A CLINICAL REVIEW OF CALCIUM ANTAGONISTS IN ACUTE MYOCARDIAL INFARCTION

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Calcium antagonists can dilate peripheral and coronary arteries, reduce heart work and decrease the rate of conduction within sinoatrial and atrioventricular nodes [1]. These are properties which enable calcium antagonists to effectively control angina [2], hypertension [3] and supraventricular arrhythmias [4]. However they are also characteristics which might be used to redress the imbalance of heart work and myocardial blood supply which occur in ischaemic heart disease and also possibly the arrhythmias that arise in the damaged heart. Accordingly there are good reasons to believe that calcium antagonists may be cardioprotective [5].

The therm cardioprotective has been used loosely but it is used here to suggest that the drugs, to which it refers, reduce the mortality and morbidity from ischaemic heart disease. To establish whether calcium antagonists are cardioprotective it may one day be possible to answer the following questions.

Do calcium antagonists: 1) have experimentally demonstrable effects which would be expected to reduce the adverse effects of ischaemic heart disease?; 2) protect the hearts of animals whose coronary arteries are obstructed?; 3) reduce the incidence and severity of ischaemic problems suffered by patients on long term treatment for angina and hypertension?; 4) appear to assist patients who are taking them at the time they have an infarct?; 5) decrease mortality and morbidity if given acutely after a myocardial infarct?; 6) improve the long term prognosis of patients who recover from a myocardial infarct?

Data on some of these questions are available for beta blockers, for example questions 2[6], 4[7] and 6[8] and this wide subject has recently been reviewed[9]. A complete set of answers will not be available on calcium antagonists for some time. However it is already possible to comment on mechanisms and briefly on animal data. More important clinical data on patients, who have been given a calcium antagonist after an acute infarct, is beginning to be published. The main aim of this review is to present some of the evidence on mechanisms and then to discuss the emerging data on the acute use of calcium antagonists post infarction.

MECHANISMS

Calcium antagonists[5] may reduce the adverse effects of coronary artery disease by: improving coronary blood flow, reducing heart work and exerting and antiarrhythmic effect.

1) Coronary Blood Flow

a) Arterial Dilatation - Calcium antagonists reduce coronary artery spasm [10] and may be expected to dilate the arteries not in spasm [11]. Though these drugs have been considered particularly applicable to Prinzmetal's angina, there can be little doubt that their therapeutic role is not confined to the reversal of spasm alone.

b) Platelets - Platelet aggregation is calcium dependent [12,13] and is one of the processes which reduces the blood supply to the myocardium. in a patient suffering from an infarct [5,14]. Calcium antagonists may reduce this deleterious process [15].

c) Viscosity and Flow - It is possible that the loss of flexibility of red cells associated with increased red cell calcium [16] may be restored by calcium antagonists[17]. Theoretically this might improve flow.

2) Heart Work - Calcium antagonists will reduce heart work both by lowering peripheral resistance and hence after load[11]and by reducing myocardial contractility These actions have been well demonstrated and are accepted.

3) Antiarrhythmic effects - The ability of calcium antagonists to control supraventricular arrhythmias has been repeatedly demonstrated[4]: they are first line treatments for atrial tachycardia. They are not, however, regarded as being effective against the ventricular arrhythmias which are the more serious complication of an acute infarct. Nevertheless several studies have shown that in animal models calcium antagonists do appear to supress ventricular fibrillation induced by ischaemia [18].

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These several ways in which calcium antagonists may exert a cardioprotective effect, together with the positive supportive data derived from some of the animal studies [5,19] have encouraged clinicians to assess these drugs in patients who have just suffered a myocardial infarct. Before proceeding to discuss the trails it is important to emphasise the problems asociated with trying to extrapolate from animal data to man. These include first the variability of collateral blood supply in different animal models and the uncertainty regarding the role of these collaterals in determining infarct size and myocardium, at risk in the human heart [20]. Second, cardiovascular reflexes are disturbed to variable extents through anaesthesia and thoracotomy in the frequently used open-chest animal preparation [21]. Though this provides important data regarding direct cardiac effects of these drugs, the non-physiological nature of the model limits the usefulness of this data with respect to man, and in particular the patient with coronary artery disease. Finally, the end-points used such as delay of infarct extension or infarct size reduction are not clearly defined in many experimental models [22]. Animal data therefore, though apparently convincing, may be a poor predictor for clinical management. As a result, extensive and rigorous clinical trials are needed to more precisely define the place of calcium antagonists in post-infarction treatment strategies.

