Original Articles

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Geriaforce* for the treatment of age-induced memory disorders

A placebo-controlled double-blind study with two dosages

With advancing years people complain increasingly of deterioration of memory and other mental abilities. For this reason drugs that at least partially eliminate disorders of brain function are of increasing interest. Geriaforce is a tincture prepared from fresh *Ginkgo biloba* leaves whose efficacy in age-induce disorders of memory and concentration was investigated in the present multicentre study. It was carried out using objective and subjective test parameters in a randomised manner with two different doses of Geriaforce in comparison with placebo in 241 patients aged between 55 and 85 years. After a wash-out period of 4 weeks, 77 patients were given twice the recommended dose for the commercial product (G1) for 6 months, and 82 patients each received either the usual dose of Geriaforce (G2) or a placebo tincture (Pl). To maintain the double-blind character of the study, the dosages were set generally to 40 drops t.i.d. For this purpose the Geriaforce tincture for the G2 group had to be diluted to half strength with placebo solution in order to be able to administer the corresponding dosage of commercial preparation of 20 drops t.i.d. Assessment of treatment success was based on the results of the following psychometric tests: the extended mental control test (EMCT) for measuring attention and concentration, the Rey test, part 1, for measuring short-term memory and learning ability as well as part 2 for measuring long-term memory and the Benton test for measuring visual short-term memory. In addition, subjective impressions of memory and concentration were recorded by the patients. Monitoring with these tests took place immediately before starting treatment and after treatment for 12 and 24 weeks. In the course of the study a relevant improvement in mental capacity developed in all 197 patients who completed the study (G1 = 62, G2 = 68, Pl = 67). A marked improvement in comparison with placebo was demonstrated for Geriaforce 40 drops t.i.d. only with the Benton test and at the concentration equivalent to 20 drops t.i.d. this was even statistically significantly greater than the learning effect. The tolerance was reported to be «good» and did not differ significantly between the three treatment groups. From the present results it can therefore be deduced that in patients with age-induced disorders of memory and concentration the dosage corresponding to the commercial preparation of Geriaforce is not only superior to the placebo but also to the double dose of Geriaforce.

Age-induced deterioration of perception ability is characterised by a qualitative and quantitative reduction of powers of observation, memory, attention and cognitive psychomotor conditions. These disorders of brain function are frequently associated with a reduction of cerebral circulation, whose cause may be due to arteriosclerosis, which may precipitate multiple infarctions in the brain. The cause of this degenerative damage, which can lead in many cases to dementia, is, however, often unknown. With the increasing life-expectancy and the rise of the age-limit in the population, a proportional increase of the disorders of central nervous function has been observed. Recently an alcohol/water extract from the leave of *Gingko biloba* has gained increasing interest for the treatment of these disorders. Active constituents that have been isolated are flavone glycosides and the terpene lactones, such as ginkgolides and bilobalide. The flavone glycosides have proved to be potent antioxidants for scavenging free radicals, which arise primarily in the presence of is-

chaemia and hypoxia as well as in some metabolic disorders from bivalent oxygen molecules. They cause destruction of the cell membrane via oxidation of its lipid structure. The terpene lactones are antagonists to platelet activating factor (PAF) and thus inhibit platelet aggregation, degranulation of neutrophil leucocytes and the production of free radicals. These mechanisms of action result in an increase in both circulation and cerebral metabolism and also neuroprotection.

Although this has been confirmed in numerous in vitro and in vivo investigations, there have so far been only a few studies *Ginkgo biloba* leaf extract for the assessment of subjective improvement of these disorders of brain function and not one single study with objective psychometric tests for assessment of memory, attention and concentration during this therapy. This was the reason for performing the present treatment study with two different concentrations of *Ginkgo biloba* extract in comparison with placebo in patients with age-induced loss of psychomotor function, but excluding the presence of dementia and depression.

