

Ginkgo special extract EGb 761® in vertigo: A systematic review of randomised, double-blind, placebo-controlled clinical trials

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Citation

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Abstract

Background. The concept for medical treatment of vertigo has changed during the last 30 years, because the dependence of the vertiginous sensation on vestibular compensation and the dependence of vestibular compensation on the state of vigilance were recognized.

Methods. In this systematic review experimental studies of the influence of the special Ginkgo extract EGb 761® on vestibular compensation in animals and randomized, double-blind clinical studies of EGb 761® in vestibular and non-vestibular vertigo are described and critically evaluated.

Results. The beneficial effect of EGb 761® on vestibular compensation was demonstrated in preclinical and clinical studies.

Conclusion. Evidence of efficacy of EGb 761® in the treatment of vertiginous syndromes can be derived from the available studies.

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BACKGROUND

As is generally known, vertiginous symptoms are on the whole amongst the most frequently registered complaints. Although the fact that different pathological conditions could cause different types of vertigo was recognised early on, for a long time attempts were made to treat the symptom vertigo without further differentiation. As a result, antihistamines such as dimenhydrinate were commonly used in the forties. These had considerable sedative side effects, however. Other substances such as thiethylperazine (Torecan®), dihydrobenzperidol or even diazepam, which may be classified as tranquillisers, were also used as antivertiginous drugs. Although the short-term therapeutic effects were

unquestionable, the concomitant sedative effects excluded long-term therapy. Moreover, at about the begin of the seventies – at first only in animal experiments – the underlying mechanisms of vestibular compensation (1), i.e. the recovery processes following vestibular lesions, and their dependence on vigilance and pharmaceuticals (2) were elucidated. The finding that sedative substances inhibit vestibular compensation processes led to conventional “antivertiginous agents” only being recommended for acute therapy, not for long-term treatment. This is an important aspect with regard to different clinical pictures (3) and driving capability (4).

VESTIBULAR COMPENSATION

The basis for all the concepts about vestibular compensation is the observation that the unilateral loss of a peripheral vestibular organ initially leads to marked symptoms with severe rotational vertigo, spontaneous nystagmus to the healthy side and ataxia (5). However, this complex of symptoms becomes less severe and largely disappears after a certain period of time, which differs considerably between

individuals and from species to species. These natural recovery processes may also be observed in animal behaviour experiments and are possibly related to neuronal phenomena which may be described as an imbalance at the level of the vestibular nuclei (6,7). Certain parameters of neuronal activity, such as spontaneous activity, and response to dynamic stimuli (such as gain and phase) show a tendency to reequilibrate. What is interesting is that vestibular compensation may be improved by additional input from the visual system (8). These phenomena have been considered to be the neuronal correlates of the vestibular recovery processes.

The recovery from static symptoms, such as vertigo at rest, spontaneous nystagmus and ataxia, which may be completely restored, should be differentiated from the recovery of dynamic symptoms, such as asymmetrical rotation-induced nystagmus reactions and asymmetrical optokinetic nystagmus, which is only incomplete (9). What is certain is that vestibular compensation is associated with re-adjustment processes in central nervous structures, primarily in the vestibular nucleus (10).

POSSIBILITIES FOR IMPROVING COMPENSATION

When these findings are taken into account, the recommendations made in the forties for treating vestibular diseases by physical therapy appear, retrospectively, to have a rational basis. Cawthorne and Cooksey's methods (11) form the basis of many training programmes. These have been extended or modified many times. In Germany, the single-blind studies of Hamann (12) and later Strupp et al. (13) were able to confirm the clinical success of vestibular exercise programmes.

The goal of all habituation training exercises is to more or less specifically stimulate vestibular performance, but above all to include auxiliary systems, such as the visual and proprioceptive systems, in the compensation processes. Numerous observations and studies have demonstrated that vestibular compensation may be influenced by pharmacological agents (2,7).

