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FILE: ■Ginkgo (*Ginkgo biloba*)

■EGb 761®

■ Bleeding and Hemorrhagic Complications

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RE: No Alteration in Bleeding Time in Elderly Patients Taking Ginkgo Extract EGb 761®

Halil M, Cankurtaran M, Yawuz BB, Ozkayar N, Ulger Z, Dede DS et al. No alteration in the PFA-100 *in vitro* bleeding time induced by the *Ginkgo biloba* special extract, EGb 761, in elderly patients with mild cognitive impairment. *Blood Coagul Fibrinolysis*. 2005; 16:349-353.

Clinical studies have demonstrated that the special extract EGb 761® (standardized extract of dried leaves of ginkgo [*Ginkgo biloba*], a highly concentrated [50:1] standardized extract containing 24% ginkgo-flavonol glycosides and 6% terpene lactones) has therapeutic activity in early stages of Alzheimer's disease (AD), cerebrovascular dysfunction, mild cognitive impairment (MCI), as well as peripheral arterial occlusive disease (PAOD). The use of EGb 761 has therefore increased among the elderly. Some medical experts are concerned about possible hemorrhagic complications in these individuals. Bleeding problems are a significant cause of morbidity and mortality in the elderly population, and ginkgo is known for its effects on blood cells, including platelets, and the circulatory system.

The data in the medical literature regarding the haemostatic safety (i.e., effects on blood parameters, including blood pressure, bleeding and clotting time, etc.) of EGb 761 is conflicting. A recent study in healthy volunteers supports the short-term (7 days) safety of EGb 761. However, there have been case reports of hemorrhagic complications in the geriatric population. Most of these cases have occurred in individuals with co-morbid conditions who were taking anticoagulant medications concurrently so there it usually not possible to ascribe causality to the use of the ginkgo preparation.

The purpose of this prospective study is to expand upon the current understanding of the haemostatic safety of EGb 761 by evaluating its effects on PFA-100 *in vitro* bleeding time in elderly patients with MCI. MCI is a condition in which memory impairment is greater

than what would be expected for an individual of a particular age, while general cognitive function is preserved. However, 12-15% of MCI patients have been found to subsequently develop AD, compared to 1-2% of normal controls. The PFA-100 platelet function analyzer (Dade Behring Marburg GmbH, Marburg, Germany) is a relatively new instrument designed to detect *in vitro* bleeding time (of blood samples taken from such patients) in a sensitive and specific manner.

The study enrolled 40 elderly patients between the ages of 65 and 79 years old (30 women and 10 men) at the Department of Internal Medicine, Division of Geriatric Medicine, Hacettepe University, Ankara, Turkey. All participants in the trial underwent a comprehensive geriatric assessment that included the geriatric depression scale test and mini mental state examination (MMSE). Patients diagnosed as having dementia were excluded from the study. A broad spectrum of blood chemistry tests were performed (including complete blood count, fasting glucose, and HDL, LDL, and total cholesterol), as well as thyroid-stimulating hormone, chest x-ray, and electrocardiogram. Subjects with a history of osteoarthritis or atherosclerosis, as well as those who had taken medications such as aspirin or non-steroidal anti-inflammatory drugs in the previous 3 weeks were excluded from the study. Curiously, the authors do not mention whether any of the study subjects were using anticoagulant or antiplatelet drugs, or whether such individuals were disqualified from the study. Although patients with coronary artery disease were specifically excluded, study participants had a variety of other chronic diseases with a circulatory component, such as diabetes, heart failure, and hypertension.

Study subjects were given one 80 mg. tablet of EGb 761 3 times per day, to be taken with water. The PFA 100 *in vitro* bleeding time and coagulation parameters were assessed prior to initiating treatment and on the 7th day of treatment. The following parameters were measured: prothrombin time (PT), activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR). The PFA instrument "reflects *in vitro* primary hemostasis by simulating platelet adhesion and aggregation under high shear stress." The sensitivity and specificity of this device have been validated previously, and it is believed to be a more accurate indicator of the haemostatic effects of drugs than the conventional skin bleeding time test.

The authors state "After a 7-day treatment there was no statistically significant prolongation in PFA-100 *in vitro* bleeding time and coagulation parameters in patients receiving EGb 761 that lead to discontinuation of the treatment." However, only the mean values of the group as a whole are presented in the article. While most parameters changed very little, the change in PT time — from 17.11 seconds at baseline to 17.46 seconds on the 7th day — approached, but did not reach, a level of statistical significance ($P=0.06$). The results of this study would perhaps be more unmistakable if the individual PT time numbers for each participant had been included in this report.

Previously, several clinical trials have been published showing that EGb 761 did not produce bleeding under the conditions of the trial.^{1,2} According to the authors, this inquiry supports previous research suggesting that "clinical bleeding events in patients receiving *Ginkgo biloba* extracts are not related to pharmacological properties of EGb 761." Since

elderly patients may need to take ginkgo for the duration of their lifespan, studies are needed to establish its long-term vascular haemostatic safety.

— Cathleen Rapp, N.D.

References

1. Kohler S, Funk P, Kieser M. Influence of a 7-day treatment with Ginkgo biloba special extract EGb 761 on bleeding time and coagulation: a randomized, placebo-controlled, double-blind study in healthy volunteers. *Blood Coagul Fibrinolysis*. 2004 Jun;15(4):303-9.
2. Bal Dit Sollier C, Caplain H, Drouet L. No alteration in platelet function of coagulation induced by EGb761 in a controlled study. *Clin Lab Haem* 2003;25:251–3. [For a detailed review of this trial, see *Ginkgo biloba* Extract EGb 761[®] Shows No Effect on Bleeding Time in Healthy Volunteers. *HerbalGram*. 2004;62:21-22. <http://www.herbalgram.org/herbalgram/articleview.asp?a=2676>]

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