Eur Arch Psychiatr Neurol Sci (1988) 237:253–257

European Archives of Psychiatry and Neurological Sciences

Treatment with an i.v. Calcium Overload Blocker (Flunarizine) in Acute Stroke

A Pilot Study

P.-J. Hülser, H. Bernhart, C. Marbach, and H. H. Kornhuber

Department of Neurology, University Hospital, Steinhoevelstrasse 9, D-7900 Ulm, Federal Republic of Germany

Summary. In an open pilot study 55 patients suffering from acute stroke were treated with Flunarizine, a calcium overload blocker, in addition to standard therapy including diet, physiotherapy, adequate management of accompanying disorders, and hemodilution. The initial high-dose i.v. treatment (2 × 25 mg Flunarizine/day) and the subsequent oral regimen were well-tolerated. The main side effect was slight transient weariness. No adverse effects regarding blood pressure, heart rate, enzymes, blood analysis, renal function and, especially, no extrapyramidal motor symptoms or depression were detected. Flunarizine may be regarded as a relatively safe drug in acute stroke. The probable beneficial effect on the patient's recovery will be evaluated in a multicenter double-blind study.

Key words: Flunarizine – Calcium overload blocker – Acute stroke – Pilot study

There are more cases of stroke due to arteritis than assumed so far [11]; most cases, however, and especially those in patients below 70 years of age are due to cardiovascular risk factors. Since it is more efficient to prevent than to treat a stroke the best way to manage the stroke problem is to reduce these risk factors [1, 7, 9, 10, 12–15, 17–19]. However, even if prevention were better organised, strokes would still occur and must be treated. Hemodilution with Dextran 40, still used in some countries, did not prove to be effective in a randomized multicenter study [22]. There are some arguments that hydroxyethyl starch might have a better effect [8], but there are no results from controlled studies. In cases with heart failure, hypervolemic hemodilution may cause lung edema. Thus, better methods of stroke treatment are needed. In animal experiments Flunarizine, a calcium overload blocker passing the blood-brain barrier, has proved to be a cerebral protecting agent [29]. Flunarizine reduces postischemic hypoperfusion [27], lowers blood viscosity [3, 25] and, most of all, has a cytoprotective action, at least partly explained by blocking calcium overload of the ischemic cell [2, 4, 24, 26]. We investigated the possibility of using Flunarizine as i.v. high-dose treatment firstly by studying its side effects and cerebral pharmacodynamics (measuring the velocity of saccadic eye movements) in normal man [16] and secondly by an open pilot study in patients suffering from acute stroke; the results of this pilot study are reported in this paper. Both investigations show that even at high doses Flunarizine is well-tolerated; the main side effect is transient weariness. A randomised controlled double-blind multicenter study is now underway.

Offprint requests to: H. H. Kornhuber

Patients and Methods

Criteria for inclusion were age between 50 and 85 years, and time lag between stroke and onset of therapy less than 24 h. Excluded were patients with coma at onset of therapy, with earlier stroke in the patient's history (except for transient ischemic attacks). A total of 55 patients was treated, 37 males and 18 females. The average age of the males was 68 years (SE 1.6) and the females 70 years (SE 2.5). The stroke was in the right hemisphere in 29 patients. In 1 patient the stroke was in the brain stem.

The neurological, mental, and behavioral symptoms were investigated and quantitatively scored on the day of admission and on the consecutive days 1, 4, 7, 14, 21, and 28 and, if the patient stayed longer in hospital, on every consecutive week. The standardized neurological examination followed the

Mathew scale [20] and included assessment of the patients' mental status, sensorimotor functions, and activities in daily life.

In addition to the usual laboratory tests, a series of enzymes were investigated in the urine (by Dr. Junge, Kiel, FRG) to exclude side effects on the kidney. Complete blood counts and investigations of the urine were carried out on days 0, 4, 7, 14, 21, 28, and on the day of discharge.