Initially, animal experiments were used to investigate how the compensation processes are influenced by pharmaceutical agents. In general, it appears that stimulants such as amphetamine, caffeine or even strychnine accelerate compensation, while sedatives such as high doses of alcohol or barbiturates slow down the process (2). Consequently, an

ideal compensation-enhancing substance should have no sedative properties but should have central stimulatory actions in the vestibular nuclei.

COMPOSITION AND PHARMACOLOGY OF EGB 761

EGb 761® is a special extract of Ginkgo biloba leaves (herbal drug-extract ratio 35-67:1) standardised to 22 - 27 % Ginkgo flavone glycosides and 5 - 7 % terpene lactones (ginkgolides, bilobalide) which contains less than 5 ppm ginkgolic acids. Experimental investigations have shown flavone glycosides and terpene lactones to be the most important active ingredients (14).

EGb 761® has been shown to have neuroprotective effects, including improved energy supply by the mitochondria, antioxidative or radical capturing properties, and to improve cerebral perfusion (through reduction in blood viscosity) and glucose utilisation (14). The EEG shows that EGb 761® appears to have effects that increase vigilance and cognitive activation (15,16). One of the main indications for EGb 761® is dementia (Alzheimer's disease and vascular dementia). Which mechanisms play the decisive role in the action of EGb 761® in vertigo and vestibular compensation cannot be stated definitively. Depending on the pathogenetic background, both antioxidative properties and activation of cerebral metabolism may be possible as well as vigilance-enhancing and cognitive activation effects.

EGB 761 AND VESTIBULAR COMPENSATION IN ANIMAL EXPERIMENTS

An influence of EGb 761® on the vestibular system and vestibular compensation could be demonstrated in animal experiment models. In rats with experimentally-induced unilateral labyrinth loss, Denise and Bustany (6) found a significantly accelerated reduction in pathological signs and symptoms such as nystagmus under light and dark conditions as well as in postural and motor disorders with EGb 761® treatment compared to control animals.

M. Lacour's team (7) found that several vestibular compensation parameters recovered more rapidly in cats treated with EGb 761® than in untreated control animals. The treated animals regained their motor capacities in the "Rail Test" to a greater extent than the untreated animals. At the neurophysiological level, this is reflected in the EMG of the cervical muscles, which, following an initial asymmetrical innervation, showed a more symmetrical pattern after treatment with EGb 761® than without. The

compensation-enhancing effect could be demonstrated morphologically by an increased new formation of synapses in the vestibular nuclei region in the treated cats. The relevance of this experimental animal model was confirmed by similar studies using betahistine (17).

The investigations by Yabe et al. (18) on Guinea pigs produced results corresponding to the findings of Lacour in the cat. Unilateral perfusion of the vestibular nuclei regions with EGb 761® produced postural and motor patterns indicative of an excitatory effect in these structures.

K. MacLennan et al. (19) also performed experiments on compensation acceleration in Guinea pigs using ginkgolide B, a component of special extract EGb 761®. Following unilateral ablation of the labyrinth, compensation for spontaneous nystagmus was improved at a dose of 25 mg/kg compared to control animals, but not at higher doses.

Improved compensation in rats after unilateral labyrinth lesion was reflected biochemically as an increase in protein synthesis in the region of the vestibular nuclei (20), which would be consistent with an enhancement of neosynaptogenesis.

CLINICAL TRIALS

Favourable effects of EGb 761® on the symptom vertigo were already described (21,22,23) in earlier, sometimes open and non-controlled, trials and in controlled trials compared to reference substances. With regard to vestibular compensation, the findings of an open, randomised study of 45 patients suffering from vertigo induced by peripheral-vestibular lesions are interesting. All patients participated in a physical training programme, 23 patients received EGb 761® in addition. In these patients, posturographic investigations showed a more rapid reduction in sway amplitude (24).

Only randomised, placebo-controlled, double-blind studies, in which vertigo was the inclusion diagnosis and not only a concomitant symptom, were taken into consideration in this review, however. The diagnostic criteria of these studies enabled classification according to vestibular or non-vestibular vertigo for patient selection, real randomisation was performed and double-blind conditions were ensured.

