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Specific memory effects of Ginkgo biloba extract EGb 761 in middle-aged healthy volunteers

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ABSTRACT

Introduction: Recent reviews showed that *Ginkgo biloba* extract EGb 761[1] is effective to enhance performance in patients with cognitive impairment (e.g., dementia). The aim of this study was to investigate the effects of EGb 761 on memory and the specificity of such effects on distinct memory functions in middle-aged healthy volunteers.

Methods: A total of 188 healthy subjects aged 45–56 years were randomised to receive EGb 761 (240 mg once daily) or placebo for 6 weeks. Outcome measures were the change in memory performance in a demanding standardised free recall paradigm (list of appointments) and a less demanding standardised recognition test (driving-route). Based on previous findings we predicted superiority of EGb 761 in recall testing. Specificity in effects was assessed by separating immediate vs. delayed and quantitative vs. qualitative free recall measures.

Results: After 6 weeks, EGb 761-treated subjects improved significantly in quantity of recall, i.e., the number of correctly recalled appointments (drug–placebo differences: $p = 0.038$ for immediate and $p = 0.008$ for delayed recall). Effects on qualitative recall performance (ratio of false to correct items) were similar (drug–placebo differences: $p = 0.092$ for immediate and $p = 0.010$ for delayed recall). No superiority of Ginkgo was evident in another everyday memory test which asked for recognition of a driving route (drug–placebo differences: $p > 0.10$). The incidence of adverse events was low and not significantly different between treatment groups.

Discussion: EGb 761 (240 mg once daily) improves free recall of appointments in middle-aged healthy volunteers, which requires high demands on self-initiated retrieval of learned material. This function is known to be sensitive to normal aging, i.e., reduced in healthy middle-aged subjects. No effects are seen in a less demanding everyday memory task which does not tap this critical function. This ties in with previous studies which found specific patterns of benefit from EGb 761 in demanding cognitive tasks.

Introduction

Ginkgo biloba extracts are widely used for the enhancement of cognition in aging-related conditions such as mild cognitive impairement and dementia. The efficacy of the standardised extract EGb 761 has been demonstrated by a number of randomised controlled trials and meta-analyses (IQWiG 2008; Weinmann et al. 2010; Wang et al. 2010) and this extract has been registered for the treatment of dementia syndromes in Germany and elsewhere. However, effects of EGb 761[1] in healthy younger subjects are less clear, as only a few randomised controlled trials (RCT) do exist. Mix and Crews (2000) conducted a 6-weeks RCT in 40 cognitively intact elderly (mean age: 67.5 years). 180 mg EGb 761 per day improved performance in the colour-naming trial of the Stroop test but did not alter other cognitive tests. Furthermore, more subjects in the Ginkgo group rated their ability to remember as better than did in the placebo-group. Mix and Crews (2002) replicated their finding of better self-rated memory performance after 180 mg of EGb 761 per day in a larger RCT ($n = 262$; mean age: 67.0 years in the Ginkgo and 68.6 years in the placebo group). Subjects with evident cognitive decline (MMSE < 26) were excluded. They also reported significant enhancement for delayed recall and recognition sub-tests in the active treatment group after 6 weeks and this was consistent for auditory-verbal (selective reminding test) as well as for visual-nonverbal material (faces-test of Wechsler Memory Scale III). Thus, results from both objective psychometric tests and subjective self-report questionnaires provided complementary evidence for improved delayed long-term memory. By contrast, Solomon et al. (2002) reported no effects in a 6-weeks RCT using 120 mg per day of a Ginkgo extract in 130 subjects of a mean age of 69.3 years, but there have been serious concerns regarding the way of double-blinding in this particular trial. Snitz et al. (2009)

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reported no difference in change of cognitive function over 6 years between placebo and 240 mg per day of EGb 761 in a secondary analysis of a dementia prevention trial. However, appropriate tests of cognitive functioning were not performed consistently during the first half of the trial, attrition rates were high and compliance was as low as 60% at the end of the trial. Both positive and negative findings have been reported from trials using other Ginkgo biloba leaf extracts in healthy young as well as in elderly persons (Canter and Ernst 2007).

A number of reasons may account for these divergent findings: In cognitively intact individuals running an RCT asks for specific methodological pre-requisitises, psychometric assumptions and a refined consideration of methodological demands. They have to take into account specific characteristics of cognively intact individuals still seeking to improve their cognitive everyday-performance. If these methodological features are neglected, studies in healthy individuals tend to provoke beta-errors, i.e., they falsely suggest a lack of effectiveness without considering poor methodology. Therefore, Ginkgo may not even have had a fair chance to demonstrate its efficacy in healthy individuals (Kaschel 2009).