Treatment

In the first 7 days the patients received i.v. infusions of 25 mg Flunarizine (dissolved in a solution of cyclodextrin) diluted in 100 ml 0.9% NaCl twice a day (that is 50 mg Flunarizine/day). The Flunarizine infusions were administered over 10 min in the morning and in the evening. In addition, hydroxyethyl starch 200/0.5 250 ml was given twice a day for 7 days. If necessary isovolemic hemodilution was carried out in order to reduce the hematocrit below 40% within 2 days. Furthermore the patients received 200 mg/day aspirin. Most patients were not able to walk; and these patients received 5,000 units heparin s.c. twice a day. If the blood pressure was higher than 160/90 mm Hg, it was slowly reduced using Urapidil or Triamterene-Hydrochlorothiazide. Patients with paresis of the leg wore elastic stockings to prevent thrombosis. All patients received physiotherapy as early as possible. Patients with diabetes, high blood pressure, or who were overweight received a 800 kcal diet rich in salads, vegetables, and protein, but low in fat and carbohydrates [1]. After the first 7 days the treatment with Flunarizine was continued with daily oral doses of 10 mg in the morning and 20 mg in the evening for 3 weeks. Thereafter the dose was reduced to 10 mg/day, given in the evening.

Results

The Flunarizine and other treatments were well-tolerated by all patients. Only 18 patients reported slight weariness during the infusion of Flunarizine. There was no parkinsonism, tardive dyskinesia, akathesia, or depression induced by Flunarizine despite the high dosage. There was a 1 mm Hg systolic blood pressure decrease on average over all patients (insignificant) when blood pressure was measured before and after the Flunarizine infusion. Significant blood pressure decrease occurred from day 0 to day 14 (similar to earlier stroke patients not treated with Flunarizine) due to the diet regime. There was no significant change in serum creatinine and serum urea. Serum creatinine was 87 μmol/l on average before the first Flunarizine infusion and 90 after the 1st week (the difference being insignificant). Serum urea was 6.40 mmol/l before Flunarizine on the day of admission and 6.37 on day 7 on average. Investigation of enzymes in the urine revealed no sign of renal alteration in consequence of the treatment. No influence on the heart rate was observed, and complete blood counts, blood coagulation, hepatic enzymes, serum electrolytes etc. were unchanged except for the effect of hemodilution.

Table 1. Outcome of patients treated for less than 14 days

No.	Patient	Sex	Age	Duration of treatment (days)	Outcome
1.	A.T.	M	65	1	Complete recovery (transient ischemic attack)
2.	A.D.	M	56	1	Dead on 3rd day (bronchopneumonia, pulmonary embolism)
3.	H.G.	M	76	1	Much better, but development of alcoholic delirium
4.	J.L.	M	81	7	Much better
5.	M.R.	F	81	7	Much better
6.	H.K.	M	64	8	Much better
7.	A.S.	M	78	9	Better
8.	W.K.	M	63	9	Much better
9.	M.N.	M	75	9	Better
10.	M.H.	F	74	11	Better
11.	M.G.	M	84	12	Dead on 14th day (hypertensive crises, left ventricular failure)
12.	I.S.	F	47	13	Much better

The course of the neurological symptoms was favorable on average. Detailed statistical analysis was done in those 43 patients who remained in hospital for at least 14 days. Those treated over a shorter period are presented in Table 1. There were 2 patients who died: A.D. exhibited severe bronchopneumonia on the day of admission and died suddenly 2 days later, probably due to pulmonary embolism despite low-dose heparin treatment; M.G. suffered from a long standing exceptionally severe arterial hypertension with sudden exacerbations. During these periods signs of severe cardial insufficiency developed. Despite treatment in an intensive care unit he died after 2 weeks due to irreversible left ventricular failure. Thus in both cases the lethal outcome was unrelated to the Flunarizine treatment. All the other patients