Method

After the trial protocol had been approved by the ethical committee «Medisch Spectrum Twente» in Enschede, it was possible to start recruitment of patients with age-induced disorders of memory in 22 Dutch General Practices. The disorders of memory could be delineated from dementia with the aid of the score of the Mini Mental State Examination, which consists of short questions and tasks for assessing memory, orientation in space and time, concentration, colloquial language and physical skills. In addition, assessment of depression was carried out with Beck's method in order to rule out depression, which can be assumed to exist if the score exceeds 21 points. Further exclusion criteria were loss of memory for a known cause that needed other treatment, psychoses and secondary cerebral insufficiency as the result of intoxication or metabolic disorders. These included liver and renal failure, diabetes mellitus, diseases of the gastro-intestinal tract, heart failure, malignant diseases as well as abuse of alcohol and medicaments. Concomitant anticholinergic medication and prior treatment with *Ginkgo biloba* in the last 3 months also led to exclusion from the study. After giving their informed consent, a total of 143 women and 98 men aged between 55 and 85 years (mean age: 68.9 ±7.8 years) were enrolled in the study, which started with a 4-week wash-out period without any medication in order to obtain a steady state.

Two psychology assistants were trained by a clinical psychologist to perform the subsequent investigations with standard psychometric tests. The monitoring with the tests took place immediately before starting treatment and after 3 and 6 months' treatment. The tests used were the extended mental control test (EMCT), the Rey tests 1 and 2 and the Benton test. The EMCT registers attention and concentration, e.g. by continuous memorising of even (from 2 to 30) or odd numbers (between 1 and 29) as well as serial calculations (e.g. continuous addition of 7s starting with 1, or with continuous subtraction, multiplication and division of set numbers and starting values). The Rey test 1 is used to measure the short-term memory and learning effect (e.g. by repetition of 15 previously spoken words from a text that was read out). The Rey test 2 provides insight into long-term memory (e.g. by naming the months and weekdays in the correct order) and the Benton test permits assessment of visual memory (e.g. by the recognition of preset geometric figures in a complex presentation). Assessment is by means of a maximum score laid down for each test. In addition, assessment of the subjectively experienced memory disorders by the patients was carried out with a 5-point LIKERT scale.

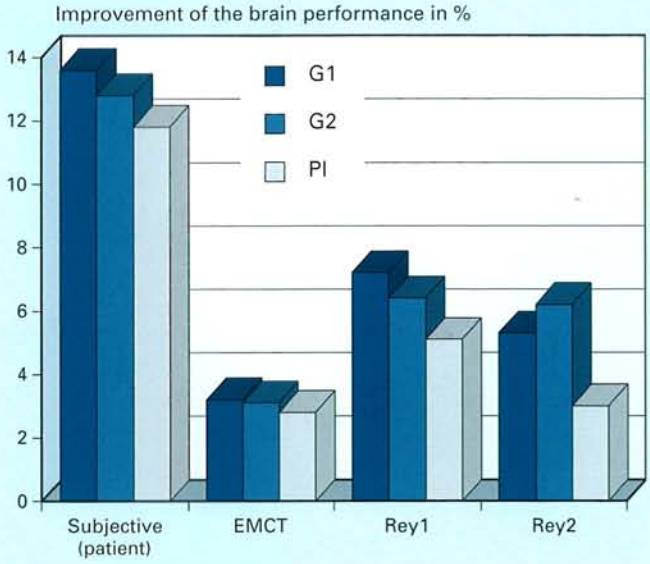
The commercial preparation Geriaforce is an alcohol/water extract from *Ginkgo biloba* leaves with a total content of 0.20 mg/ml flavone glycosides and 0.34 mg/ml ginkgolides. The placebo tincture used for control consisted of an alcohol solution of chlorophyll that had been clarified with caramel powder. To ensure the double blind character the dose was set for all three forms to 40 drops t.i.d. (1.9 ml). For Geriaforce this corresponds to twice the intended dose for the commercial preparation of 20 drops t.i.d. In order to obtain this dosage with the administration of 40 drops t.i.d., the Geriaforce had to be diluted with a placebo solution in the ratio 1:1.

For statistical analysis, the patient record sheets were entered in two separate data bases independently with suitable coding of missing data. ANOVA models were used as contrast and post-hoc tests. In addition, the KOLMOGROV-SMIRNOV test, MANN-WHITNEY, WILCOXON and t-tests were used.

