Why Ca$^{2+}$ antagonists will be most useful before or during early myocardial ischaemia and not after infarction has been established

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Anything that looks simple at the outside can be made to look complicated at the inside.

Recent publications in the medical literature have conclusively shown that calcium antagonists, in particular nifedipine$^{[1,2]}$ and verapamil$^{[3]}$, when administered after the signs of human myocardial infarction have become evident, cannot ‘reduce’ infarct size or avoid subsequent complications or decrease mortality. Yet, many physicians involved in cardiovascular pharmacotherapy continue to think that, because calcium antagonists have been so effective in improving coronary bloodflow and because they have been shown to have direct cardioprotective effects, they should be used in patients with proven acute myocardial infarction.

We believe it timely to reemphasize that these drugs, powerful as they are, should be administered only under the proper circumstances for the proper indications, as originally proposed by those carrying out the pharmacological research both in the experimental animal and in the human$^{[4-8]}$. It has never been shown, by any author, that Ca$^{2+}$ antagonists have a significant contribution to make once the cell membrane has been disrupted and the cardiac cell has died. Admittedly, the peripheral vasodilating action of these drugs may lower afterload and reduce the work of the heart as a whole, which may be important when a patient with a fresh infarct is also hypertensive. Furthermore, the coronary vasodilating action may, particularly in a marginally perfused peri-infarction zone or in the partially opened collateral bed, lead to an increased coronary flow but these must be considered to be of minor efficacy once the cells in the centre of the ischaemic area have died. On the other hand, dangers from excessively reduced arterial perfusion pressure would seem to be larger, particularly, when combined with tachycardia which is usual with nifedipine. Then there is the coronary ‘steal’ syndrome (or ‘paradoxical’ angina) reported to occur under some circumstances. In fact, it was this adverse phenomenon in relation to coronary perfusion pressure which robbed diprydamole of its initially promising role. All these aspects are negative. When one considers, in contrast, that calcium channel blockers have been shown to protect tissue threatened with ischaemia or in the very early phases of ischaemia, by slowing excessive Ca$^{2+}$ influx, by blocking early catecholamine release, by avoidance of high-energy phosphate break-down with suppression of attendant loss of purine derivatives, provided these drugs are given before or immediately after the ischaemic condition has been established, powerful support is given to those who advocate that these drugs have a place in the clinic only when used under similar circumstances. We$^{[4-6]}$ as well as Verdouw$^{[7]}$, De Jong$^{[8]}$, Harmesen$^{[9]}$, and Henry$^{[10]}$ have in various animal preparations under various circumstances, repeatedly shown that treatment with nifedipine, verapamil or diltiazem, renders the cardiac cell either impervious to ischaemic insult for several hours — or reduces the extent of damage to cell membrane and cell interior to acceptable proportions — allowing other interventions such as reperfusion efforts to be instigated, provided sufficient amounts of the drugs were present in the tissue prior to the ischaemic episode. Recently Yoshida et al. have shown that nifedipine treatment can actually limit infarct size over a period of up to 24 h$^{[11]}$, when given before interruption of the bloodsupply in contrast to other experiments, where the drug was given after ligation of the artery, in which case there was no protection.$^{[12]}$ Its
Figure 1 Myocardial ischaemia and reperfusion: events taking place in the cardiac cell shortly after ischaemia and or during reperfusion, most of which are related to rapid depletion of ATP and CP stores.

Use of Ca\(^{2+}\) antagonists

In the human has been shown by a multitude of authors\(^ {13,14}\), and both in open and in randomized double blinded studies\(^ {22,28,29,31,32,33}\) in unstable angina, a clinical situation in which intermittent ischaemia is classically present, to be effective, by reducing symptoms and signs of ischaemia within the first few hours. As in most of these study populations, the presence of early acute myocardial infarction cannot be excluded, the risk exists, as shown in the recent HINT study from the Netherlands, that the efficacy of these drugs may be masked or even to appear to be non-existent. However, efficacy has been shown when they were given as an adjunct to cardioplegia\(^ {12}\) and in various other conditions in which ischaemia is induced, such as during coronary occlusion while the coronary artery is dilated (and briefly obstructed) with a balloon catheter\(^ {13}\). All these data are consistent with a nearly complete protective effect against ischaemia for periods at least up to three hours from the onset of ischaemia as is convincingly shown in Fig. 2 to be the case for nifedipine.

