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Prolotherapy for Chronic Musculoskeletal Pain

By Dónal P. O'Mathúna, PhD

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EACH OLYMPICS BRINGS THRILLS, TRIUMPHS, TEARS, AND, NOWAdays, tales of the latest controversial drugs among athletes. This year's Winter Olympics in Turin, Italy, was no exception. As the athletes made final preparations to hit the slopes, news hit the airwaves of an injectable treatment for injuries. Two prominent U.S. skiers were injected for knee injuries at a Mexican clinic. The treatment does not contain banned substances, but remains controversial.[1] So too is its most high-profile practitioner, Milne Ongley. A physician from New Zealand, Ongley's license to practice medicine was revoked for malpractice in 1973. He moved to the United States where he was later barred from practicing medicine; then he moved to Mexico.[2]

Ongley injects a solution of dextrose, glycerin, and phenol. Other prolotherapists use different mixtures. Prolotherapy is or has been known by other names, including reconstructive therapy, proliferative therapy, or sclerotherapy. The latter also refers to a completely different procedure used for vessel occlusion in gastroenterology and surgery.[3] One review found 21 different names for prolotherapy.[4] While media attention has focused on prolotherapy for sports injuries, other uses include treating chronic back pain and osteoarthritis. Physicians should be aware of this increasingly popular therapy.

Background

Prolotherapy was developed in the 1930s by Louis Schultz, an oral surgeon. He described the injection of psyllium seed extracts for temporomandibular joint pain.[5] He conducted animal experiments which led George Hackett, a general surgeon, to apply the injection protocols more generally in the 1950s.[3] Hackett proposed that some chronic musculoskeletal pain arose from ligamentous laxity which led to joint instability.[5] The laxity could arise from injury, poor posture, or age-related degeneration. Hackett also changed the name from sclerotherapy (derived from the idea that the injections cause

scarring to overcome joint laxity) to prolotherapy (from the idea that the injections promote proliferation of new tissue).[6]

Prolotherapy injections are currently used to treat various musculoskeletal injuries. Among athletes, 85% of sprains are due to ligamentous injuries and the injections reportedly strengthen ligaments that have been stretched or torn.

Prolotherapy is practiced in many different ways. The injections are administered at different intervals, for different lengths of time, and with various co-interventions, including exercise regimens, physical manipulations, and vitamin supplements.[7] A review of clinical trials found that 20 different mixtures had been used in the studies.[4] Sixteen solutions used dextrose and nine combined dextrose, glycerin, and phenol. Most procedures also used a local anesthetic because of the discomfort caused by the injections. Although various mixtures are used, almost half the studies injected "P2G," which contains dextrose 12.5%, glycerin 12.5%, phenol 1.25%, and lidocaine 0.25%. The solution is typically prepared by compound pharmacists using USP-grade ingredients and autoclaved to ensure sterility. Several injections of around 1-2 mL are made into the ligament(s) at the site of pain or tenderness, with total volumes ranging from 5 to 30 mL.

Mechanism of Action

Prolotherapy solutions are believed to cause a local inflammatory reaction that leads to growth and strengthening of collagenous structures. The three commonly used components are believed to act in different ways to promote this response. One component is an irritant, such as phenol, guaiacol, or tannic acid.[5] This causes local oxidative damage, which initiates an inflammatory cascade. Pumice flour is sometimes used as a particulate irritant.[4] The second component is an osmotic agent, such as dextrose, glycerin, or zinc sulfate. This causes cell dehydration or damage, which further promotes the inflammatory response. The third component is a chemotactic agent, usually sodium morrhuate. This fatty acid salt is derived from cod liver oil and is a precursor of inflammatory mediators, including prostaglandins and thromboxanes.[5] The mixture is believed to bring various growth factors to the site of injury. These promote growth and strengthening of collagenous structures, which is hypothesized to reduce joint laxity, improve biomechanics, and reduce pain.[3]

Clinical Studies

A number of animal studies with prolotherapy have been conducted since the 1930s. While the early studies found improved ligament size and strength, study design was often poor compared to more recent methodology.[4] The older studies were carried out with healthy animals, while more recent studies with injured animals have not found statistically significant improvements.[4]

A comprehensive review of prolotherapy for chronic musculoskeletal pain identified 42 clinical studies.[3] Of these, 34 were case reports or case series studies involving a wide variety of indications. Low back pain was studied in almost three-quarters of the cases. The results were consistently positive as measured by pain reduction and improved function. However, methodology quality was often poor and none of these 34 studies included randomized control groups. The review also identified six randomized controlled trials (RCT), two involving intra-articular injections for osteoarthritis and four involving low back pain. Only the studies involving low back pain will be reviewed here as they fit into the general claim that prolotherapy is effective for conditions caused by ligament laxity and resulting joint instability. Three other systematic reviews identified the same four RCT and one additional one.[4,5,8]

The first published RCT was carried out by the man at the center of the skiing controversy, Milne Ongley.[9] He recruited 81 patients who had chronic back pain for an average of 10 years. On the first day, both groups received a 0.5% lidocaine injection and a spinal manipulation. However, the treatment group received a manipulation of typical force while the control group received one of suboptimal force. On the second day,

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both groups began a series of weekly low back injections for six weeks and were taught flexion exercises. The treatment group received the P2G solution and the control received saline injections. The treatment group also received steroid injections (triamcinolone) into the gluteus medius muscles. After six months, the treatment group had significantly better outcomes than the control group for pain scores ($P < 0.001$) and disability rating ($P < 0.003$).

