infarction, non-fatal stroke and cardiovascular death) has provided some very relevant data. Thus the study showed not only that the long-acting formulation of felodipine was effective in producing a sustained reduction in blood pressure on a once-a-day treatment basis but also that there was no increase in the incidence of cardiovascular events, including cardiovascular mortality [35], despite the inclusion in the trial of patients with previous histories of myocardial infarction or other forms of coronary heart disease. The results of the HOT study contrast with those reported for sustained release formulations of verapamil [36], or immediate release formulations of either nifedipine [37] or nisoldipine [38] but in these later cases pre-existing cardiac failure may have been responsible for the negative outcome. Indeed in some trials the same is true for felodipine [39]. The overall picture which is beginning to emerge, therefore, is that whilst calcium antagonists effectively lower both systolic and diastolic blood pressure in hypertensive patients, neither the first nor the second generation (Table 1) of these drugs can be safely used for long term therapy in patients with pre-existing heart failure. Data is rapidly accumulating relating to the efficacy of amlodipine as an effective antihypertensive agent, able to control blood pressure for twenty-four hours when given on a once daily treatment basis [40]. Whilst the efficacy of amlodipine as a blood pressure lowering agent has never been in doubt there are several questions which need to be addressed concerning its use in this regard. These are:

(a) Is its blood pressure lowering effect accompanied by a reduction in the attendant left ventricular hypertrophy?

(b) Does it worsen heart failure or increase the risk of death in patients with advanced left ventricular dysfunction [41]?

In some ways these two questions are linked, because left ventricular hypertrophy is a common and serious complication of hypertension with a possible correlation between the development of hypertrophy, the incidence of heart failure and the occurrence of cardiovascular complications [42], including arrhythmias [43].

Calcium antagonists and their effect on hypertension-induced left ventricular hypertrophy

Antihypertensive drugs are generally agreed as having disparate effects on left ventricular hypertrophy (LVH) independent of their blood pressure reducing activity [44, 45]. Thus, in a recent study in which captopril, hydrochlorothiazide and atenolol were all shown to cause a reduction in LVH over a treatment period of one year, clonidine and prazosin were ineffective in this regard, although they, too, effectively lowered blood pressure [44].

Felodipine ER is effective in reducing LVH [46] irrespective of whether it is used in conjunction with a beta-blocker [47]. Nifedipine [48], isradipine [49, 50], nilvadipine [51], slow release nifedipine [52, 53], nifedipine GITS [54] and nitrendipine [55] have all been shown to be effective. The ability of calcium antagonists to reduce LVH in hypertensive patients is, however, not peculiar to the dihydropyridine-based compounds. For example once-daily treatment with sustained release formulations of either diltiazem [56] or verapamil [57] can be effective. What then of amlodipine? Early laboratory studies in spontaneously hypertensive rats showed that it, too, reduces left ventricular hypertrophy in this animal model of the disease [14]. Its efficacy in man was established quite early in the history of its clinical use [58].

Calcium antagonists in patients with compromised left ventricular function: Are any of them safe?

Some readers of this short review might think this an odd question to be asking particularly when the early literature relating to the use of these drugs is peppered with clinical evidence relating to the use of these drugs leading to a worsening of pre-existing heart failure, resulting in an increasing risk of death in patients with advanced left ventricular dysfunction [36, 41, 59, 60]. Until recently this was thought to be a class effect, which was unfortunate because patients with left ventricular dysfunction often require treatment for other cardiovascular disorders – including angina pectoris and hypertension [61]. Now, however, and primarily because of the availability of amlodipine, this problem, is being reconsidered and investigated, with some impressive results [41]. Thus, in a recent study involving over a thousand patients with severe chronic heart failure and ejection fractions of less than thirty percent Packer and his colleagues [41] have found that amlodipine actually reduces the risk of fatal and non-fatal cardiac events in patients with non-ischaemic cardiomyopathy. The reduction is of the order of more than thirty percent, with the risk of death being reduced by more than forty five percent. This beneficial effect was found to be relatively selective, in that it applied to patients with non-ischaemic dilated cardiomyopathy, whereas patients with ischaemic heart disease did not actually benefit but at the same time did not exhibit any worsening of their condition [41]. Both these findings – a beneficial effect in patients with non-ischaemic dilated cardiomyopathy and the absence of a deleterious effect in patients with ischaemic heart disease – contrast with earlier results obtained during short term treatment with verapamil, nifedipine and diltiazem where clinical deterioration occurred [62–64], and during long term treatment of patients with left ventricular dysfunction, where there was an increased risk of worsening heart failure, myocardial infarction and death [60, 65].

Possibly then, there are three reasons why amlodipine can be regarded as the prototype of a new generation of dihydro-

pyridine-based calcium antagonists. Two of these reasons have already been discussed. Perhaps its relative safety when used in patients with non-ischaemic induced cardiac failure secondary to cardiomyopathy provides a third reason.

Conclusion

(1) On the basis of their tissue selectivity, pharmacokinetic profiles, molecular chemistry and clinical use the calcium antagonists can be divided into three classes, or generations. The most recently introduced drug, amlodipine, provides the prototype for the third generation partly because, although it is a dihydropyridine, its intrinsic chemistry differs from its predecessors. This difference centres around the fact that it is highly ionized at physiological pH, a property which allows it to penetrate into and modify the physio-chemical properties of membrane lipid bilayers. This third generation calcium antagonist therefore exerts a two-prong attack – one at the Ca^{2+} channel, where, like its predecessors, it slows L-type Ca^{2+} channel function and the other at the lipid-bilayer, where it exerts a normalising action.

(2) Amlodipine can also be separated away from its predecessors in terms of its pharmacokinetics – a slow onset of action, accompanied by a high bioavailability, long duration of action and a high volume of distribution. These are inherent properties of the molecule and therefore do not require the incorporation of the slow release mechanisms required by the first and second generation drugs of this type.

(3) Clinical usage of amlodipine has provided ample evidence of its efficacy as a blood pressure lowering agent in hypertensives, where it also reverses left ventricular hypertrophy. This almost certainly contributes to its overall safety.

(4) Importantly, there is growing evidence in favour of the conclusion that amlodipine's safety extends to its long term use in patients with severely compromised left ventricular function including the chronic heart failure associated with non-ischaemic dilated cardiomyopathy. This finding alone provides amlodipine with a status not yet enjoyed by any other currently available calcium antagonist and raises questions relating to the basis of its safety under these conditions. Does it reflect its molecular structure, its calcium antagonist activity, its pharmacokinetic profile or does it result from its ability to penetrate membrane lipid bilayers? The development of other third generation antagonists should help to answer these questions.

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