It is understandable, therefore, that clinicians hope for similar beneficial action from these drugs to take place after ischaemia has been present for some time. After all, ‘Hope springs eternal’. It is the purpose of this review to reduce this thesis to wishful thinking. The arguments for denouncing the use of calcium antagonists once infarction has been established are based on two main tenets: (a) a proper understanding of the pathophysiology of the ischaemia in the human heart with its essential time-relationships and (b) a proper interpretation on the mode of action of calcium channel blockers on the cardiac cell itself.

It is generally accepted that ischaemic injury to the myocardium arises from an imbalance between myocardial oxygen supply and demand. When there is already considerable narrowing in one or more of the coronary arteries, with marked reduction in flow reserve, angina or ischaemia will manifest themselves when demand is suddenly increased as a result of augmented work of the heart. Such angina and attendant ischaemia will be brief because the patient usually reduces his effort and balance will be restored quickly. When the decrease in oxygen supply is primary, because coronary flow suddenly decreases as a result of abruptly increased vasomotor tone and resistance in the coronary arterial and capillary system or by a thrombotic obstruction, the degree of ishaemia is often more severe, but may still be reversible. When thrombosis is sudden and leads to complete occlusion, ischaemia nearly always leads to infarction, unless lysis of the clot occurs spontaneously (as may occur in 15% of the cases with suspected myocardial infarction) or is induced within hours. Since the latter now has been shown to be feasible, protection during 3–4 h from onset of symptoms or signs of ischaemia to ultimate reperfusion is a tremendous gain, if one aims for reversal of a potentially lost part of the myocardium.

Clinical proof will be difficult to obtain, and it
has yet to be established at which time these drugs are of no further benefit and could threaten the precarious balance or become actually detrimental.

Recent studies in Rotterdam\textsuperscript{[16,22]} have demonstrated that during balloon dilatation of a human coronary artery, up to 5 min of complete occlusion can be tolerated without any permanent defects. However, there is already within 10–20 s a rise in potassium, and lactate with hypoxanthine breakdown products of high energy phosphate metabolism in the efflux of the coronary circulation. Such biochemical markers of ischaemia denote, at least initially, a temporary metabolic disruption, which heralds the onset of cellular destruction. These abnormalities precede the other classical clinical signs of ischaemia, such as ST-segment elevation and changes in the mechanical performance of the heart (of which acute loss of diastolic tone and somewhat later impaired relaxation of the myocardium are the earliest to manifest themselves), enzyme release, anginal pain and arrhythmias. Other clinical observations have shown that even when desobstruction of coronary artery thrombosis by means of thrombolysis is successful within 30 min after the onset of symptoms, some myocardial damage has already become irreversible in the core of the ischaemic area. Thus, severe interference with coronary bloodflow lasting between 5 and 30 min will herald the beginning of infarction in the human, depending on the functional activity and the metabolic state of the myocardium immediately preceding the ischaemic episode. Hearts which are beating fast against a high afterload, particularly when there has been no pre-existing restriction in the myocardial blood supply and thus with poorly developed collateral flow, will be far more susceptible to extensive damage than hearts which are beating slowly and have ample reserve from coronary collateral flow. It is a well-known clinical observation, substantiated by autopsy evidence, that older individuals with coronary artery disease may show surprisingly little myocardial damage when their obstruction has been developing gradually with the coincident growth of collateral supply. Conversely, younger individuals, with their first myocardial infarction often have severe sequelae of their disorder. These variations will make the critical period during which any type of intervention could be effective rather longer as most patients with infarction are older.