Course of the Study

A total of 241 patients were recruited for the study. Of these 77 patients were randomised to 40 drops of Geriaforce primary tincture t.i.d. (G1) and 82 patients each were given either the diluted Geriaforce primary tincture equivalent to 20 drops t.i.d. (G2) or placebo drops (Pl). With a drop-out rate of a total of 44 patients during the 24-week treatment period, there were 62 patients in the G1 group, 68 patients in the G2 and 67 patients in the Pl at the end of the study. The reasons for dropping out in 25 patients was the occurrence of adverse events during the treatment, whereby the distribution was almost the same with 8 patients each in the two Geriaforce groups and 9 patients in the placebo group. The reasons for the remain-

		A	B
Subjective	G1	54.8–68.4%	+13.6%
(patient)	G2	56.6–69.4%	+12.8%
	Pl	57.2–69.0%	+11.8%
TCMA	G1	88.7–91.9%	+ 3.2%
	G2	89.6–92.7%	+ 3.1%
	Pl	89,1–91.9%	+ 2.8%
Rey1	G1	70.4–77.6%	+ 7.2%
	G2	73.9–80.3%	+ 6.4%
	Pl	77.8–82.9%	+ 5.1%
Rey2	G1	85.8–91.1%	+ 5.3%
	G2	86.5–92.7%	+ 6.2%
	Pl	87.8–90.8%	+ 3.0%



Tab. /Fig.1: Placebo-controlled, double-blind study in patients with age-induced disorders of brain function (n = 197): percentage range of brain performance (subjective and determined with the psychometric tests EMCT, Rey 1 and Rey 2, see text) before **(A)** and their improvement after **(B** and **Figure)** 24 weeks' treatment with 40 drops Geriaforce primary tincture t.i.d (G1), a dose equivalent to 20 drops Geriaforce primary tincture t.i.d. (G2) and placebo.

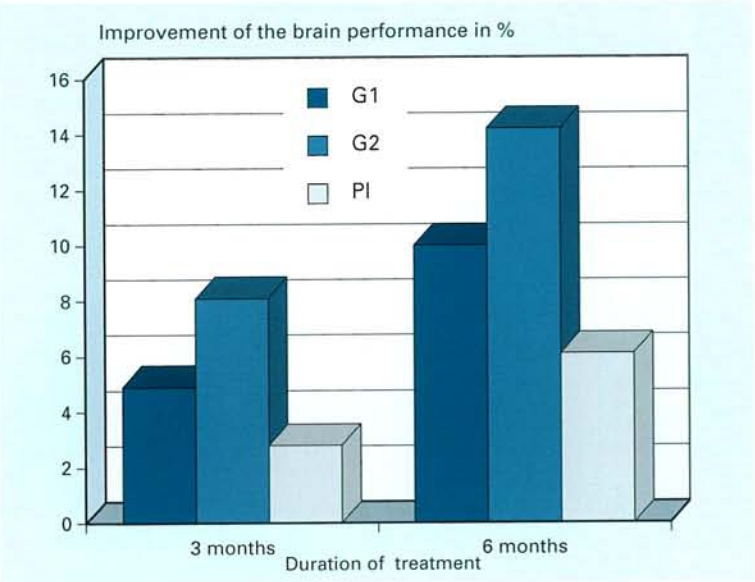
ing 19 drop-outs were: lack of motivation in 6 cases (G1 = 3, G2 =2, Pl =1), social conditions in 3 cases (G2 = 2, Pl = 1), insufficient intake of the medicament in the doctor's opinion (Pl =2), or death from unknown causes in two cases (G1 =1, Pl = 1). The remainder consisted of one case each of the following: hospitalisation (Pl), trigeminal neuralgia (G1), a whiplash syndrome after a motoring accident with a car (G1), subsequent exclusion from the study as the result of erroneous enrolment in spite of depression according to the score in the Beck assessment (G2), and age >85 years, which was set as the upper age limit for the study population (G2), and finally 1 patient who failed to return for follow-up for unknown reasons (G1).

