CLINICAL RESEARCH

Treatment of angina pectoris with nifedipine: importance of dose titration

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Abstract

The effects of different doses of nifedipine on frequency of angina and objective measurements of myocardial ischaemia during exercise were studied in 10 patients with stable angina pectoris. In a single blind trial over nine weeks patients received one week's treatment each with placebo, nifedipine 10 mg, 20 mg, 30 mg, 40 mg, 30 mg, 20 mg, 10 mg, then placebo three times a day. The response to the different doses of nifedipine was highly variable. On exercising, three patients achieved a consistent improvement in workload attained before onset of ST segment depression and maximum ST depression during exercise testing during all active phases. Four patients improved with 10 mg three times a day but deteriorated at higher doses. In two patients there was no objective or subjective improvement with any dose of the drug, while in one patient anginal frequency increased and there was objective deterioration during exercise testing at doses above 10 mg three times a day.

Thus a dose of nifedipine that is beneficial in one patient may have minimal or opposite effects in another. These results indicate the importance of careful titration of doses for individual patients if the maximum benefit from nifedipine is to be obtained in patients with exertional angina.

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Introduction

Calcium antagonists have been shown to be valuable in the treatment of angina that occurs predominantly at rest.[1 2] Beneficial responses have also been found in patients with stable exertional angina,[3-5] with these agents, both alone and in combination with beta adrenergic blockers.[6] The precise mode of action in exertional angina remains uncertain. Benefit may result from peripheral vasodilatation with decrease in afterload, reduction of myocardial contractility, coronary vasodilatation, or a combination of these mechanisms. An excessive fall in blood pressure or coronary steal may, however, compromise regional myocardial perfusion and a rise in heart rate may increase myocardial oxygen consumption. This might account for the reports of production of ischaemic cardiac pain by nifedipine.[7 8] The balance between the advantageous and potentially adverse effects has been shown to be dose related during experimental myocardial ischaemia in dogs[9] but has never been fully investigated in man.

We examined the effects of dose titration of nifedipine using objective criteria of myocardial ischaemia in patients with stable exertional angina pectoris.

Patients and methods

Ten patients (seven men, three women), aged from 42 to 75 (mean 61) years were studied. All were known to have typical exertional angina pectoris that had not altered in frequency or severity over at least six months. These patients all had a reproducible, positive result of exercise test for ST segment depression.[10] Six of the ten patients had undergone coronary arteriography; all had three vessel coronary disease ($\geqslant$75% stenosis).

The trial design was single blind and consisted of a one week run in period followed by nine one week treatment periods. The sequence of treatment was: placebo, nifedipine 10 mg, 20 mg, 30 mg, 40 mg, 30 mg, 20 mg, 10 mg, and placebo three times daily. A double dummy technique was used to ensure that the tablets appeared identical during all phases. Patients received no other antianginal medication during the study apart from sublingual glyceryl trinitrate as required. Throughout the study patients kept diaries in which they recorded episodes of angina and also any side effects experienced.

EXERCISE TESTING

Each patient performed a maximal exercise test at the end of the run in period and at the end of each of the nine one week treatment periods. The exercise tests were performed for each patient at the same time of day—namely, about two hours after meals and ingestion of nifedipine.

The tests were performed on a bicycle ergometer, using a system with which the patients had previously been familiarised. A 16 point precordial electrocardiogram was recorded before exercise, at one minute intervals during exercise, and after 10 minutes of recovery as previously reported.[12] Recordings were made with a direct writing ink jet Mingograf (Elema-Schonander), recording four channels simultaneously. The 16 unipolar electrodes were evenly distributed over the left hemithorax in a grid from the right sternal border to the left midaxillary line, from the second intercostal space to 6 cm below the costal margin.

Each tracing was analysed by an observer who was unaware of the patient's treatment phase. ST segment changes were recorded from the PQ segment and considered to be depressed when there was a shift of 1 mm or more lasting for 0·08 second or longer. Measurements were made from three consecutive complexes at each precordial position.

The heart rate and blood pressure were recorded at rest and at one minute intervals throughout exercise and recovery.

The following information was derived from each exercise test: (*a*) workload to the onset of ST segment depression; (*b*) heart rate and blood pressure at rest and at fixed maximal exercise; and (*c*) number of precordial positions of ST segment depression at fixed maximal exercise (area).