PATIENTS WITH AN ACUTE INFARCT

We will consider only randomised, placebo-controlled trials, using infarct size or mortality as end points of therapy and will use the Hampton diagram technique [23] for presenting some of the data. The only calcium antagonists that have been studied in trials of this design are verapamil and nifedipine, though some animal studies have suggested that diltiazern may be more effective [19].

Verapamil

Hansen et al [24] randomised 28 patients with acute myocardial infarction (AMI) to intravenous verapamil therapy, 0.1mg kg-1 over 5 mins (i.e. 5-10mg iv) proceeding to 120 mg three times daily by mouth for 8 days, and 33 patients to a non-verapamil control group. Otherwise, identical care was provided to each group. Patients in each arm of the trial were comparable.

The outcome of this study id presented in figure 1. It demonstrated an increased incidence of sinoatrial and atrio-ventricular block in the verapamil treated group but this was associated with no clinically significant complications at the end of the study. In this group over, the 3 week period, 3 patients died but there were no additional non-fatal reinfarctions. In the non-verapamil treated group 4 reinfarctions occurred and 4 patients died.

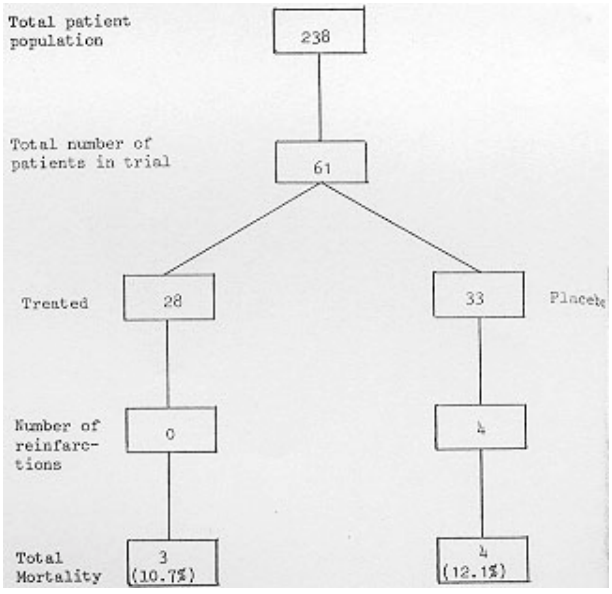

Fig. 1 - Hampton diagram demonstrating the atrial of Hansen et al [24] using verapamil in acute myocardial infarction.

A subset of patients was examined on the premise that the effects of verapamil intervention were most likely to be beneficial in patients early after onset of symptoms and signs. The criterion used for diagnosis of an early evolving infarct was a creatine kinase (CKMB) level less than 5 IU; 26 patients fulfilled this. The results showed that of the 14 patients not verapamil treated, 3 died and one reinfarcted while of those treated with verapamil (12 of 26) none died or reinfarcted. This result, though not achieving statistical significance, is encouraging. However a number of these patients had symptoms for over 6 hours and some for over 24 hours in spite of the fact that animal data show that for successful myocardial salvage, intervention needs to be initiated around 5 - 6 hours after onset of symptoms. Only 17 of this 26 patient group had had symptoms for less than 6 hours prior to admission. Since their analysis was not confined to the 17 it would seem that the trial design was not ideal, though it did appear to show verapamil used in this way is safe and possibly beneficial.

In 1984 the Danish Multicentre study was reported[25]. This was a double blind randomised placebo controlled trial. 7415 patients were suspected of having an AMI, 3489 included into the study and 1436 of these subsequently diagnosed as having a definite infarct. 717 patients were treated with 0.1 mg kg^{-1} intravenous verapamil, followed by 120 mg orally then 120 mg three times a day for 6 months. 719 patients received placebo (fig. 2). The patient groups were comparable. A significant number of patients (145 versus 67) on verapamil therapy had to be discontinued from the treatment due to sino-atrial or atrioventricular block.