In this regard the concept of a significant border zone, marginally perfused, but susceptible to manipulation by interventions has to be discussed. Hearse et al.\textsuperscript{[18]} in a succinct overview on the uncertainties of reduction in infarct size have speculated that 3 distinct states of reduced flow and ischaemic injury may (co)exist, which should determine the practicability of tissue salvage (Fig. 3). They distinguish between ‘tolerable’, ‘critical’ and ‘lethal’ ischaemia. In ‘tolerable’ ischaemia flow is reduced up to 50% and tissue energy stores are hardly depleted. The vasodilator characteristic of Ca\textsuperscript{2+} antagonists is dominant here in terms of reasonable therapy, keeping in mind that nifedipine also has been shown to delay or to block the release of catecholamines\textsuperscript{[19]}, which if excessive under these circumstances might lead to focal necrosis. In ‘critical’ ischaemia, flow is reduced to 20% of control. Intracellular energy levels are seen to decline, tissue becomes jeopardized\textsuperscript{[20]} and only timely (0–4 h) reperfusion can lead to recovery\textsuperscript{[17]}. It is in this stage that Ca\textsuperscript{2+} antagonists may have their ‘Finest Hour’\textsuperscript{[7]} in as much as they block the excessive calcium influx which, if left unchecked, would destroy the inner structure and functioning of the cell (Fig. 2). Nifedipine also improves flow particularly to the endocardium\textsuperscript{[7]}. All Ca\textsuperscript{2+} blockers reduce the inotropic activity of surrounding healthy tissue and thereby lengthen the period of time during which reperfusion efforts (thrombolytic therapy, PTCA or bypass grafting) may be undertaken. In ‘lethal’ ischaemia, where flow reduction exceeds 80% and tissue energy stores are rapidly depleted—tissue is ‘condemned’ to die, rather than ‘jeopardized’, unless flow is restored within 1–4 h after onset of symptoms. Recent data from the Netherlands\textsuperscript{[17]} have shown in 533 patients with acute infarction randomized either to conventional therapy in the CCU, 264 patients, or to early (within 4 h) thrombolytic therapy with streptokinase, 269 patients, that a strategy aimed at early and complete restoration of bloodsupply leads to marked reduction in 8 month mortality (8.5% vs 15.5% in controls). The fact that infarct size in the treated group was smaller (by 30%) and ventricular function—both regionally and globally—better (ejection fraction 53 vs 46%) indicates that the reduced mortality can be ascribed to the beneficial effect of rapid and early reperfusion. The best results (mortality of 1%) were obtained when i.v. administration of streptokinase within 2 h was followed by intra-coronary streptokinase and PTCA. It is in this setting of ischaemia without infarction that the cardioprotective effects of Ca\textsuperscript{2+} antagonists (with
or without beta blockade) would seem to have their greatest potential application. Whether or not in this context the concept of a borderzone is relevant becomes a moot point. In fact, we agree with Hearse and Yellon\textsuperscript{[21]} that the borderzone has a rather sharp though irregular boundary (Fig. 3).

Jennings \textit{et al.}\textsuperscript{[23]} have in animal studies, detected rather specific times for the onset of irreversibility. 20–60 min of severe ischaemia depending on the species, when arterial blood flow is reduced to below 85\% of control. This is lengthened to 60–180 min when flow was reduced to between 30–80\%. They showed that, after occlusion, the extent of the area at risk, which ultimately became completely necrotic after an ischaemic episode of only 40 min even with

\textbf{Figure 2\textit{(a)}} Four sections of left ventricular wall of untreated heart in which the left anterior descending artery was completely ligated: \textit{(upper left)} just before, \textit{(upper right)} one hour after, \textit{(lower left)} two hours after and \textit{(lower right)} three hours after ischaemia. It is obvious that the unprotected myocardium rapidly loses its cellular integrity.
subsequent perfusion, would be restricted to 30% whereas it would be larger, when the occlusion period before reperfusion extended to three hours.

