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RE: The Effect of Botanical Supplementation on Cytochrome P450 Phenotypes in the Elderly


Elderly patients may be at higher risk for herb-drug interactions than other populations. The putative mechanism for many herb-drug interactions is "phytochemical-mediated modulation of cytochrome P450." There is also evidence that cytochrome P450 (CYP) activity may decrease with age. Since this group is more likely to be ingesting prescription drugs concurrently with botanical supplements "herb-mediated changes in CYP activity may take on greater clinical relevance in this population."

The authors have previously studied "the effects of long-term supplementation with St. John's wort [SJW; Hypericum perforatum], garlic (Allium sativum) oil, [Asian ginseng] P. ginseng and [ginkgo] G. biloba on CYP1A2, CYP2D6, CYP2E1 and CYP3A4 activity in young, healthy volunteers." The current inquiry investigates the same botanicals and the same enzymes, in 12 healthy volunteers between the ages of 60 and 76 years (6 men and 6 women, mean age 67 years). Both studies employed "a widely accepted methodology for assessing possible CYP-mediated drug-drug interactions." This approach measures herb-induced changes in the clearance of probe drugs that are substrates for specific CYP enzymes. These in vivo, single time point metabolic ratios do not replace traditional concentration-time profiles for assessing drug clearance. However, they make it possible to identify botanicals that modulate CYP activity, and to perform in vivo evaluations of multiple CYP enzymes with a "limited blood sampling scheme."

Subjects were nonsmokers, in good health, who did not use botanical dietary supplements. None of the subjects were using prescriptions medications, with the exception of two women taking Prempro™ 0.3 mg (conjugated estrogen/medroxyprogesterone acetate). Debrisoquine urinary recovery screenings were utilized to confirm that all participants were extensive metabolizers by CYP2D6. During medication periods, subjects were instructed to refrain from use of both
prescription and nonprescription medications, as well as to avoid alcohol, caffeine, fruit juices, cruciferous vegetables, and charbroiled meat.

"The ability of garlic oil, *P. ginseng, G. biloba,* and St. John's wort (*Hypericum perforatum*) to modulate human CYP activity was evaluated individually on four separate occasions in each subject." Each twenty-eight day supplementation period and thirty-day washout period was repeated until each subject had received all four botanical supplements. The study design was open-label and randomized for supplementation sequence. Single lots of each botanical supplement were purchased from the same vendor (Vitamer, Lake Forest, CA) to avoid intra-product variation in phytochemical content. The following doses of the botanical supplements were employed in the study: garlic oil — 500 mg. 3 times daily, Asian ginseng (5% ginsenosides) — 500 mg. 3 times daily, ginkgo (24% flavonol glycosides and 6% terpene lactones) — 60 mg. 4 times daily, and SJW (0.3% hypericin) — 300 mg. 3 times daily. In addition, researchers independently analyzed each supplement for specific 'marker compounds' by HPLC.

All subjects reported to the General Clinical Research Center at the University of Arkansas for Medical Sciences on the day of each scheduled probe drug administration. Four isoenzyme phenotypes (CYP1A2, CYP2D6, CYP2E1, and CYP3A4) were assessed before (days –1 and 0) and at the end (days 27 and 28) of the supplement period. Oral doses of caffeine and midazolam were administered 48 hours before supplementation (day –1). Blood samples were collected at 1 and 6 hours after the probe, and centrifuged to obtain serum for determination of CYP activity. Twenty-four hours later (day 0) subjects received an oral dose of chlorzoxazone and debrisoquine. Both blood (at 2 hours) and urinary samples (at 8 hours) were collected and frozen until analyzed. The following serum ratios were used to determine the various enzyme phenotypes:
1) CYP3A4 activity: 1-hydroxymidazolam/midazolam ratio determined one hour after administration
2) CYP1A2 activity: paraxanthine/caffeine ratio, obtained at 6 hours after administration
3) CYP2E1 activity: 6-hydroxychlorzoxazone/chlorzoxazone ratio, obtained at 2 hours after administration
4) CYP2D6 activity: 8-hour debrisoquine urinary recovery ratio (4-hydroxydebrisoquine/debrisoquine + 4-hydroxydebrisoquine)

"The CYP modulatory capability of each botanical supplement was evaluated by comparing individual differences in phenotype before and at the end of 28 days of supplementation."
Thus, researchers were able to evaluate the CYP modulatory capability of each botanical supplement by comparing individual phenotype differences before, and at the end of each 29-day supplementation period.

The most significant result observed in this study was a 141% (range 58-725%) increase in the mean 1-hour 1-hydroxymidazolam/midazolam serious ratio (P < 0.001), after 28 days of SJW administration. In contrast, long-term supplementation with garlic oil, ginkgo, and Asian ginseng did not cause a significant change in the CYP3A4 phenotype. Similarly, SJW induced a significant increase in CYP2E1 activity, as evidenced by a 26% increase in the mean 6-hydroxychlorzoxazone/chlorzoxazone ratio at the end of the supplementation period (P = 0.006). In contrast, supplementation with garlic oil resulted in a significant 22% decrease in the same ratio, which is suggestive of inhibition of CYP2E1 activity (P = 0.005). No modulatory effects on CYP1E2 were observed with ginkgo or Asian ginseng.