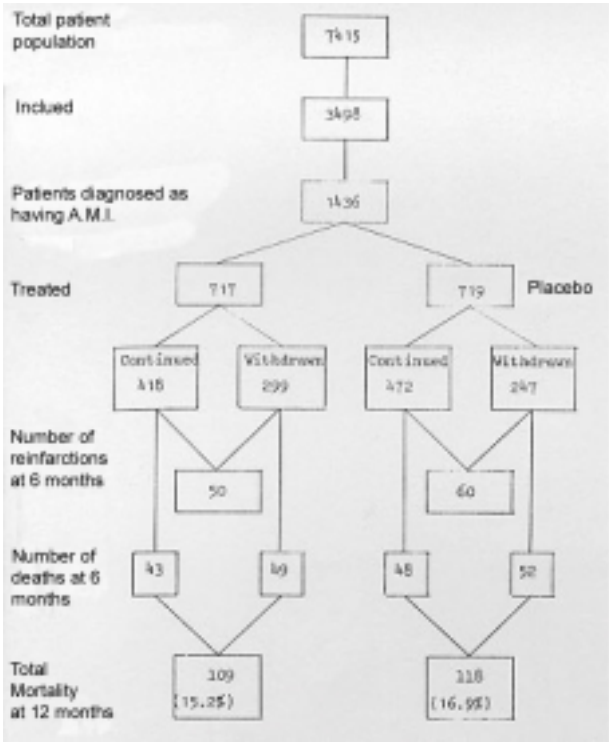

Fig. 2 - The Danish Multicentre Study [25] is shown. The figures for six and twelve months were all non-significant. A.M.I. Acute Myocardial Infarction.

The mortality rates at 6 and 12 months were 12.8% and 15.2% respectively for verapamil and 13.9% and 16.4% respectively for placebo. These differences were not significant. The number of reinfarctions at 6 months in the verapamil group was 50 as compared to 60 in the placebo group. This too was non significant. However, the number of reinfarctions in the first week was greater for verapamil than placebo (24 versus 15).

Retrospectively four sub-group analyses were performed. Mortality was significantly less at 6 months using verapamil in patients over 65 years of age and when symptoms lasted 6-24 hours. In addition, the number of deaths from days 22-180 was significantly reduced as were the number of reinfarctions from day 15-180.

Overall, this study must be reported as a negative result. However, the optimist who feels that there may be a role for calcium antagonists may derive some comfort from some of the subset analyses. Since 145 out of 717 (20%) of patients had to discontinue their study medication due to various forms of conduction block, the applicability of these findings remains equivocal.

The lack of effect of calcium antagonists in relation to reinfarction rate as | demonstrated | in this large study has been supported by a much smaller single blind placebo controlled trial[26]. Eight Patients with transmural infarction were randomised to verapamil therapy (10 mg IV at 30 min intervals up to 40 mg and then 80 mg orally three times daily until discharge) and 9 to a placebo control (total 17). In both subgroups 4 patients reinfarcted. 4 patients on verapamil developed complications of heart block (3) and hypotension (1).

In a further study Bussmann et al [27] have reported on the effect of 5-10 mg hr^{-1} of IV verapamil over 48 hours in 29 patients with an acute infarct randomised to such therapy. In 25 of these 29 patients, 5 mg IV was first given as a bolus in order to accelerate the attainment of therapeutic blood levels. The mean time lapse between symptoms and treatment was 8 hours. When comparing this group to an otherwise separate but comparable group of 25 patients on no specific treatment, they found that using CKMB levels there was a highly significant reduction in infarct size in the verapamil treated group (31 ± 18 g.Eq as compared to 49 ± 28 g. Eq: $p < 0.005$). This is said to suggest a 37% reduction in infarct size. Three patients in each group developed a conduction block and one in each group developed bypotension. This is the only favourable randomised trial so far reported, using a calcium antagonist, with a 'hard' trial end point.

Nifedipine

Two trials on the use of this more vascular selective calcium antagonist in the treatment of acute infarct patients have recently been reported.

Muller et a1[28] reported on 3143 patients who had experienced chest pain for greater than 45 minutes (fig. 3); 2900 patients were excluded from this study and of the 171 finally included, 105 were diagnosed as having a threatened myocardial infarction (TMI and 66 as having a definite infarct. These patients were randomised into groups receiving either 20 mg nifedipine orally 4 hourly for 14 days or placebo and standard care. Treatment was begun on average 4.6 ± 0.1 hours after onset of pain. The index of infarct size used was CKMB estimation [29]. Patient groups were comparable.