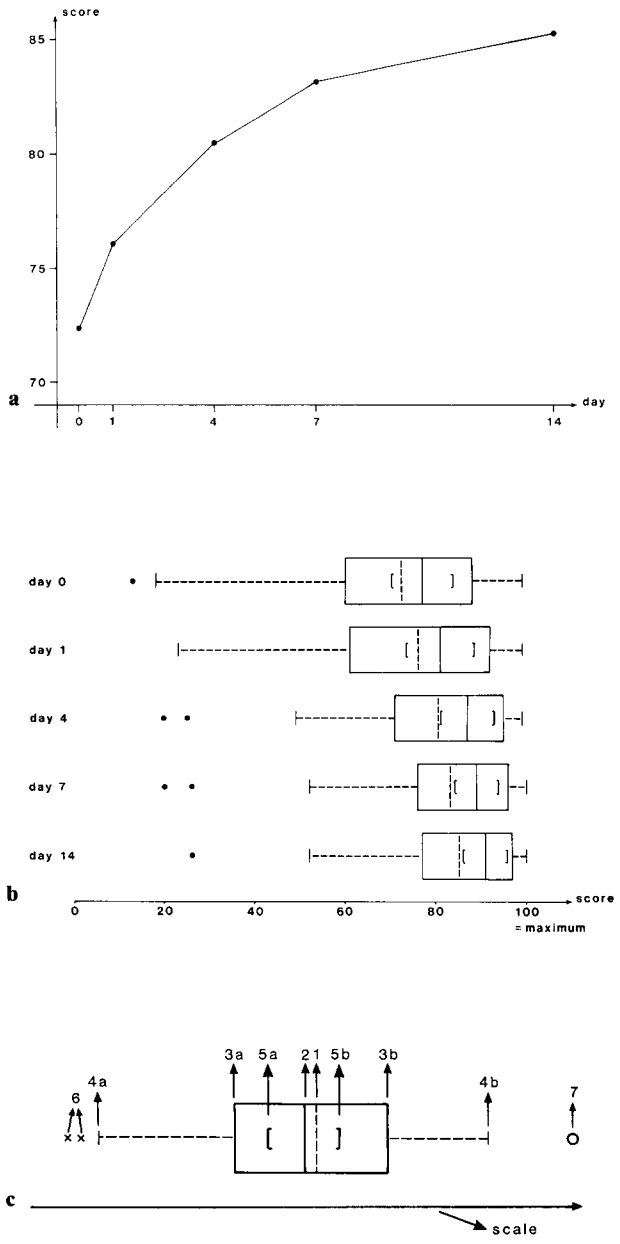

Fig. 1a–c. Mathew score of 43 patients over 14 days after acute stroke, **a:** average score, **b:** distribution of the individual scores and several statistical markers by means of box-plots **c:** explanation of the symbols used in Fig. 1b: 1 is the arithmetic mean of the Mathew score of the 43 patients, 2 is the median: half of the patients are below, half above of the median, 3 includes 50% of the patients who are above the 25% of the lowest and below the 25% of the highest cases, 3a is the margin of the lower quartil, 3b the margin of the highest quartil, 4a is the lower adjacent value, that is the smallest value which is larger than [lower quartil minus 1.5 × (upper quartil − lower quartil], 4b the upper adjacent value, that is the largest value which is smaller than [upper quartil plus 1.5 × (upper quartil − lower quartil)], 5a and 5b depict the lower and upper notch values. The interval between the lower and the upper notch is the 95% confidence interval for the median of the patients. When there is no overlap of the notch interval, the corresponding medians are different at the 10% level of significance, 6 shows the outlyers in the statistical sense