The studies were identified by searching literature collected during our own research on the topic and their references, by literature search in the National Library of Medicine

PubMed data bank (key words: Ginkgo, Gingko and Ginko, combined in each case with vertigo, dizziness and vestibular) and by inquiries of the EGb 761® manufacturer. The data also included two studies, the complete text of which has not yet been published. Details of the studies included in the review are given in Table 1.

STUDIES ON VESTIBULAR VERTIGO

In 1986, Haguenaue et al. published the results of a study (25) on 70 patients with vertigo of vestibular origin, according to the diagnostic criteria given by the authors. After a three-month treatment period, EGb 761® was found to be significantly superior to placebo with regard to the improvement in subjective vertigo symptoms, expressed as a reduction in intensity, frequency and duration of vertigo symptoms, and the associated impairments in daily life. In the caloric test, electronystagmographic measurements showed a normalisation in 80 % of those patients having pathological values on enrolment into the study under treatment with EGb 761® and in 57 % of those who received placebo. Even if no results were given for the Romberg or Babinski-Weil tests, and neuro-otological findings such as spontaneous nystagmus or the results of rotational tests were not taken into account as efficacy parameters, efficacy for the clinical complex “vertigo”, based on electronystagmographic findings, was demonstrated.

Claussen and Kirtane (26) assessed the efficacy of a twelve-week EGb 761® versus placebo treatment of patients with equilibrium disorders (vertigo and ataxia symptoms) by means of cranio-corpography (CCG). The body sway amplitudes decreased significantly more in the active substance group than in the placebo group, and a corresponding improvement in the vertigo symptomatology by 20 % in the placebo group and by 50 % in the active substance group was reported.

STUDIES ON NON-VESTIBULAR VERTIGO (DIZZINESS)

Non-vestibular vertigo (dizziness, ICD-10 R42) was one of the included diagnoses in one of our own still unpublished studies, in which the symptom tinnitus was also investigated. The medical history and neuro-otological screening investigations, such as vibration and vestibulo-spinal tests, excluded a peripheral-vestibular origin of the vertigo symptoms. Of 86 patients aged 76 years on average (range 65 - 93 years), 45 were treated with EGb 761® and 41 received placebo. Following a twelve-week period of

treatment, the dizziness symptoms, taken as the target parameters, had decreased by 58 % in the active substance group as quantified on a visual analogue scale, and by 43 % in the placebo group ($p < 0.05$).

These results indicate that EGb 761® also acts on central structures of the orientation system.

COMPENSATION ENHANCEMENT STUDIES

In order to demonstrate the central compensation-enhancing effect of EGb 761®, Hamann⁽¹²⁾ used a trial model which had not previously been applied. The effect of EGb 761® on compensation-enhancing physical therapy was investigated. The patients, who were all suffering from a non-compensated unilateral vestibular hypofunction, participated in a vestibular habituation training programme under medical supervision. In addition to the training programme, half of the trial collective received EGb 761® (2 x 80 mg/day), the other half a placebo. As expected, improvement in the vertigo disorder, adjustment in nystagmus reaction to rotatory stimuli and improvement in body posture, measured posturographically as a reduction in body sway amplitude, were found in both groups. A comparison of both treatment groups showed a significantly greater reduction in body sway amplitude for the patients who had received EGb 761® in addition to the physical therapy, however. This finding is consistent with the compensation-enhancing action found later in animal experiments^(6,7).

In a similar study design, Heide et al.⁽²⁷⁾ tested Ginkgo special extract EGb 761® in patients with central-vestibular lesions following acute ischaemic events, in whom vertigo symptoms were still present more than three months after the event. In this study, all patients also underwent habituation training similar to that used by Hamann. During the course of treatment, the intensity of vertigo decreased in those patients who received additional EGb 761® therapy to a greater extent than in the placebo group. The frequency and intensity of the pathological nystagmus forms decreased in both groups, but, as the individual pathological findings were detectable in only a few patients, the statistical comparison is of little use.