Of those with a TMI the incidence of progression to infarction was 75% for both nifedipine and placebo groups. Infarct size was determined in those with a definite AMI and those with TMI who progressed to an AMI. There was no significant difference in CKMB estimation.

Follow up continued for 6 months. Overall 6 month mortality did not significantly differ between the two groups. However, mortality at 2 weeks post-randomisation was 7.9% with nifedipine and 0% for placebo. This difference was significant ($p = 0.018$). Though disturbing, this result is probably a chance anomaly since it is highly unusual for zero mortality in a placebo group such as this. The usual range is 4 - 12% [30]. The inference that this trial argues against the efficacy of nifedipine treatment is therefore premature.

Finally, extrapolation of these conclusions to a

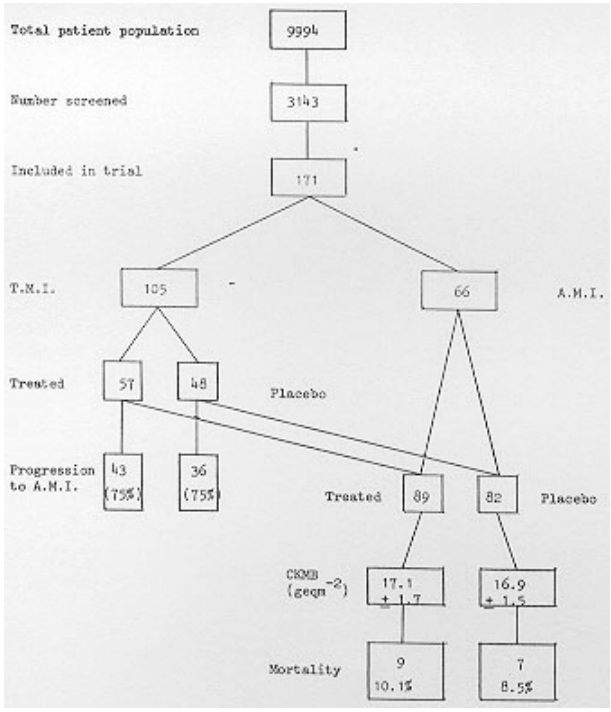

Fig. 3 - Müller et al [28] use nifedipine to study the effects on threatned (T.M.I.) and acute myocardial infarction (A.M.I.). The differences found in relation to creatine kinase MB (C.K.M.B.)and mortality were not significant.

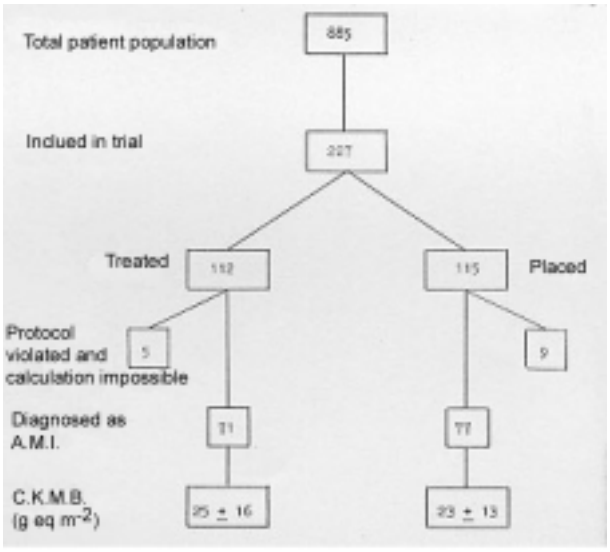

Fig. 4 - Sirnes et al [31] also demonstrated insignificance regarding C.K.M.B. and mortality.

wider clinical situation is complicated by the fact that so few of the patients screened actually fulfilled the inclusion criteria. The choice of this highly select patient subgroup therefore reduced the applicability of this study considerably.