The only other statistically significant result in this study was a 7% decrease in debrisoquine urinary recovery ratios with administration of Asian ginseng (P = 0.003). However, this change in CYP2D6 phenotype was not considered large enough to be clinically relevant.
The results of the present study confirm previous research utilizing single-timepoint phenotypic ratios to document CYP3A4 induction by SJW. These results have been confirmed with "area-under-the-curve" (AUC) assessments. Phenotypic ratios have also been used to document that bitter orange (Citrus x aurantium), milk thistle (Silybum marianum), ginkgo, Asian ginseng, and saw palmetto (Serenoa repens) do not effect CYP activity. Again, results have been confirmed by more conventional AUC assessments for the latter three botanicals.

The authors compare this research on elderly subjects with their earlier findings on SJW in young volunteers. The magnitude of CYP3A4 induction was similar in both studies: 141% in the elderly, and 98% in the young. However, the hyperforin dose received by the young volunteers was 2.5 times greater than that received by the elderly — 12.2 mg. per day vs. 4.8 mg. per day. Nevertheless, serum concentrations of hyperforin were similar in both groups — 42.6 ng/mL in the young vs. 51.2 ng/mL in the elderly. Although "It is unknown whether hyperforin exhibits age-related differences in pharmacokinetics…similar serum concentrations between the two age groups, despite disparate doses, suggest that hyperforin clearance may be reduced in the elderly subjects." Other possible causes of age-related reductions in hepatic drug clearance include: reduced liver blood flow and/or diminished liver weight. Therefore, "relatively small doses of hyperforin may produce significant induction of CYP3A4 activity in elderly patients." At the same time, most SJW products on the market do not provide information regarding hyperforin content on the label.

With regard to CYP2E1, SJW induced a 26% increase in activity in elderly subjects in contrast to a 110% in the young. This data "may point towards an age-related reduction in CYP2E1 activity."

However, other research on this issue has yielded contradictory results, and there have been no case reports of interactions between SJW and CYP2E1 substrates. Although there are few orally administered drugs that are metabolized by CYP2E1, clinicians should bear in mind that several inhalation anesthetics are substrates for this system, and "their halogenated byproducts can produce liver injury."

The garlic oil induced 22% decrease in mean 6-hydroxychlorzoxazone/chlorzoxazone ratio observed in this study was similar to the 40% reduction in CYP2E1 phenotype observed in young volunteers. This inhibition of CYP2E1 can be attributed to the organosulphur compounds in garlic oil, especially "the allyl sulphides, which are the chief constituents of steam distilled garlic oil products." The discrepancy in inhibition between the two age groups can be attributed to either age-related changes in CYP2E1 responsiveness, or dissimilar allyl sulphide content in different supplements. Garlic oil did not affect any of the other CYP enzymes tested in this study or in young volunteers. After considering all the data, the authors "suggest that garlic oil supplements pose a minimal risk for CYP-mediated herb-drug interactions."

Both ginkgo and Asian ginseng showed little impact on the CYP enzymes investigated in this study. These results are similar to the authors' findings in earlier research with young volunteers. This data supports the view that reported interactions between ginkgo and warfarin are attributable to inhibition of platelet activating factor (PAF) by various ginkgolides, rather than effects on CYP activity. However, both a case report involving Asian ginseng and warfarin, and a randomized trial investigating American ginseng (P. quinquefolius) and warfarin, point to a possible interaction between CYP2C9 and ginseng species. In addition, regarding ginkgolide activity, a recent publication questions the importance of the PAF antagonistic effect of ginkgolides in hemorrhage associated with consumption of ginkgo leaf extract: induction of the anti-PAF effect in human platelets requires ginkgolide concentrations more than 100 times greater than peak plasma values measured after oral intake of a standardized proprietary extract at recommended doses.
The authors conclude that botanical medicine can "modulate drug metabolism" and "adversely affect the pharmacokinetics of a variety of medications used in the elderly." Therefore, they call for healthcare providers to question elderly patients about their use of dietary supplements, and to discourage the use of herbal supplements in conjunction with prescription medicines.

Many experts in the field of holistic health might view this recommendation as "over the top" or at the least "throwing out the baby with the bath water." Familiarity with the healing power and relative cost effectiveness of herbs, in combination with an awareness of the side effects, toxicity and expense of prescription medications, might motivate a search for other possibilities. Given the limited number of herbs that are in common usage, the finite number of CYP enzymes, and the technology employed in the current study, it should be feasible to develop a database of significant herb-drug interactions for health care professionals. This would be a study of considerable magnitude, but not prohibitively so, when the long-term benefits are taken into consideration.

-Cathleen Rapp, N.D.

References

The American Botanical Council has chosen not to reprint the original article.