All these considerations have been reviewed by Parratt\textsuperscript{[24]} in an excellent review of this subject in 1983. He concluded: 'On theoretical grounds there appear two possible approaches in human ischaemia:

1. Attempts to prevent infarction in patients who are most at risk such as those with unstable angina or those threatened with reinfarction after having suffered an earlier ischaemic, tissue damaging, event.

2. Attempts to reduce the most serious consequences of ischaemia, e.g. the suppression of life-threatening ventricular arrhythmias and

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Figure 2(b)  Sections of the left ventricular wall of heart pretreated with nifedipine\textsuperscript{[7]}. Note that up to three hours after complete ligation of the left anterior descending artery in this porcine heart cellular integrity is partially preserved and only certain amorphous densities in the mitochondria suggest that the protective effects of nifedipine come from inhibition of cellular Ca\textsuperscript{2+} influx.
limiting the extent and severity of myocardial and coronary vascular ischaemic damage, preferably by a pharmacological approach to buy time until bloodflow could be reestablished, either by aggressive means, such as thrombolysis, PTCA or surgery or through the natural expansion of the collateral circulation'.

The role of calcium channel blockers is most clearcut in the first of the two approaches advocated by Parratt. It is a logical concept that a cardiac cell threatened by oxygen insufficiency, should be induced to reduce its metabolic activity to enhance its chances for survival. The same goes for the surrounding healthy cardiac tissues. De Jong et al.\cite{18} have shown that, when Ca$^{2+}$ blockers are combined with beta-adrenoceptor antagonists to optimally inhibit positive chronotropic and inotropic effects of excess sympathetic stimulation to reduce oxygen consumption, the best combination may have been reached. In addition there are reports that both groups of drugs will favourably affect the blood supply to the jeopardized myocardium. Experimental evidence recently presented by Saxena\cite{25} and Åblad\cite{26} indicate that transmural bloodflow to the ischaemic zone may or may not increase depending on which beta-blocker is employed but that there is a redistribution of flow in favour of the endocardium where the effects of ischaemia would be earliest noted and most detrimental. Similar data for nifedipine and its derivative nisoldipine have been shown by Duncker et al.\cite{27} Mechanisms for this favourable redistribution are an increase in the diastolic filling period with changes in autoregulation of the vasomotor tone. In the latter respect, the experimental evidence gathered from these two dihydropyridines, combined with propranolol\cite{7,27} confirms that the dilating action of the calcium antagonist on the larger coronary arteries overrides the constricting influence of the beta blocker, while the reflex tachycardia is blocked and protective action on high energy phosphate metabolism enhanced\cite{8,29}. It therefore seems attractive to recommend in incipient ischaemic states, a combination of beta-blockade and calcium antagonists at the outset\cite{28}.