Sirnes et al[31] conducted a multicentre, double blind trial on 227 patients with TMI (fig. 4). They were randomised within 12 hours to a nifedipine treatment group (n = 112, of whom 71 had a definite infarct) and a placebo group (n = 115, with progress to infarction in 77 cases). Nifedipine was administered 5.5 ± 2.9 hours after symptomatic onset. Treatment consisted of nifedipine 10 mg orally with a further dose at 30 mins; then 10 mg 5 times daily for 2 days followed by 10 mg 4 hourly for the next 6 weeks. Adverse reactions were reported in 32 patients in each group with 9 patients withdrawing on nifedipine and 6 on placebo.

There was no significant difference in infarct size as determined by CKMB measurement; 25 ±: 16 g.eq.M^{-2} in the treated subset as compared to 23 ± 13 g.eq.M^{-2} in the placebo subset. Treatment was continued for 6 months with 10 deaths occurring in each group, Thus, there was no change in infarct size (the primary end point) nor in mortality. However the mortality statistics are open to question since they were not calculated on an intention to treat basis [23].

Clearly, these trials demonstrate that nifedipine in the regimens used did not materially affect the progression of a threatened to a definite infarct, infarct size reduction nor mortality.

Conclusion

The limited data currently available do not provide evidence for the acute use of calcium antagonist therapy in an acute MI.

Verapamil is best used by an intravenous route initially due to its variable pharmacokinetic profile, when taken orally. Six months of treatment by the Danish group[25] caused no change in mortality orl reinfarction rates. Though inadequate dosage may be a possible explanation it would be undesirable to use increased doses in future trials since the incidence of heart block may rise even further than the 20% reported. In addition, the excess of first week reinfarctions with verapamil is of concern and is possibly related to the conduction disturbance but perhaps also to the potential haemodynamically deleterious effects that may occur with poor dose titration. However, verapamil may be of value in an older group of patients. This requires further investigation.

The small but dramatic study by Bussman and colleagues[27] who report infarct size reduction by a 48 hour course of intravenous verapamil, unfortunately lacks any data on mortality and reinfarction in the longer term. Though one may intuitively expect morbidity and mortality to be reduced with such significant infarct size reduction (37%), the clinical relevance has to be a matter of speculation. However, the possible efficacy of longer courses of IV treatment means that further trials to examine its effects on more clinically relevant end points are desirable.

The major problem with the nifedipine trials is the small sample sizes. Larger trials are therefore required before we discard nifedipine as a potentially

useful treatment in acute infarction. The timing of treatment (4-5 hours after symptoms) is probably at the limit of what is practically attainable. Thus, the argument that earlier intervention is required to demonstrate a positive result is clinically unhelpful.

Diltiazem, the third major calcium antagonist currently in use, has not been studied in randomised, double blind protocols. Hence, although there is sound experimental evidence favouring the cardioprotective actions of this drug especially in relation to its lack of negative inotropic activity[31], we must await comparable clinical data.

The use of CKMB, though reported to be a useful indicator of the infarct size, is controversial [32]. Newer techniques involving thallium scanning[33] may be of more use in the future and need to be evaluated further to determine the efficacy of infarct size reducing agents. Finally, accurate dose titration needs to be explored more fully. This would establish whether there is a finite point for each patient where a balance exists between administering enough drug to achieve a therapeutic effect but not sufficient to precipitate hypotension and hence, possible infarct extension.

Although a number of points regarding these trials need to be reviewed further (sample size, length of follow up, infarct size quantitation and dosage regimens) they do suggest that it may be necessary to evaluate treatment in patient subsets rather than treat all infarct patients, in order to detect a possible beneficial effect of calcium antagonists. To this end it would be of interest to determine their effects upon infarct size and mortality in patients who happen to be taking a calcium antagonist at the time their infarct occurs. Furthermore we know that infarct size reduction with calcium antagonists may well depend upon the extent of collateral blood flow. Thus patients with a longstanding history of coronary artery disease are a subset who need to be investigated in order to delineate the effects of these vasodilator drugs in situations with widespread collateral supplies that may well respond to such treatment.

It would be possible to decide, on the clinical data currently available, that calcium antagonists have no role in the management of an acute myocardial infarction. This would be premature. Firstly there are good experimental reasons for believing that these drugs may have a beneficial effect. Secondly the trials to date have been relatively small scale and have had some design defects. Finally only two calcium antagonists have even been partially assessed. Diltiazem or one of the second or third generation calcium antagonists may prove effective.

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