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FILE: ▪ Ginkgo (*Ginkgo biloba*)
▪Drug Interactions
▪Flurbiprofen
▪ Cytochrome P450-2C9 Inhibition

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RE: Ginkgo Extract Does Not Interact with Flurbiprofen or Induce CYP2C9 Enzyme

Greenblatt DJ, von Moltke LL, Luo Y, et al. *Ginkgo biloba* does not alter clearance of flurbiprofen, a cytochrome P450-2C9 substrate. *J Clin Pharmacol*. 2006;46:214–221.

Several case reports in humans of hemorrhagic events associated with the use of ginkgo (*Ginkgo biloba*) leaf extract have been published. This adverse effect is thought to possibly be due to one or more components of ginkgo that are responsible for platelet aggregation. In patients taking warfarin concomitantly with ginkgo, reported hemorrhagic events may result from an impairment in the cytochrome P450-2C9 (CYP2C9)–mediated metabolism of (S-)warfarin, the active enantiomer of warfarin, and, thus, in excessive anticoagulation. CYP2C9 is an enzyme in the P450 system in the human liver that breaks down various exogenous chemicals as a natural defense, including certain types of drugs.

The hydroxylation of flurbiprofen, a nonsteroidal anti-inflammatory drug, is known to be mediated by CYP2C9; therefore, flurbiprofen has been used as an indicator in clinical and in vitro studies to monitor the role of CYP2C9 activity. The objective of this study was to evaluate the short-term effects of a standardized extract preparation of ginkgo on the kinetics of a single dose of flurbiprofen in humans.

Twelve healthy subjects (n = 8 men and 4 women aged 19–40 years) were enrolled in this randomized, double-blind, 2-way crossover study, which was conducted at the Clinical Psychopharmacology Research Unit at Tufts University School of Medicine (Boston, MA). The study consisted of 2 phases, the order of which was determined by randomization: (1) a single dose of 100 mg flurbiprofen (The Upjohn Co) preceded by 3 doses of 120 mg ginkgo (Ginkgold®; Nature's Way Products, Springville, UT), and (2) a single dose of 100 mg flurbiprofen preceded by 3 doses of matching placebo given according to the same schedule as the ginkgo. Venous blood samples were collected before and 0.5, 1.0, 1.5, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours after the dose of flurbiprofen for the determination of the elimination half-life, maximum plasma concentration, area under the curve (AUC), and clearance of flurbiprofen and for the measurement of the truncated AUC for the flurbiprofen metabolite 4-OH-flurbiprofen.

One of the 12 subjects did not comply with the study protocol; therefore, the results apply to only 11 subjects. No significant differences ($P > 0.05$) in elimination half-life (4.3 ± 0.5 and 4.0 ± 0.3 hours), maximum plasma concentration (12.1 ± 1.0 and 11.6 ± 0.8 mcg/mL), AUC (area under the curve) (71 ± 15 and 70 ± 15 mcg/mL · h), or clearance (30.6 ± 4.4 and 29.4 ± 2.8 mL/min) of flurbiprofen or in the truncated AUC for 4-OH-flurbiprofen (1.16 ± 0.20 and 1.14 ± 0.18 mcg/mL · h) were observed between the placebo and ginkgo conditions, respectively. In all subjects, 4-OH-flurbiprofen formed in concentrations that were "considerably lower" than those of the parent drug. High-performance liquid chromatographic analysis showed that each 60-mg Ginkgold tablet contained 6.6 mcg of amentoflavone and 61.2 mcg of quercetin; both of these compounds were previously identified as CYP2C9 inhibitors.

Short-term exposure of healthy humans to standardized preparations of ginkgo had "no detectable effect on the pharmacokinetics of a single dose of flurbiprofen or on the apparent extent of formation of the principal hydroxylated metabolite", i.e., 4-OH-flurbiprofen. This finding suggests that the specific ginkgo preparation studied does not inhibit CYP2C9 activity, perhaps because the concentrations of amentoflavone and quercetin in the ginkgo preparation were too low. It is quite possible that due to different quality control practices at different companies, the chemical composition of different commercial preparations of the same herb can vary considerably. Therefore, the authors note that the results pertaining to the ginkgo preparation used in this study are not necessarily applicable to all ginkgo products currently available to consumers. The ginkgo preparation used in this trial was presumably chosen due to its being one of the market leaders; neither Nature's Way nor its parent company (W. Schwabe Pharmaceuticals of Karlsruhe, Germany), were involved in the funding nor the design of this trial.

—Brenda Milot, *ELS*