This leaves unconsidered the many other agents which are currently under discussion as additive agents during ischaemia and reperfusion\cite{30} but the unique cardioprotective effects of the calcium antagonists in reducing excessive calcium influx through a 'protective' role on the cell membrane, thus avoiding early disruption of the intracellular apparatus, combined with beta blockade require
major attention. De Jong et al.\[8,29\] have shown that release of purine breakdown products can be blocked by timely administration of dihydropyridines in combination with propranolol and that this combination is more effective than the use of either compound alone (Fig. 4). Since in their preparation the role of coronary blood flow per se was excluded, it is the direct action on the cardiac cell which must be held responsible for the beneficial effects of the combination, an important consideration during interruption in coronary bloodflow. In other words, in situations where ischaemia is induced, or where clinically one can anticipate the occurrence of an ischaemic episode, the timely administration of Ca\(^{2+}\) antagonists has been proven to be of benefit in the human situation depending on which profile one wishes the Ca\(^{2+}\) antagonist to have. On the other hand, recent data from Norway\[11\], the United States\[3\] and Denmark\[3\] have clearly shown that neither nifedipine nor verapamil can provide any benefit once these drugs are administered in existing myocardial infarction. Quite recently, in two collaborative studies, Muller et al. have contrasted the role of nifedipine in 126 patients with unstable angina\[31\] and in 171 others\[1,2\] with impending or proven infarction. In the former category, pain was not associated with enzymatic evidence of cardiac necrosis, while in the latter patients were included who had the symptoms of a typical myocardial infarction. In the second trial Ca\(^{2+}\) blocking agents were given a mean of 4-6 h after the onset of symptoms while in the unstable angina trial it was given within 2 h. These data show that while nifedipine and the combination of nifedipine plus beta blocker is most efficacious in terms of reducing pain and signs of ischaemia in 100 of 126 patients with unstable angina, as had been shown in previous investigations from our unit\[13\] and by the trial of Gerstenblith et al.\[32\] no effect could be demonstrated on any parameter in patients already having sustained a myocardial infarction. In fact death rates were identical or even higher than in the control group. A recent oral communication from the HINT trial (a comparison of nifedipine, metoprolol, their combination, and placebo in early, non severe, unstable angina for up to 48 h carried out in the Netherlands) are not inconsistent with this view as no differences were observed in terms of reduction in symptoms or the occurrence of signs of infarction (ECG, enzymes) at 48 h after their administration. The authors observed that in their trial the progression from unstable angina to myocardial infarction was impossible to establish. Thus, in the absence of a formal document these data must be interpreted to mean that unless a beneficial action is seen within 4-6 h after administration of any of these drug regimes, the fundamental derangement in these patients is complete obstruction, rather than increased vasomotor tone or ischaemia. When such patients considered refractory to pharmacological therapy, are taken to the catheter laboratory in an effort at recanalization, de Feyter et al.\[16\] as well as Meyer
Table 1 Indications for use of Ca\(^{2+}\) antagonists as 'cardioprotective' in (pre) or (re) ischaemic states

1. Unstable angina with signs of 'tolerable' ischaemia (by ECG, echo, thallium or biochemical markers)
2. Within 0–3 h after onset of symptoms and signs of myocardial ischaemia
3. During post infarction recurrent ischaemia
4. When 'stunned' myocardium is suspected (repeated brief ischaemic attacks, 'crescendo angina')
5. Prophylactically after sustained infarction when residual stenoses are suspected
6. During intentional disturbance of coronary perfusion (PTCA, aorta crossclamping during coronary surgery)
7. During thrombolytic therapy of coronary obstruction, provided the latter is carried out within 0–4 h after onset of symptoms
8. When rapid afterload reduction seems advisable (hypertensive crisis, CHF) but then in conjunction with a beta blocker to avoid reflex tachycardia
9. Prophylactically when recurrent spasm and ischaemia is anticipated: Prinzmeltal's variant angina, intracoronary manipulation such as PTCA, etc.

et al.\(^{[33]}\) and Bonzel et al.\(^{[34]}\) have shown that PTCA within 6 to 18 h after drug refractoriness has resulted in a marked reduction in occurrence of infarction with an attendant reduction in mortality. In fact in our hands the latter is 1% in 115 cases over a 12 months follow up\(^{[16]}\). Again the data recently published by Duncker et al.\(^{[27]}\) and by Yoshida et al.\(^{[11]}\) suggest a supportive role for the dihydropyridines in PTCA procedures as experimentally shown by Verduw et al.\(^{[35]}\).

In conclusion, the proper role of calcium antagonists in the clinical syndrome of ischaemia is becoming much clearer. These drugs are finding their proper place as our understanding of the physiological derangement grows. Potential indications for their use are given in Table 1. In contrast, when coronary flow is not reestablished and myocardial infarction has evolved, their role, at best, will be a minor one. It would be sad if misinterpretation of clinical signs separating myocardial ischaemia from infarction, admittedly a difficult area, as sensitive quantitative indicators of this process are as yet not routinely available, would lead to inappropriate prescription and administration of the Ca\(^{2+}\) antagonists. The risk then looms high that unwarranted administration will lead to disenchantment and disappointment with their usefulness in the area of clinical ischaemia.

References


