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Treatment of hypertensive emergency

Comparison of a new dosage form of the calcium antagonist nitrendipine with nifedipine capsules

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Abstract. *Objective:* To present the efficacy and tolerability of a new oral dosage form of the calcium antagonist nitrendipine compared to nifedipine capsules in patients with hypertensive emergency.
Design: Multicenter randomized double blind clinical study.
Setting: 23 study centres (hospitals) in Germany.
Patients: 161 patients between 20 and 70 years with acutely elevated blood pressure (systolic 200–250 mmHg, diastolic between 110–140 mmHg) with and without concomitant clinical symptoms.
Interventions: Double blind treatment with 10 mg nifedipine or 5 mg nitrendipine. Nifedipine was administered as capsules, nitrendipine was given from a small plastic tube (vial), containing 1 ml alcoholic solution. Every patient received in addition to the test medication a placebo corresponding to the other product. Patients with insufficient treatment after 45 min were given either an additional capsule of 10 mg nifedipine or a further vial containing 5 mg nitrendipine according to their group and maintaining the double dummy procedure.
Measurements and results: Blood pressure and heart rate were measured repeatedly during 4 h, before and 90 min after beginning of the treatment a 12 channel resting ECG was recorded. At 45 min after administration the blood pressure had fallen significantly from 216.0/117.4 mmHg to 170.0/93.3 mmHg under nifedipine and from 216.9/117.3 mmHg to 177.4/94.4 mmHg under nitrendipine. 61.6% of the nifedipine patients and 58.8% of the nitrendipine patients had already reached blood pressure values < 180/100 mmHg after 45 min and in both groups 83% of these patients were still in this limit at the end of the observation period after 4 h. Tolerability was very good in both groups.
Conclusion: The new dosage form of nitrendipine (vial with 1 ml of alcoholic solution) represents an alternative in the treatment of hypertensive emergency.

Key words: Nitrendipine – Vial – Nifedipine – Hypertensive emergency

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A new oral formulation of nitrendipine with a rapid onset of action has been developed. It consists of an alcoholic solution in a small plastic tube (vial), containing 5 mg nitrendipine in 1 ml.

The purpose of the study reported here was to investigate the antihypertensive efficacy of the new dosage form of nitrendipine in hypertensive emergency. The reference substance was the calcium antagonist nifedipine (capsules of 10 mg), whose antihypertensive efficacy in this indication and dosage is well documented [1, 3, 6, 13].

Patients and methods

The multicentre study, which involved a total of 23 study centers in Germany, was a randomized, double-blind parallel-groups comparison. Patients aged between 20 and 70 years with acutely elevated blood pressure (systolic 200–250 mmHg and diastolic 110–140 mmHg at two supine measurements within 10 min) were included. Exclusion criteria were pregnancy and lactation, myocardial infarction within the 6 months prior to the start of the study, clinically relevant ECG abnormalities at rest like arrhythmia ≥ Lown III, AV-block grade II or III, disturbances or diseases of the gastrointestinal tract or liver that might affect the absorption, metabolism or excretion of the test substances, and intolerance reactions to nifedipine, nitrendipine or related substances. Treatment with other drugs capable of influencing blood pressure, including psychotropics and analgesics, was forbidden within the 3 h immediately prior to the start of the study and during the observation phase.

All the patients had given their oral or written informed consent to participation in the study according to the Helsinki criteria and had not taken part in any other clinical study within the last 30 days. The study had received the approval of the Ethics Committee of the Mannheim Faculty of Clinical Medicine of the University of Heidelberg.

Patients satisfying the inclusion and exclusion criteria were randomized to double-blind treatment with 10 mg nifedipine or 5 mg nitrendipine. The nifedipine capsules were bitten and immediately swallowed, nitrendipine was given from a small plastic tube (vial) containing 1 ml alcoholic solution. The contents were poured into the patient's mouth and was similarly swallowed immediately. To preserve the double-blind character of the study, every patient received, in addition to the test medication, a placebo corresponding to the other product ("double dummy").

Blood pressure and heart rate were measured 10, 20, 30, 45, 60 and 90 min and 2 and 4 h after the start of treatment. Patients whose blood pressure had not fallen by ≥ 20 mmHg (systolic) and ≥ 15 mmHg (diastolic), relative to the last baseline value, after 45 min were given either an additional capsule of 10 mg nifedipine or a further vial containing 5 mg/1 ml nitrendipine, in accordance with their group, maintaining the double dummy procedure to preserve the double-blind character. Patients, however, could be excluded from the study at any time if due to medical reasons.