A paired sample Student's *t* test was used to compare measurements during the two treatment periods at the same drug dose and between each treatment period and placebo.

After the exercise test 10 ml blood was drawn into a blackened syringe, spun, drawn under sodium light, and stored in a blackened tube at −20°C before assay of plasma nifedipine concentration by gas chromatography.[11]

Results

In each patient there was consistency of response between the two treatment periods at the same drug dose and there was no significant difference in haemodynamic and electrocardiographic measurements or chest pain between the placebo periods at the beginning and end of the study.

ST SEGMENT DEPRESSION

There was a small improvement in the number of precordial positions with ST depression and the workload to the onset of ST depression as the dose of nifedipine was increased from placebo (5·5±2·5 positions on placebo versus 4±2 positions on nifedipine 120 mg/day: 11±8 MJ on placebo versus 19±15 MJ on nifedipine 120 mg/day). None of these effects, however, achieved statistical significances owing to the highly variable response of individual patients.

Four response patterns in exercise ST segment changes were noted to the different doses of the drug.

Consistent improvement—Three patients achieved a consistent increase in the workload to the onset of ST segment depression, with a reduction in the maximum precordial area of ST segment depression on exercise during all active phases of the study. In all three patients maximum benefit was seen at nifedipine 30 mg thrice daily and increase of the dose was of no further benefit. In only one of the three patients (fig 1) was there an associated subjective improvement with reduction in the frequency of angina.

No improvement at any dose—In two patients no change was seen in the workload or heart rate to the onset of ST segment depression, in the maximum area of ST segment depression, or in the frequency of angina at any dose of nifedipine.

Improvement at low dose with deterioration at higher doses—In four patients, nifedipine in low dose produced improvement in workload to ST segment depression and maximum area of ST segment depression. In all cases the optimum dose of nifedipine was 10 mg three times a day. When the dose of nifedipine was increased further there was a deterioration in both measures of myocardial ischaemia. In one case (fig 2) treatment with nifedipine 10 mg was accompanied by a reduction in anginal attacks that was not maintained at higher doses of the drug. In the other patients no effect was noted in the number of anginal attacks at any dose.

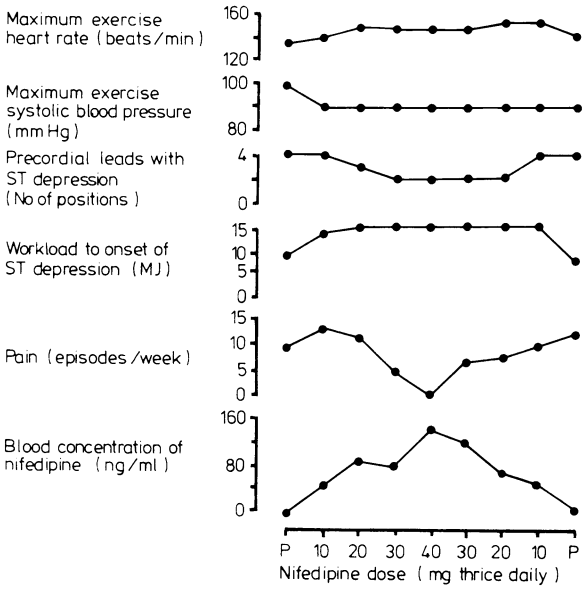

FIG 1—Results from a patient showing improvement in exercise ST depression and in workload to the onset of ST depression, accompanied by a decrease in angina with nifedipine. Objective and subjective response between treatment periods at the same drug dose were consistent. P=placebo.