Compliance with drug taking was assessed by the doctor by the degree of fill of the medicine bottles that the patients brought with them after 6, 12 and 24 weeks. In 135 cases there was a mean ingestion of 37.5 ml per week with a statistically non-significant distribution of the differences between the treatment groups (p = 0.615). The mean ingestion for the entire treatment period was 896.0 (157.0 ml in 45 cases in G1, 917.7 (164.0 ml in 46 cases in G2 and 886.0 (146.0 ml in 44 patients in Pl). Here, too, there was no significant difference between the groups (p = 0.381). A fall in compliance was recorded in all groups after treatment for 12 weeks.

Response to the Therapy

A marked improvement of the measured mental abilities was seen in the observation period in almost all patients because of the learning effect. For this reason a statistically significant improvement at the end of the treatment compared with the values at the start of the treatment was found in every treatment group and each test. On comparison of the results between the groups at the same times during treatment, there was, however, no significant difference in the improvement of memory and concentration according to the subjective assessment of the patients in the 2-sided ANOVA. In the EMCT and Rey tests 1 and 2 also, in which attention and concentration were already rated as good before starting treatment, there was no statistically significant difference in the between-group comparison with the two-tailed ANOVA **(Tab./Fig. 1)**. Only on testing the visual short-term memory with the Benton test was there a statistically significant improvement compared with placebo (p = 0.0076 according to ANOVA) with the 6-month's treatment with the lower dose of Geriaforce corresponding to 20 drops t.i.d. The higher dose of 40 drops t.i.d. also proved to be clearly superior to placebo in this test than in the other psychometric tests **(Tab. /Fig. 2)**.

The tolerance, which was assessed both by the patients and their doctors according to a 4-point scale (none, moderately good, good, very good), was rated as «good». Altogether 40 adverse events of a mild nature occurred in 34 patients. In 14 cases (G1 = 5, G2 5, Pl = 4) these consisted of non-specific and transient gastro-intestinal symptoms such as nausea or epigastric pressure, in 7 cases of dizziness and stupor (G1 = 3, G2 = 4), in 4 cases of headache (G2 =3, Pl = 1) and two



		A	B	C
Benton	G1	55.3–65.3%	+4.9%	+10.0%
	G2	52.7–67.9%	+8.1%	+14.2%
	PI	56.2–62.3%	+2.8%	+ 6.1%

Tab. /Fig. 2: Placebo-controlled, double-blind study in patients with age-induced disorders of brain function (n = 197): percentage range of brain performance (Benton test) before **(A)** and its improvement after 3-month **(B** and **Figure)** and 6-month treatment **(C** and **Figure)** with G1, G2 and PI.

cases of tiredness (1 each in G1 and G2). In addition, the occurrence of tinnitus and arthritic symptoms was reported once each in the high-dose Geriaforce, while in the treatment group with the low-dose Geriaforce tincture there was one case each of back pain and transient nose-bleeds. In the placebo group there was pain in the kidney region in 2 cases and 1 case each of cardiac asthma, weight-loss and deterioration of mood.

Conclusions

The concordant linear increase in performance for all of the tests during treatment, even under placebo, indicates a learning effect which was not completed even after an observation period of 6 months. Only in the Benton test for short-term visual memory could a statistically significant superiority of the commercial preparation Geriaforce over placebo at the doses given be seen after this treatment period. From this it can be seen that Geriaforce is capable of improving brain performance and appears to be indicated for age-induced memory disorders. The clearly demonstrated therapeutic success as shown by the psychometric tests, however, can only be demonstrated objectively when the learning effect has definitely ceased and is no longer superimposed on the drug-induced increase in mental ability. For this a considerably longer observation period than 6 months' treatment with Geriaforce is necessary. The better response to the lower dosage, corresponding to the commercial preparation of Geriaforce, in comparison with 40 drops t.i.d. and placebo permits the conclusion that for this medicament the dosage of 20 drops t.i.d. is optimum for long-term treatment of age-induced disorders of concentration and memory.

The tolerability of Geriaforce was extremely good on the basis of the assessment by patients and doctors. Adverse events of concordantly mild degree did not occur very frequently, whereby it may be assumed that they were due to a not inconsiderable degree to the cerebral changes that are the cause of disorders of brain performance.

This report is based on the results of a clinical study by M. Brautigam et al. which was organised by a Dutch company in co-operation with Bioforce AG. Detailed findings of this study will be published elsewhere in English.

References are available from the author.

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