Before and 90 min after the start of treatment a 12-channel resting ECG was recorded (Fig. 1).

Blood pressure was measured in the supine position by the Riva-Rocci method using a calibrated sphygmomanometer, Korotkoff sound 5 (disappearance of the sounds) being definitive for determination of the diastolic pressure. The pressure was to be released at a speed of 2 mmHg/s and the readings were to be accurate to 2 mmHg. If the blood pressure readings from the two arms differed, the higher value was recorded. Heart rate was determined by counting the radial pulse over 30 s.

In accordance with the protocol, the main variable for comparing the efficacy of the two treatments was the reduction in diastolic pressure 45 min after the start of treatment. A difference in the diastolic mean values of more than 5 mmHg between the groups was regarded as clinically relevant. To test the statistical significance between treatment groups (45 min after start of treatment) an analysis of covariance was used. In the model study centers were included as a factor, further as adjustment for different baseline values, these were included as a covariate.

For the quantitative anamnestic variables the ANCOVA group comparison was used. The Pearson χ^2 test was employed to test for equality of distribution of the qualitative variables.

The analyses were performed with the statistical program systems SAS (version 5.18) and BMDP (version 1987).

Results

A total of 82 patients from 23 study centers were treated with nifedipine and 79 patients with nitrendipine. There were 20 patients who deviated from the inclusion and exclusion criteria stipulated in the protocol or who belonged to centres with fewer than 2 patients per treatment group; these were excluded from the confirmatory analysis. A comparison with the results of the intention-to-treat analysis based on the total population showed that this did not affect the evaluation of the efficacy variables.

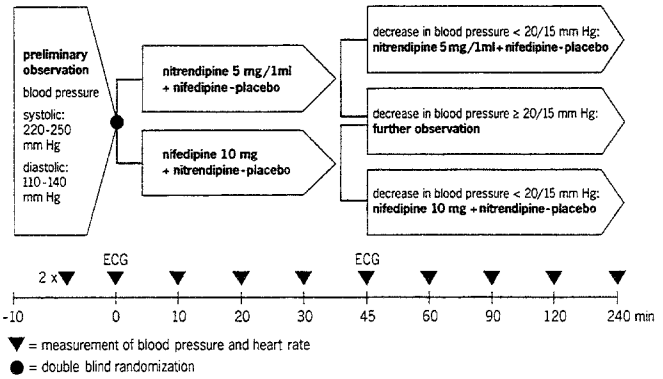

Fig. 1. Study schedule

The confirmatory analysis comprised 73 patients from the nifedipine group and 68 patients from the nitrendipine group. The two groups were comparable with regard to demographic and anamnestic data (Table 1).

The baseline blood pressure values and the blood pressure reduction within the first 45 min after the start of treatment were comparable in the two groups. Starting from baseline values of 216.0±11.4/117.4±8.8 mmHg, the blood pressure in the nifedipine group fell by 46.0±23.2/24.1±13.7 mmHg, to 170.0±24.5/93.3±15.1 mmHg.

In the nitrendipine group the baseline values were 216.9±12.8/117.3±9.0 mmHg. Within the first 45 min the blood pressure fell by 39.5±18.9/22.9±11.8 mmHg to 177.4±23.9/94.4±14.0 mmHg. Blood pressure after 45 min was comparable in both groups with no significant difference concerning systolic ($p = 0.07$) and diastolic ($p = 0.7$) values (Table 2).

The heart rate recorded over the same period showed no clinically relevant changes in either group (see Table 3 for details).

After 45 min, 57/73 (78.1%) of the nifedipine patients and 53/68 (77.9%) of the nitrendipine patients showed a blood pressure reduction of at least 20 mmHg (systolic)/15 mmHg (diastolic). According to the protocol, all patients who had still not reached this therapeutic target were to receive, at this point, an additional dose of nifedipine or nitrendipine, as appropriate to their group. As some investigators did not comply rigorously with the

Table 1. Demographic and anamnestic data

Treatment	Nitrendipine	Nifedipine
No. of patients	68	73
Age (years)	59.1±9.3	60.4±9.2
Body weight (kg)	78.0±11.3	78.5±13.5
Height (cm)	170.4±7.5	170.4±7.3
Sex		
male	38	45
female	30	28
History of hypertension (years, median)	6	7
Hypertension		
essential	62	60
other causes	6	13
Concomitant clinical symptoms	45	45