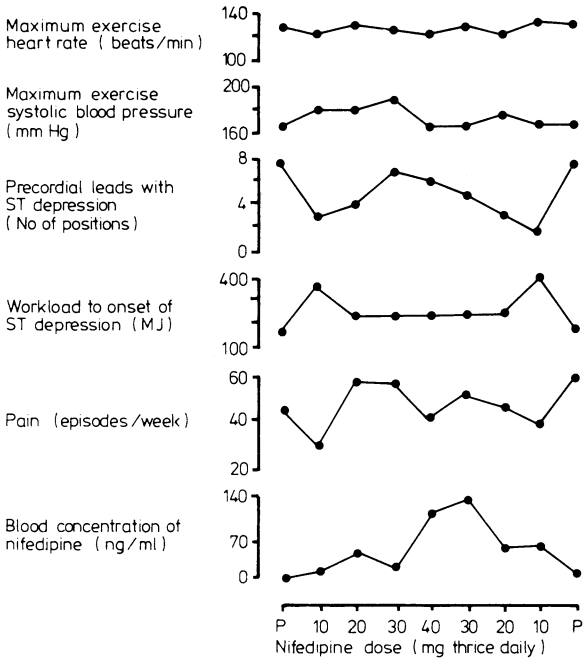

FIG 2—Results from a patient showing an initial decrease in exercise ST depression and an increase in workload to the onset of ST depression associated with a reduction in angina with 10 mg nifedipine three times a day. This improvement was not maintained at higher doses. P=placebo.

Consistent deterioration—In one patient there was a deterioration in both the workload achieved to the onset of ST depression and in the ST changes during exercise when the dose of nifedipine was increased above 10 mg. This was accompanied by a pronounced increase in the frequency and severity of angina so that the patient was unable to tolerate a dose of more than 30 mg (fig 3).

HEART RATE AND BLOOD PRESSURE

No significant effect was seen at any dose on the resting and peak heart rate achieved during exercise (resting heart rate on placebo 88 ± 6·4 beats/min, resting heart rate on nifedipine 40 mg 89 ± 13·4 beats/min ($p > 0·05$); maximum heart rate on placebo 137 ± 13 beats/min, on nifedipine 146 ± 18 beats/min ($p > 0·05$)).

There was a small fall in systolic blood pressure at peak exercise at the high doses of nifedipine (132 ± 16·5 mm Hg at rest and 159 ± 35 mm Hg at maximum exercise on placebo *v* 130 ± 22 mm Hg at rest and 138 ± 27 mm Hg at maximum exercise on nifedipine 120 mg/day).

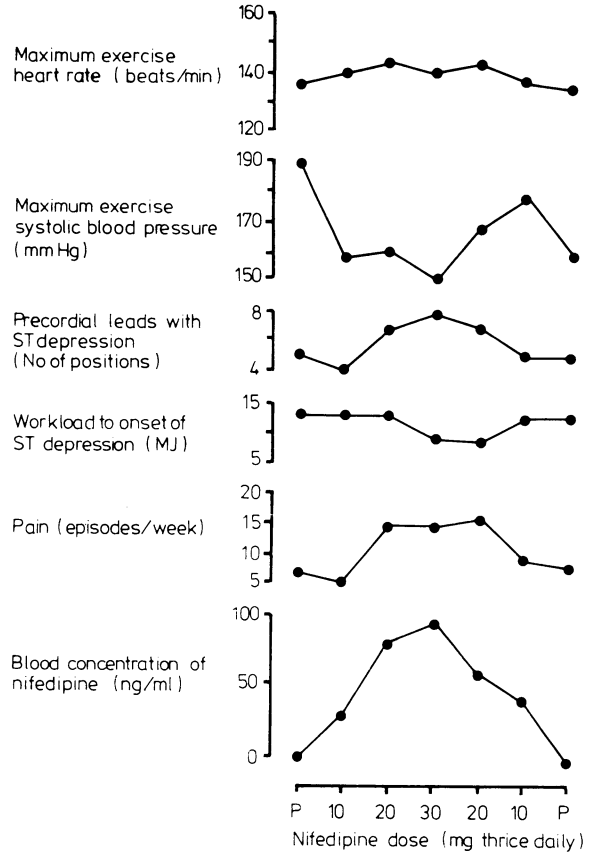

FIG 3—Results from a patient showing increase in exercise ST depression and decrease of workload achieved to onset of ST depression on nifedipine. Objective deterioration was accompanied by an increase in angina, and patient was unable to tolerate a dose of nifedipine above 30 mg thrice daily. There was systematic objective and subjective improvement on withdrawal of the drug.