Whereas respective scales for clinical conditions such as Alzheimer's disease are well established, in non-demented subjects the selection of tests is often arbitrary and there is a lack of operationalization of distinct cognitive functions by a corresponding test, thus leading to a confusing, redundant and unstructured array of cognitive outcome measures (cf. Crews et al. 2005; pp. 57–58).

A corresponding methodological prerequisite is the claim for not just demonstrating objective effects in the structured situation of a memory test, but also to improve subjective well-being in terms of everyday memory failures. This is usually assessed by metamemory questionnaires and there is sound evidence from healthy and abnormal aging that objective memory tests and subjective memory questionnaires yield qualitatively different information. For example, subjective memory complaints, even in the absence of objective memory impairment, appear to be a strong predictor of future cognitive decline and dementia (Schmand et al. 1997; Schofield et al., 1997a,b; Geerlings et al. 1999). The notion that memory-questonnaires tap aspects of well-being is shown by its close relationship to dysphoric mood and depressive disorder. For example, in a cross-sectional perspective, subjective memory complaints were associated with depression rather than with objective cognitive impairment, but this did not affect their predictive value for cognitive decline in the longitudinal perspective (Schmand et al. 1997).

Following these methodological considerations, we report here on a trial assessing the clinical efficacy and tolerability of EGb 761 in cognitively intact, middle-aged, well-educated individuals. Apart from adequate power of selected samples and adequate intensity and duration of treatment, we selected ecologically valid everyday memory tests and questionnaires which were shown to be able to monitor change in neuropsychological rehabilitation (Kaschel 1993; Kaschel et al. 2002; Wagner et al. 2008).

The study aimed:

- to assess effects on long-term memory using delayed recall tasks
- to replicate evidence suggesting that objective improvement is paralleled by changes in subjective memory ratings and
- to link changes in objective psychometric test performance with everyday life in terms of ecological validity (memory tests relevant to daily living).

Given hints from the existing literature we postulated effects of medication in complex recall but not in simple recognition tests.

Methods

Selection of subjects

Male and female subjects were eligible for inclusion in this study, if they were mentally healthy, aged 45–65 (both inclusive), had higher-level secondary education (at least middle or high school), sufficient language skills to understand and respond to all interview questions and undergo neuropsychological testing without difficulties and without assistance, and who had provided written informed consent.

Criteria for exclusion were: participation in another experimental drug trial within the past 4-weeks before enrolment, prior participation in a clinical trial with Ginkgo biloba, hospitalization, ischaemic stroke within the last three months, cognitive impairment due to any neurological origin or psychiatric disorder, history of recurrent major depression or recurrent anxiety disorder. Those patients with a history of a single episode were accepted if the episode was finished at least one year before enrolment. Further exclusion criteria were: Use of antidementia drugs or cognition enhancers, anticholinergic drugs, haemorrheological drugs, antiepileptics, anti-Parkinson drugs, continued use of psychoactive (including sedating) drugs. At least 8-weeks washout was required if any prohibited drug had been used before. Occasional use (up to 3 times a week) of tranquilizers for sleep disturbances was permissible, but not within 48 h prior to test sessions. Substance addiction or abuse within the last 5 years, severe, uncontrolled cardiovascular disease, severe renal or hepatic dysfunction, insufficiently controlled insulin-dependent diabetes mellitus or any other severe illness were reasons for exclusion. Subjects with any condition that could compromise the absorption of orally applied drugs were excluded, as were those with severe and insufficiently corrected loss of vision or hearing, severe language difficulties or any other disability that could have compromised the subject's ability to cooperate adequately. Female patients of childbearing potential were not enrolled either.

Randomization procedure

A randomised, double-blind, placebo-controlled, mono-centre trial design was chosen. The trial was approved by the Independent Ethics Committee of the Ruhr University Bochum and run in Germany between December 2005 and March 2006. It was conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice (GCP) issued by the International Conference on Harmonisation (ICH). Informed consent was obtained from all patients before enrolment.

Eligible subjects were randomly allocated to receive 240 mg (once daily in the morning) EGb 761 or placebo. For a period of 6-weeks, they underwent the investigational treatment without undertaking further memory-enhancing activities. EGb 761[2] is a dry extract from Ginkgo biloba leaves (drug-extract ratio 35-67:1), adjusted to 22–27% Ginkgo flavonoids and 5–7% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide, with a content of ginkgolic acids below 5 ppm. Active drug and placebo were of identical appearance.

Randomisation in a 1:1 ratio was performed by a validated computer program. The length of the balanced blocks was fixed in a separated document that was withheld from the study sites. The investigators received sealed emergency-envelopes for individual patients, all of which were returned unopened after completion of the trial.

[2] EGb 761® is a registered trade mark of Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals, Karlsruhe, Germany.