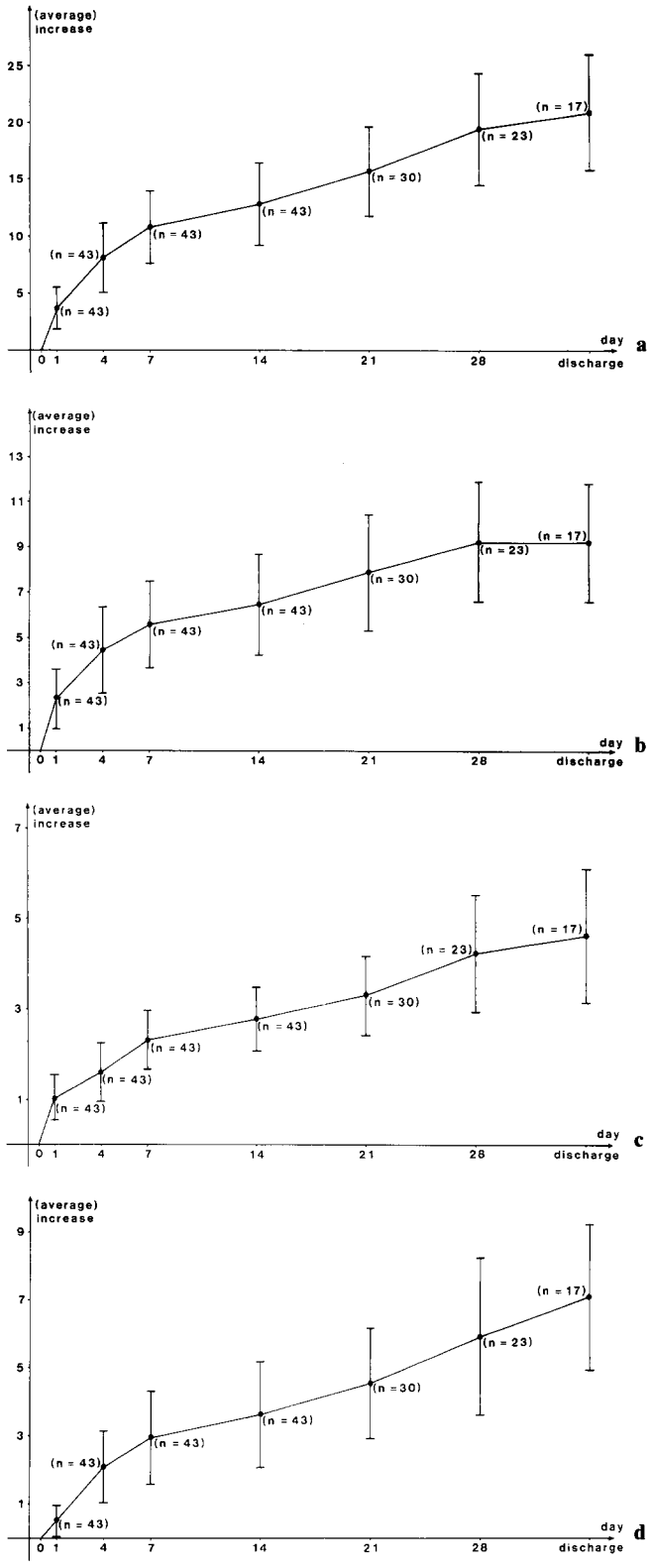

Fig. 2a–d. Increase of the average Mathew score compared with the initial value. The *bar* indicates twice SD. The curves depicts the average values for 43 patients during the first 2 weeks. Thereafter the number of patients decreases because more and more patients were discharged from hospital. **a:** total score. **b:** mental status score. **c:** sensorimotor score. **d:** ability of daily life score

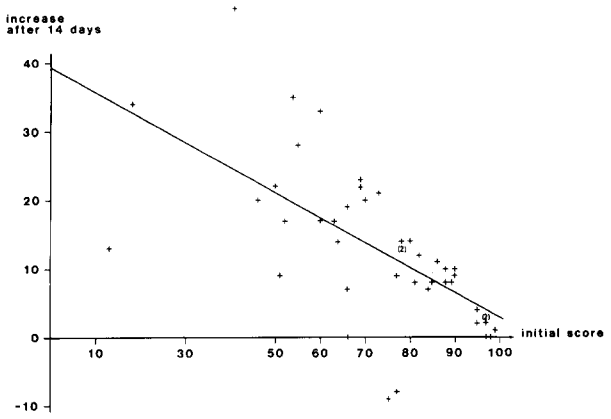

Fig. 3. Change of the individual score *(ordinate)* during the first 2 weeks in relation to the initial value *(abscissa)*

treated for less than 14 days showed an improvement in their initial deficits.

The data of 43 patients who stayed in the hospital for 2 weeks or longer were statistically analyzed in detail. The average Mathew score increased most in the first days, the curve resembling an exponential course (Fig. 1a). The individual scores within the examined population exhibited a broad dispersion at the beginning which decreased during the period of observation. This could mean that even patients with severe deficits had a favorable outcome on average (Fig. 1b, 1c). The increase in score was most pronounced in the 1st week (11 points), in the 2nd slightly more, but in those who stayed for more than 2 weeks further amelioration was noted (Fig. 2a). The separated scores for mental status (Fig. 2b), sensorimotor function (Fig. 2c), and the ability in daily life (Fig. 2d) were essentially similar. On the Mathew scale a maximum of 100 points can be reached. Therefore patients with slight deficits at the time of the stroke, with a score near to 100, can only make a small increase. This predicted relation between initial score and increase was confirmed by our data: the patients with a severe deficit tended to show a higher increase, though with large scatter (Fig. 3).

