Evaluation of nitrendipine — a new calcium channel blocker

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Summary

Nitrendipine (Baypress; Bayer-Miles), a new calcium channel blocker, was administered to 38 hypertensive patients in an oral dose of 20 mg once or twice daily. Both systolic and diastolic blood pressures were reduced to a clinically relevant extent within 2 hours of taking the medication. There was no loss of effect during the 57 days of the trial. No significant changes in heart rate were noted. On the whole, side-effects were mild and transient and consisted mainly of dizziness, headache, joint pains and oedema.

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The place of calcium channel blockers in the medical management of coronary heart disease has been well established over the last few years.[1-4] These agents act by inhibiting calcium ion entrance into the vascular smooth muscle,[5] thereby promoting vasodilation.[6] Since essential hypertension is haemodynamically characterised by an elevated vascular resistance, it is not surprising that calcium channel blockers have also been used with success in the treatment of systemic hypertension.[7,8] For example, nifedipine has been shown to be an effective form of therapy both in hypertensive emergencies[9] and in less severe forms of hypertension.

Significant pharmacological and pharmacokinetic differences exist between calcium blocking agents, particularly in regard to their effects on cardiac conduction and contractility, and the haemodynamic response to these compounds is not uniform.

Nitrendipine (Baypress; Bayer-Miles) was synthesised by H. Meyer *et al.* at the research laboratories of Bayer AG in Wuppertal, West Germany. Like its predecessor, nifedipine, nitrendipine relaxes vascular smooth muscle. A number of studies have shown the efficacy of nitrendipine in the treatment of patients with hypertension.[12,13] An open study was conducted in order to confirm that nitrendipine does show efficacy and tolerability in patients with mild-to-moderate hypertension.

Patients and methods

After a wash-out period of 14 days, 40 adult black hypertensive patients participated in a study to evaluate the efficacy and safety of nitrendipine 20 mg tablets when used alone or in combination with other antihypertensive agents. Patients were fully informed and were required to sign a consent form. Blood pressures were recorded by one doctor (R.A.P. du Pont) using a standard mercury sphygmomanometer equipped with a 135 mm cuff. The procedure was standardised by recording the systolic value at the first perception of sound, and the diastolic at the 5th phase level (by perception of disappearance of sound). All blood pressures were recorded with patients in the sitting position after 15 minutes' rest. A total of 38 patients (28 women) completed the study; none was excessively obese. On day 0, systolic and diastolic blood pressures, as well as heart rate, were measured before treatment.

These measurements served as baseline values. One 20 mg nitrendipine tablet was administered to each patient and systolic and diastolic blood pressures and heart rate were measured after 15, 30, 60 and 120 minutes. The measurements were repeated on days 14, 28, 42 and 56 during which time the patients took 20 mg nitrendipine alone, or in combination with other antihypertensive drugs, daily. The daily dosage of nitrendipine could at any stage be increased to 20 mg twice daily, depending on the discretion of the investigator. In a few

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TABLE I. SYSTOLIC BLOOD PRESSURES DURING 2 HOURS AFTER MEDICATION ON DAY 0

Time (min)	Mean ± SD (mmHg)	Change from baseline (mmHg)	CI (mmHg)
0 (baseline)	154 ± 21	—	—
15	140 ± 19	−14	−17 - −8
30	131 ± 15	−23	−26 - −18
60	126 ± 16	−28	−32 - −23
120	125 ± 16	−29	−34 - −24

patients, the dosage was reduced to 20 mg every alternate day. The 95% confidence intervals (CI),[14] based on the paired *t*-test, were calculated for the respective changes from baseline in systolic and diastolic blood pressures and heart rate.

Results

Systolic blood pressure

The mean systolic blood pressures for the 2-hour period after administration of nitrendipine on day 0 are shown in Table I. The mean systolic blood pressures before treatment on days 0, 14, 28, 42, and 56 are shown in Table II.

TABLE II. SYSTOLIC BLOOD PRESSURES BEFORE MEDICATION

Day	Mean ± SD (mmHg)	Change from baseline (mmHg)	CI (mmHg)
0	154 ± 21	—	—
14	141 ± 21	−13	−22 - −6
28	136 ± 20	−18	−26 - −11
42	131 ± 16	−23	−30 - −16
56	128 ± 15	−26	−34 - −20

The mean systolic blood pressure decreased from 154 mmHg (range 125 - 210 mmHg) to 125 mmHg (range 105 - 170 mmHg) 2 hours after administration of nitrendipine, and to 128 mmHg (range 102 - 165 mmHg) before medication on day 56 (12 or 24 hours after the previous dose).

The mean decrease in systolic blood pressure 2 hours after treatment with nitrendipine (with or without concomitant medication) was 29 mmHg. The 95% CI of 24 - 34 mmHg shows that the true mean decrease in systolic blood pressure 2 hours after treatment with nitrendipine was at least 24 mmHg, and that the treatment has the potential to lower mean systolic blood pressure by as much as 34 mmHg during this period. The mean decrease in systolic blood pressure after 56 days of treatment with nitrendipine was 27 mmHg (CI 20 - 34 mmHg).

Therefore not only was there a rapid decrease in systolic blood pressure during the first 2 hours after medication, but the daily decrease continued up to day 56. In fact, there was a gradual decrease in systolic blood pressure from day 0 to day 56 and all indications are that this tendency might have continued for some period after day 56 before the acceptable minimum systolic blood pressure was reached. Furthermore, it seems that the approximate maximum inhibition of systolic blood pressure was reached between 1 and 2 hours after medication. All the decreases in mean systolic blood pressure were considered to be clinically relevant.