Table 2. Blood pressure (mmHg; mean±SD) in the first 45 min after medication

Time	Treatment			
	Nitrendipine ($n = 68$)		Nifedipine ($n = 73$)	
	Systolic	Diastolic	Systolic	Diastolic
Last pretreatment value	216.9±12.8	117.3± 9.0	216.0±11.4	117.4± 8.8
10 min after first medication	201.1±19.1	107.2±11.8	197.2±21.4	106.1±11.0
20 min after first medication	190.7±21.8	101.1±11.8	185.5±24.4	100.7±13.8
30 min after first medication	180.6±23.5	97.5±12.2	174.9±24.0	96.8±15.5
45 min after first medication	177.4±23.9	94.9±14.0	170.0±24.5	93.3±15.1

protocol, however, the second medication was given in 9 cases in the nifedipine group and 18 cases in the nitrendipine group.

After administration of the second medication there was a further decrease of blood pressure so that after 4 h the blood pressure level in both treatment groups was comparable irrespective of whether the patients had been given a second dose or not (Table 4).

A further aim of therapy was to reach or fall below a given target blood pressure. Table 5 shows, that blood pressure in the majority of patients fell below 200/100 mmHg resp. 180/100 mmHg after 45 min and remained below these values until the end of the observation period after 4 h.

The evaluation of tolerability comprised all the patients, including those excluded from the confirmatory analysis of efficacy. The medication was found to be very well tolerated, both for nifedipine and for nitrendipine. Under nifedipine there were two reports of vomiting, one of palpitations and one of overflow incontinence; under nitrendipine there were two reports of side effects (one flush, one restlessness). Their connection with the medication was evaluated as at least possible. The ECG findings showed no sign of changes induced by the study medication.

Table 3. Heart rate (beats per min; mean ± SD) in the first 45 min after medication

Time	Treatment	
	Nitrendipine ($n = 68$)	Nifedipine ($n = 73$)
Last pretreatment value	88.8 ± 18.0	84.1 ± 15.2
10 min after first medication	88.3 ± 17.9	86.0 ± 15.1
20 min after first medication	88.9 ± 14.8	86.4 ± 14.4
30 min after first medication	87.3 ± 15.0	85.8 ± 13.4
45 min after first medication	86.1 ± 16.8	85.7 ± 14.0

Discussion

Critical increases in blood pressure are among the commonest clinical emergency situations and require treatment tailored to the needs of the individual patient. No fixed blood pressure limits as a criterion for the diagnosis of hypertensive emergency have been defined because the clinical symptoms and prognosis are determined not so much by absolute blood pressure as by the dynamics of the blood pressure increase, the initial blood pressure or pre-existing organ damage. The guide values that have been given for hypertensive emergency are diastolic pressures in excess of 110–120 mmHg and systolic pressures in excess of 200–220 mmHg [8, 11].

The optimal therapy should reduce the blood pressure rapidly to prevent hypertensive organ damage, but not so rapidly or so far as to pose any risk of hypoperfusion of vital organs. Depending on the initial blood pressure, the therapeutic aim is to reduce the systolic pressure to below 160–180 mmHg and the diastolic pressure to below 100–110 mmHg [5].

Owing to the pathophysiological relationships, drugs that specifically reduce the elevated vascular tone are particularly suitable and effective. Thus the therapeutic efficacy of the calcium antagonist nifedipine in patients with hypertensive emergency has been demonstrated in numerous studies and the drug is used as first-line treatment in this indication especially in out-patients [3, 6, 13].

Nitrendipine is a further development of nifedipine, from which it is distinguished by a particularly high specificity for vascular smooth muscle so that at therapeutic doses it produces marked vasodilation while its cardiac effects remain negligible [10]. Since the onset of the antihypertensive effect of the tablet is too slow for the treatment of hypertensive emergency, a new liquid dosage form of nitrendipine (5 mg/1 ml) was developed and was investigated in the present double-blind study versus the reference substance nifedipine (10 mg). Nitrendipine 5 mg/1 ml was found as most effective compared to lower dosages (unpublished results).