Discussion

Despite a large amount of literature on stroke, stroke treatment, and stroke rehabilitation, there are few comparable quantitative data in the literature [5, 6, 28]. Our figures showed a remarkable similarity of the quantitative course of the sensory motor, mental, and daily life activity aspects of the Mathew scale data which underline the validity of the method. The course of improvement was similar to an exponential course up to day 14. Our data thereafter refer to a patient group with more and more discharged patients, therefore the presumably exponential course is distorted. This slight kinking towards a higher improvement results from the fact that the possible improvement is limited at the upper end of the scale. The larger the initial disability following the stroke, the more possible improvement as time goes on under treatment. The less severely disabled patients were, however, discharged from hospital sooner. The relation between improvement and initial score makes it likely that the collection of data was competent. Most of the improvement was presumably due to a spontaneous course under a good general patient care including suitable positioning of the limbs to prevent spasticity, prevention of bed sores, prevention of urinary retention, prevention of deep venous thrombosis and aspiration pneumonia etc., due to physiotherapy, hemodilution, treatment of arterial hypertension, normalization of metabolism by suitable diet, etc.

Regarding therapy of acute stroke, we cannot be sure of the beneficial effect of Flunarizine before a placebo controlled trial is completed but we feel justified in publishing this paper considering the wide use of Flunarizine and the controversy of possible side effects. It can be stated that there were no adverse cardiovascular reactions including blood pressure. The main side effect was slight weariness even with the large doses used in this study. No adverse effects regarding enzymes, blood analysis, and kidney function were detected. It is remarkable that in contrast to some claims in the literature even with the large doses given no extrapyramidal motor side effects were detected. In this connection we should add that despite widespread use of Flunarizine for the treatment of vertigo, migraine, and cerebrovascular disease, in 20 years we have never seen a patient with extrapyramidal motor symptoms or depression due to Flunarizine either in inpatients (150 beds) or outpatients (about 15,000 per year). This does not mean that we consider extrapyramidal motor side effects of Flunarizine to be impossible, however, they seem to be very rare. A recent study [23] came to the same conclusion. Thus, considering the well-documented therapeutic value of Flunarizine at least in vertigo and migraine, it may be regarded as a relatively safe drug. The slight weariness decays within a few hours even after large i.v. doses.

The effect of Flunarizine on stroke will be evaluated in a multicenter double-blind study now underway. From the present pilot study a favorable impression may be stated. In animal experiments there was a significant positive effect on cerebral ischemia [21, 24, 25, 29].

Acknowledgment. We thank Prof. Dr. J. Hartung, University of Dortmund, for help with statistical analysis of the data.