Both studies showed that Ginkgo special extract EGb 761® improved the capacity for compensation induced by habituation training in not only peripheral but also central vestibular disorders.

DISCUSSION

Primarily, Ginkgo special extract EGb 761® is used for the symptomatic treatment of dementia syndromes and the improvement of memory and concentration performance, but also for the treatment of vertigo of different origin. The improvement in perfusion, radical scavenger properties and the effects on energy metabolism demonstrated experimentally are considered to be the rationale for treatment⁽¹⁴⁾, but the vigilance-enhancing and cognitive-activating effects^(15,16) are also likely to play a role, especially in the compensation of vestibular deficits. The influence on the vestibular system, particularly on compensation after vestibular lesions, has been clearly demonstrated in animal experiments^(6,7,17,18,20). The clinical trials of EGb 761® with vertigo syndromes of various origins were thus performed on a rational basis.

The clinical efficacy of EGb 761® in vestibular and non-vestibular vertigo has been demonstrated in randomised, placebo-controlled, double-blind studies. The severity of the clinical vertigo symptoms, which impair the patient and lead the patient to the doctor, and the objective sway amplitudes, which reflect the severity of damage and the risk to the patient, are relevant parameters for assessing efficacy. In both peripheral and central vestibular vertigo, it could be demonstrated that with habituation training as the basic therapy, additional treatment with EGb 761® may effect a further improvement in the capacity for compensation. This is consistent with the findings of animal experiments which have shown EGb 761® to have an enhancing effect on compensation in several experimental models. The concept of the central nervous action is supported by some of the results of one or our own studies, in which efficacy could be demonstrated for non-vestibular vertigo (dizziness), i.e. the correlate of a central nervous dysfunction.

Altogether, the randomised and controlled studies presented provide convincing evidence of the efficacy of EGb 761® in vertiginous syndromes.

CONCLUSIONS FOR GENERAL PRACTICE

Central recovery processes in the orientation-equilibrium system play a key role in both vestibular and non-vestibular vertigo. Long-term drug treatment must ensure that these essential compensation processes are not inhibited. They should rather be promoted by physical (habituation training) and medicinal measures. Preclinical and double-blind clinical studies show that EGb 761® promotes compensation

and is therefore effective in the treatment of vertigo syndromes.

Figure 1

Table 1: Randomised, placebo-controlled, double-blind studies with EGb 761 in patients with vertigo

Authors	Patients (diagnoses)	(numbers, Treatment duration)	(dose / Superiority of EGb 761® in)
<u>Vestibular Vertigo</u> Haguenauer et al. 1986	70 patients with vestibular vertigo, 3 dropouts, 67 assessed (34 active substance, 33 placebo)	160 mg EGb 761® /day, 90 days	Scale of intensity, frequency and duration of the vertigo; Global assessment of patients (VAS); Proportion of patients free from symptoms or greatly improved; Electro-nystagmography (caloric test)
Claussen and Kirtane 1985	50 patients with vertigo and ataxia symptoms, 17 dropouts, 33 assessed (14 active substance, 19 placebo)	120 mg EGb 761® /day, 12 weeks	Lateral sway amplitude in the cranio-corpography (CCG); Proportion of subjective improvements
<u>Non-vestibular vertigo</u> Hamann 2002	86 patients with non-vestibular vertigo, 3 dropouts, all 86 assessed (45 active substance, 41 placebo)	160 mg EGb 761® /day, 12 weeks	Physician's assessment of impairment (VAS); Global assessment of efficacy (proportion of assessment "very good" or "good") by physician and patient
<u>Compensation enhancement</u> Hamann 1985	35 patients with peripheral vestibular vertigo, no dropouts, all 35 assessed (17 active substance, 18 placebo)	160 mg EGb 761® /day + standardised training, 4 weeks	Sway amplitude in posturography
Heide 1998	40 patients with vertigo after ischaemic central vestibular lesions, 7 dropouts, 36 assessed (18 active substance, 18 placebo)	240 mg EGb 761® /day + standardised training, 180 days	Vertigo score (intensity, duration, frequency)

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