Diastolic blood pressure

The mean diastolic blood pressures at each measuring during the first 2 hours after medication on day 0 are shown in Table III and the mean diastolic blood pressures before medication on day 0, 14, 28, 42, and 56 are shown in Table IV.

TABLE III. DIASTOLIC BLOOD PRESSURES DURING 2 HOURS AFTER MEDICATION ON DAY 0

Time (min)	Mean ± SD (mmHg)	Change from baseline (mmHg)	CI (mmHg)
0	101 ± 12	—	—
15	90 ± 10	−11	−14 - −8
30	86 ± 11	−15	−17 - −12
60	83 ± 11	−18	−21 - −14
120	82 ± 12	−19	−24 - −14

TABLE IV. DIASTOLIC BLOOD PRESSURES BEFORE MEDICATION

Day	Mean ± SD (mmHg)	Change from baseline (mmHg)	CI (mmHg)
0	101 ± 12	—	—
14	88 ± 13	−13	−17 - −8
28	86 ± 14	−15	−19 - −11
42	81 ± 11	−20	−24 - −16
56	81 ± 12	−20	−25 - −15

The mean diastolic blood pressure decreased from 101 mmHg (range 80 - 130 mmHg) to 82 mmHg (range 60 - 110 mmHg) 2 hours after administration of nitrendipine, and to 81 mmHg (range 62 - 108 mmHg) before medication on day 56. The results for the period up to 2 hours after medication with nitrendipine show that the mean decrease in diastolic blood pressure during this period was 19 mmHg (CI 14 - 24 mmHg), while the mean decrease in diastolic blood pressure after 56 days of treatment with nitrendipine was 20 mmHg (CI 15 - 25 mmHg).

The decrease in diastolic blood pressure during the 1st hour after medication was rapid, while the values 1 hour and 2 hours after medication were similar. There was also a gradual decrease in diastolic blood pressure over the 56-day period. It seems that the decrease in diastolic blood pressure reached an acceptable minimum after 42 days, since the results on day 42 and day 56 were similar. All the decreases in mean diastolic blood pressures were considered to be clinically relevant.

Heart rate

There were no clinically relevant changes in heart rates after medication. The mean heart rate was 73 beats/min before medication, and 75, 74, 70, 72 and 72 beats/min at 120 min and days 14, 21, 42, and 56 respectively.

Thus the heart rate remained stable not only for the 2 hours after drug administration but for the entire observation period of 56 days. There was no change in body weight during the study period.

Concomitant medication

Five patients required extra medication consisting of α-methyldopa and a diuretic (amiloride/hydrochlorothiazide 1 tablet daily) in 1 case and diuretics only in 4. The blood pressure response in these 5 patients was no different from that in patients who did not have concomitant treatment.

Side-effects

Side-effects were mostly mild, subjective and transient. None necessitated withdrawal of the drug. A total of 37 side-effects recorded by 23 patients over the 56-day period are listed in Table V. Those side-effects with a low incidence were probably not drug-related. Two patients withdrew for non-drug-related reasons after day 0 and their results have not been included.

TABLE V. SIDE-EFFECTS

Dizziness	**8**	**Itchy eyes**	**1**
Headache	**7**	**Tight throat**	**1**
Joint pain	**6**	**Tiredness**	**1**
Oedema	**5**	**Pulmonary oedema**	**1***
Hot flushes	**2***	**Pain in neck**	**1***
Sleepiness	**1**	**Skin rash**	**1**
Palpitations	**1**	**Diarrhoea**	**1**
		Total	**37**

* More than moderate.

Conclusion

There was a rapid decline in systolic blood pressure during the 1st hour following the first dose of nitrendipine (alone or in combination with other antihypertensive drugs). The systolic blood pressure remained more or less constant between 1 hour and 2 hours after medication. The mean decrease from baseline to 2 hours after medication was 29 mmHg (CI 24 - 34 mmHg). Indications are that these margins represent the maximum decrease in systolic blood pressure that will be reached in a specific day.

A gradual decrease compared with baseline in systolic blood pressure was also observed up to day 56. The mean decrease during this period was 27 mmHg (CI 20 - 34 mmHg). The fact that blood pressure was measured before medication on day 56 (12 or 24 hours after the previous medication with nitrendipine) makes this result even more remarkable. Furthermore, indications are that even slightly lower systolic blood pressures might be possible after 56 days of treatment with nitrendipine.

There was also a rapid decrease in diastolic blood pressure during the first 2 hours after the first dose of nitrendipine. The mean decrease from baseline to 2 hours after treatment was 19 mmHg (CI 14 - 24 mmHg).

There was a rapid decrease in diastolic blood pressure during the first 14 days of treatment with nitrendipine. This tendency continued to day 42, after which the diastolic blood pressure remained fairly constant up to day 56. The mean decrease from baseline to day 56 was 20 mmHg (CI 15 - 25 mmHg). The diastolic blood pressures were measured before treatment on day 56 and 12 or 24 hours after the previous dose of nitrendipine.

It is therefore concluded that nitrendipine administered once daily is an effective antihypertensive drug in black patients. It has also been proved safe and was well tolerated by the patients.

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