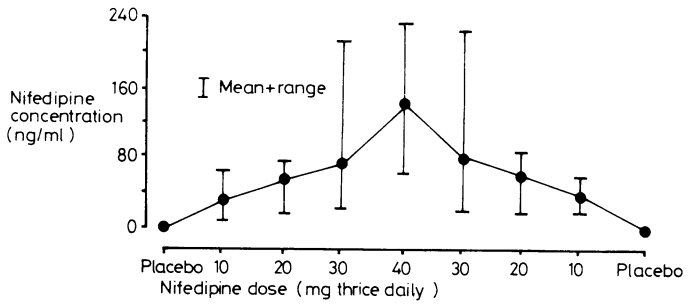

FIG 4—Plasma nifedipine concentrations for the 10 patients studied. Concentrations varied considerably between patients but increased and decreased in a manner appropriate to the prescribed drug dose.

ANGINA DIARIES

There was no significant improvement in the reported frequency of angina overall.

PLASMA CONCENTRATIONS AND SIDE EFFECTS

Figure 4 shows the mean and range of plasma concentrations in each treatment period. Plasma nifedipine concentrations varied considerably between patients, but in all patients increased and decreased in a manner appropriate to the prescribed drug dose.

Side effects were more frequent at higher drug doses and included indigestion (four patients), weakness (three patients), giddiness (three patients), ankle swelling (three patients), headache (two patients), and flushing of hands and feet (two patients). Three patients remained well at all doses of the drug and only three reported mild side effects on 30 mg a day. Five patients tolerated doses of nifedipine up to 120 mg a day, four patients 90 mg a day, and one patient 60 mg a day.

Discussion

Using objective measurements of myocardial ischaemia we have shown that clinically similar patients with stable exertional angina pectoris respond to the calcium antagonist nifedipine in a highly variable manner. A dose that improves the electrocardiographic signs of ischaemia in one patient may have the opposite effect in another. As a result, the group as a whole did not show any significant improvement or deterioration of measured ischaemia. Similarly, the grouped results from angina diaries showed no overall change in reported chest pain, with individual patients responding in a variable manner. Despite the variable individual response, however, the patient whose symptoms improved consistently also showed objective improvement, and the patient whose chest pain increased on the drug also showed deterioration on testing. The consistency of these responses was evaluated in each patient by systematically repeating each dose. Because of the number of patients studied, we cannot extrapolate and estimate the relative incidence of the different responses in other patients with ischaemic heart disease. Our findings do, however, emphasise that group results in clinical trials with nifedipine may be confusing because they obscure the responses of individual patients.[3 6]

Benefit from the drug is presumably related to a reduction in myocardial work, an increase in myocardial blood flow, or a combination of these actions. Increase in myocardial perfusion may result from vasodilatation of large coronary arteries, increase in collateral flow to ischaemic areas, or relief of coronary vasospasm.[13] This relief occurs in some patients even during exertional angina.[14]

The adverse effects of the drug may be caused by excessive fall in blood pressure or increase in heart rate resulting in diminished regional perfusion to ischaemic myocardium.[15] It has also been suggested that nifedipine may cause a coronary steal phenomenon by pronounced dilatation of normal coronary vessels.[16] The balance between these potentially advantageous and deleterious effects may explain the variability in response to the drug found in this study. This variability is largely dose related, with some patients improving at low doses of nifedipine but deteriorating as the dose was increased. Selwyn *et al* have shown a similar effect in dogs, with extension of ischaemia occurring when high doses of nifedipine caused large falls in aortic pressure and a tachycardia.[9] None of our patients showed a significant increase in heart rate either at rest or peak exercise at any dose of nifedipine. There was a small dose related fall in blood pressure both at rest and at maximal exercise. We were, however, unable to identify patients in whom nifedipine had an adverse effect from either their resting heart rate and blood pressure or from the change in these measurements during exercise.

The variability of patients' response and the differences in optimal dose between patients has not been recognised in studies using a fixed dose regimen, although many have used ST segment changes during exercise tests as objective end points. Failure to appreciate the importance of individual dose titration may explain the conflicting results that have been obtained using nifedipine in exertional angina. For example, Lynch *et al* showed that both high and low doses of nifedipine were beneficial.[6] In contrast, Balasubramanian and colleagues recently

showed that nifedipine differed little from placebo in terms of angina relief, exercise testing, and ambulatory monitoring.[17] These last results should be considered with caution, however, particularly in the light of our findings as no attempt to dose titrate the patients was made.