The patients treated in the study had, on average, blood pressure values of 216/117 mmHg, with and without concomitant symptoms like headache, dizziness, blurred vision, chest pain or nausea induced by the hy-

Table 4. Course of systolic (syst) and diastolic (diast) blood pressure (mmHg, mean ± SD) over 4 h, separately for patients with and without second medication as stipulated in the protocol

Time	Medication							
	Patients without second medication				Patients with second medication			
	Nitrendipine ($n = 50$)		Nifedipine ($n = 62$)		Nitrendipine ($n = 18$)		Nifedipine ($n = 9$)	
	Syst	Diast	Syst	Diast	Syst	Diast	Syst	Diast
Baseline	214.3 ± 10.4	117.0 ± 8.8	215.2 ± 11.2	116.3 ± 8.4	224.0 ± 16.3	118.4 ± 9.7	219.4 ± 12.1	124.4 ± 9.2
After 45 min	168.9 ± 19.1	89.7 ± 11.4	164.7 ± 21.5	89.7 ± 12.9	201.1 ± 19.7	107.5 ± 12.2	203.3 ± 18.9	116.1 ± 7.8
Second medication					Nitrendipine ($n = 18$)		Nifedipine ($n = 9$)	
After 60 min	168.4 ± 18.7	91.3 ± 9.2	163.0 ± 21.2	90.7 ± 11.8	187.7 ± 18.0	98.6 ± 10.8	178.9 ± 21.6	102.8 ± 10.9
After 90 min	166.9 ± 19.3	90.8 ± 10.9	165.1 ± 19.1	91.7 ± 11.4	176.8 ± 16.2	93.8 ± 11.2	185.0 ± 20.3	102.2 ± 8.3
After 4 h	168.5 ± 18.2	91.5 ± 11.2	167.4 ± 21.9	92.5 ± 12.5	175.6 ± 16.1	94.7 ± 12.2	173.3 ± 20.9	98.3 ± 8.7

Table 5. Amount of patients reaching the target blood pressure of 200/100 resp. 180/100 mmHg during the study

	Nitrendipine ($n = 68$)	Nifedipine ($n = 73$)
	Blood pressure ≤200/100 mmHg	
45 min	51 (75.0%)	57 (78.1%)
4 h	62 (91.0%)	60 (82.2%)
	Blood pressure ≤180/100 mmHg	
45 min	40 (58.8%)	45 (61.6%)
4 h	48 (70.6%)	45 (61.6%)

pertension. They thus satisfied the criteria for hypertensive emergency given in the literature [8, 11].

In these patients the nitrendipine solution showed the same efficacy as nifedipine. The blood pressure reduction began within 10 min and reached its maximum value of −39.5/−22.9 mmHg (nitrendipine) or −46.0/−24.1 mmHg (nifedipine) within 45 min. This result concurs with the pharmacokinetic data for the nitrendipine solution, according to which the maximum plasma level is reached after about 30–45 min, and with experience with nifedipine in the treatment of hypertensive emergency. The decrease of systolic blood pressure seemed to be more pronounced under nifedipine. This difference, however, did not reach statistical significance ($p = 0.07$) compared to nitrendipine.

The criterion for a minimal blood pressure reduction as stated in the protocol was a reduction of at least 20 mmHg systolic and 15 mmHg diastolic within 45 min. This therapeutic target was achieved by 78.1% (nifedipine) and 77.9% (nitrendipine) of the patients. Patients whose blood pressure fell less than required were given a second dose of the same drug, whereupon in most cases blood pressure reached the recommended range of 160–180 mmHg systolic and 100–110 mmHg diastolic.

The percentage of patients reaching the target blood pressure values of 200/100 (180/100) mmHg or less within the first 45 min was 78.1% (61.6%) in the nifedipine group and 75.0% (58.8%) in the nitrendipine group. After 4 h these criteria were met by most of the patients. Thus for both test substances the therapy satisfied the above mentioned guidelines in the majority of cases.

Neither treatment group had any undesirably abrupt blood pressure decreases which might pose the risk of symptoms induced by hypotension. There especially were no clinical signs of a therapeutically induced decrease of cerebral perfusion. This is in accordance with results from earlier clinical studies where no decrease of cerebral blood flow occurred with either nifedipine or nitrendipine [1, 2, 9].

Taking the baseline blood pressure values into account, the extent of the blood pressure reduction achieved with nitrendipine corresponded to the existing experience with this new dosage form [7, 12].

A familiar and commonly noted side effect of the administration of vasodilative substances such as the dihydropyridines is a reflex increase in heart rate. The investigations of Späh and Grosser in 45 patients with hypertensive emergency showed an increase in heart rate after taking 10–20 mg nifedipine capsules but not after the nitrendipine solution [12]. In contrast to this, heart rate in the present study showed no clinically relevant changes in either group. It therefore seems that the decrease in the peripheral resistance, which is severely elevated in the emergency situation, leads rather to economy of cardiac work than to further activation of the sympathetic nervous system.

In summary, the results of this double-blind study show that the new liquid dosage form of nitrendipine represents an alternative in the treatment of hypertensive emergency. It is well tolerated and easy to administer, an advantage that is of potentially decisive importance in an emergency situation.

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