References

1. Altmann J, Kornhuber AW, Kornhuber HH (1987) Stroke: Cardiovascular risks and the quantitative effect of dietary treatment on them. Eur Neurol 26:90–99
2. Betz BE, Hämmerle H, Strohschneider T (1985) Inhibition of smooth muscle cell proliferation and endothelial permeability with flunarizine in vitro and in experimental atheroses. Res Exp Med 185:325–340
3. De Clerck F, David JL (1981) Pharmacological control of platelet and red blood cell function in the microcirculation. Cardiovasc Pharmacol 3:1388–1412
4. Deshpand JK, Wieloch T (1986) Flunarizine, a Calcium entry blocker, ameliorates ischemic brain damage in the rat. Anesthesiology 64:215–224
5. Frei A, Cottier C, Wunderlich P, Lüdin E (1987) Glycerol and dextran combined in the therapy of acute stroke. A placebo-controlled, double-blind trial with a planned interim analysis. Stroke 18:373–379
6. Gelmers HJ (1984) The effects of nimodipine on the clinical course of patients with acute ischemic stroke. Acta Neurol Scand 69:232–239
7. Glocker E, Hänsel D, Kornhuber HH (1977) Übergewicht, Rauchen und andere Risikofaktoren bei 357 Fällen von Hirndurchblutungsstörungen. Dtsch Med Wochenschr 102:1437
8. Haaß A, Kroemer H, Jäger H, Müller K, Decker I, Wagner EM, Schimrigk K (1986) Dextran 40 oder HAES 200/0,5? Dtsch Med Wochenschr 111:1681–1686
9. Henkler C, Scheben B, Kornhuber A, Kornhuber HH, Molz KH, Maier U, Swobodnik W, Wechsler JG (1987) Am Anfang des Weges zum Schlaganfall. Dtsch Med Wochenschr 112:157–158
10. Hjermann I, Velve Byre K, Holme I, Leren P (1981) Effect of diet and smoking intervention on the incidence of coronary heart disease. Report from the Oslo Study Group of randomized trial in healthy men. Lancet II:1303–1310
11. Hülser P-J, Kornhuber HH, Risotto R (1985) Schlaganfall und Herzinfarkt durch Arteriitis. Dtsch Med Wochenschr 110:1753–1754
12. Kannel WB, Wolf TA, Verter J, McNamara P (1970) Epidemiological assessment of the role of blood pressure in stroke. The Framingham Study. JAMA 214:301–314
13. Kannel WB, Blaisdell FW, Gifford R, Hass W, McDowell F, Meyer JS, Millican CH, Rentz LE, Seltser R (1971) Risk factors in stroke due to cerebral infarction. Stroke 2:423–428
14. Klatsky AL, Friedman GD, Siegelaub A, Gerard MJ (1977) Alcohol consumption and blood pressure. N Engl J Med 296:1194–1200
15. Kobayashi T (1976) Epidemiology of hypertension and stroke in Japan. In: Hatano S, Shigematsu I, Strasser T (eds) Hypertension and stroke control in the community. WHO, Geneva 1976, pp 80–96
16. Kornhuber A, Jürgens R: (submitted for publication)
17. Kozararevic DN, Vojvodic N, Dawber T, McGee D, Racic Z, Gordon T, Zukel W (1980) Frequency of alcohol consumption and morbidity and mortality: the Yugoslavia cardiovascular disease study. Lancet I:613–616
18. Lavy S (1979) Medical risk factors in stroke. p 127–133. In: Goldstein M, Bolis L, Fiesch C (eds) Cerebrovascular disorders and stroke. Adv Neurol 25
19. Lipid Research Clinics Program (1984) The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 251:351–364, 365–374
20. Mathew NT, Meyer JS, Rivera VM, Charney JZ, Hartmann A (1972) Double-blind evaluation of glycerol therapy in acute cerebral infarction. Lancet II:1327–1333
21. Peters T (1984) Wirkung von Kalziumantagonisten auf zelluläre Kalziumbewegungen. Therapiewoche 34:6011–6029
22. Scandinavian Stroke Study Group (1987) Multicenter trial of hemodilution in acute ischemic stroke. I. Results in the total patient population. Stroke 18:691–699
23. Schimert GC (1987) Bewertung des cerebralen Calciumantagonisten Flunarizin. Wirksamkeit, Verträglichkeit, Erfahrungen. MMW 129:471–473
24. Schwabedal PE (1987) Anti-Arteriosklerotischer Einfluß von Flunarizin auf hypertensive Ratten. Int. Symp. Calcium Antagonists, New York 1987
25. Scott CK, Persico FJ, Carpenter KS, Chasin M (1980) The effects of flunarizine, a new calcium antagonist on human red blood cells in vitro. Angiology 31:320–330
26. Silverstein FS, Buchanan K, Hudson C, Johnston MV (1986) Flunarizine limits hypoxia-ischemia induced morphologic injury in immature rat brain. Stroke 17:477–482
27. Van Nueten JM (1982) Selectivity of calcium entry blockers. In: Albertini A, Paoletti R (eds) Calcium modulators. Elsevier Biomedical Press, Amsterdam, pp 199–208
28. Wade TD, Hewer RL (1987) Functional abilities after stroke: measurement, natural history and prognosis. J Neurol Neurosurg Psychiatr 50:177–182
29. Wauqier A, Ashton D, Clincke G, Fransen J (1985) "Calcium Entry Blockers" as cerebral protecting agents: Comparative activity in tests of hypoxia and hyperexcitability. Jpn J Pharmacol 38:1–7

Received February 2, 1988