The design of the study was single blind as we did not think we could randomise the different doses of nifedipine. As it turned out some patients were unable to tolerate the higher doses. Although there is likely to be some carry over effect with a weekly stepwise increase in the drug, it is unlikely that this was important as when deterioration occurred, it was usually at a relatively low dose and a consistency of effect was noted between the two treatments at the same dose.

In conclusion, the clinical response to the calcium antagonist, nifedipine, was highly variable in patients with stable exertional angina pectoris. A proportion of patients did not show any objective benefit, consistent improvement was seen in some patients, while others, after improvement at intermediate doses, deteriorated when the dose was increased. Therefore, in both clinical practice and therapeutic trials, dose titration is fundamental to the safe and beneficial use of nifedipine. Careful tailoring of the dose to the clinical response is recommended even when a good initial response is obtained.

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ONE HUNDRED YEARS AGO The Misericordia Hospital, which is the chief hospital of Rio de Janeiro, presents in its constitution certain altogether unique elements. It is a large building capable of accommodating two thousand patients, magnificently situated on the Praia de Santa Luzia, and overlooking the entrance to the Bay of Rio. Entering the hospital by a long flight of marble steps, the visitor arrives at a large vestibule, and finds on his left hand a spacious dispensary filled by a motley crowd of out-patients, of all ages, of both sexes, and of every nationality. Corridors extend from the vestibule, and one of them leads to a set of offices and workshops such as are not, we believe, to be found in any other hospital in the world. By an arrangement, at once ingenious and cynical, the institution enjoys a monopoly of undertaking; it makes all the coffins, and organises all the funerals for the town of Rio de Janeiro, and derives a large part of its income from this source. A great number of hands are employed in the coffin manufactory; the coffins are of the lightest description, roughly nailed together, and closed by a lid which opens on hinges; when the body has been placed in the coffin, the lid is locked. Coffins of all sizes are constantly kept in stock, ranged on shelves according to their size, so as to be ready at a moment's notice; they are covered with a thin black, red, or violet material, are bordered with gilt tinsel, and altogether have an appearance rather suggestive of bon-bon boxes. The coffins vary slightly in quality; and the funerals, also, are of the first, second, and third class, according to the sum the friends of the deceased are willing to expend. The funeral department of the hospital also supplies the candelabra, the altars, catafalque, and all the other paraphernalia of a *chapelle ardente*. The hospital has an additional source of revenue in a tax on every ship entering the harbour; in return, it is entirely free to every nationality, so that Englishmen, Germans, Italians, Spaniards, Russians, Chinese, and Negroes, are constantly to be found within its walls. There are special wards for women, for ophthalmic cases, and for children. In connection with the last, there is a small orphan school. The floor of every ward is of polished wood, and a dado of blue and white tiles runs round the walls; each wing has its own garden and special staircase leading into it. There are also private rooms for paying patients; containing one, two, or three beds, according to the tariff paid. The ventilation is carefully attended to, and is considered to be very successful. The nursing is in the hands of the Order of St. Vincent de Paul, who maintain about sixty Sisters of Mercy in the hospital. They not only nurse the patients, but render assistance in the dispensary, and have charge of the instrument room. There is a medical school attached to the hospital, and for its use a library, museum, dissecting-room, and other necessary accommodation are provided; the weekly average of in-patients is said to be about 1800, the yearly 14,000, so that there are about 230 new patients admitted weekly. The death rate is 13 per cent. (*British Medical Journal* 1883;i:71-2.)

ONE HUNDRED YEARS AGO We announced last week that the authorities at the Horse Guards had decided that "easy riding" should henceforth be adopted in the British cavalry. While the spirit of reform is active, we hope our poor troop-horses will not be forgotten. Can nothing be done to lighten the ponderous trappings of these unfortunate animals! Like the orthodox garb of civilised mankind, the regulation gear of the cavalry horse is laden with numerous and useless survivals of the unfit. The bulky breastplates and unnecessary cruppers still worn by the horses of many of our regiments are relics of the time when war-horses were armoured, and might now disappear with advantage. The hussar saddle might be reduced several pounds in weight. The Duke of Wellington had a favourite aphorism to the effect that battles are won by boots; the principle which underlies this truth might find further expression in lightening and simplifying the trappings of troop-horses, with the obvious effect of economising the endurance and increasing the activity and speed of our cavalry. (*British Medical Journal* 1883;ii:588.)