Another RCT involved 22 patients with low back pain, with 16 in the treatment group and six in the control group.[10] The prolotherapy solution contained dextrose 10%, glycerin 12%, phenol 1%, and procaine 0.3%, with saline as the control. The prolotherapy injections were given into the lumbosacral ligaments and the saline injections into an unspecified tender spot. A total of three injections were given on a biweekly schedule. After 12 months, the percentage of patients reporting no pain, occasional pain, or constant pain did not differ significantly between the two groups.

A third RCT sought to remove some of the co-intervention differences in Ongley's study.[11] Seventy-nine patients with chronic, unresponsive back pain received typical spinal manipulations under local anesthetic and intravenous sedation. All were instructed to perform daily flexion and extension exercises. Patients in both groups with hyperirritable areas were injected with triamcinolone or corticosteroid. On the next day, six weekly injections commenced with patients receiving either P2G or lidocaine 0.25% in saline. After six months, both groups had improved significantly on two pain scales and a disability score, but the improvements did not differ significantly between the two groups. The treatment group contained significantly more patients reporting more than 50% reduction in pain ($P < 0.05$).

The next RCT randomly assigned 74 patients with chronic low back pain to three weekly injections of either P2G or lidocaine 0.25% in saline.[12] Outcomes were measured at one, three, and six months. Steroid injections, spinal manipulation, and exercises were not included, and the injections were given to a limited area of the spine. No significant differences were found between the two groups in pain, disability, and range of motion scores.

The most recent RCT included 110 patients averaging 14 years with chronic back pain.[7] Patients were randomly assigned to receive either dextrose 20% and lidocaine 0.2% or saline and then randomized again to either perform flexion and extension exercises or maintain normal activity. All patients were given vitamin and mineral supplements and compliance was checked. Follow-up was continued for two years. Pain and disability scores dropped significantly in all groups ($P < 0.05$), with no statistical differences between the groups based on injection solution or type of activity.

Adverse Effects

Initial pain at prolotherapy injection sites is commonly reported, which is why local anesthetics are used.[4] A small number of patients have withdrawn from some studies because of the intensity of this pain. Cases of radiating leg pain and nausea have been reported. Usually, the pain subsides within a few days, but can be accompanied by local stiffness and headache. Apart from the initial reaction, prolotherapy is reported to be relatively free of adverse effects.

Formulation

As noted above, a number of different formulations are used. The most commonly used solution is P2G, containing dextrose 12.5%, glycerin 12.5%, phenol 1.25%, and lidocaine 0.25% made to USP standards. Injection volumes and frequency of administration are also highly variable, with six weekly injections delivering 30 mL solution being the most common regimen.[4]

Conclusion

The evidence regarding prolotherapy is unclear. RCTs of prolotherapy have focused mainly on low back pain. Three found no benefit compared to control, and two found some benefit. The results of the first RCT were "some of the most impressive ever reported in any RCT on chronic low back pain and need to be repeated to increase their credibility."[4] However, the two groups differed in several ways in addition to prolotherapy (concurrent exercise, steroid injections, and type of manipulation).[9] The other positive study eliminated these differences, but only found significant differences when subgroup analysis was conducted.[11]

The studies reporting no significant benefits also had limitations. The earliest had a very small number of participants unevenly distributed between the two groups.[10] The next did not follow the usual injection pattern[12] and the most recent used a solution not typically used in prolotherapy.[7] However, these studies did report improvements in both groups. Case reports and cohort studies on low back pain report consistent improvements in patients who have been unresponsive to other therapies for many years.

RCTs for athletic ligamentous injuries were not found, though a recent consecutive case series examined prolotherapy for chronic groin strain in 24 rugby and soccer players.[13] Dextrose 12.5% and lidocaine 0.5% injections were given monthly until pain resolved or no

further improvement occurred for two consecutive treatments. Participants received an average of 2.8 injections and were followed up for an average of 17 months. At last assessment point, 20 players had no groin pain and 22 of 24 had unrestricted sports involvement. Such impressive results warrant further controlled investigations.

Recommendation

Clarification of what precisely constitutes prolotherapy is urgently needed. The injected solutions vary widely, are administered in different ways, and are combined with various co-interventions. Such variety makes it difficult to identify the critical components. A consistent finding is that some people with unresponsive chronic musculoskeletal pain are helped by injections, regardless of what they contain. Prolotherapy may be worth a trial for those with refractory low back pain. However, the injections should be presented to patients as experimental. Until further RCTs provide better evidence on which solutions and protocols are effective for particular forms of musculoskeletal pain, recommendations must remain tentative. ❖

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Drug Pharmacokinetic Interactions Following Consumption of Plant Products

PART 2 OF A SERIES ON HERB-DRUG INTERACTIONS

By Francis Brinker, ND

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Conflicting Results in Human Studies with CYP3A4 Drug Substrates

In vitro isozyme inhibition results can yield false positives, giving rise to concerns over botanical influence on drug metabolism. Because more than 50% of medications are metabolized by CYP 3A4, the effects of herb preparations on this isozyme are particularly important. Unfortunately, not even all human research findings are consistent.[1]

Garlic (*Allium sativum*) products' impact on CYP 3A4 substrates is not predictable. Ten healthy subjects taking two garlic caplets daily for three weeks reduced the plasma content of HIV protease inhibitor and CYP 3A4 substrate saquinavir by 50%. After 10 days, plasma levels were 35% less than baseline.[2] However, 1.8 g of a standardized garlic extract daily for 14 days in 14 healthy subjects did not alter metabolism of 3A4 substrate alprazolam.[3] Furthermore, garlic oil did not affect midazolam's metabolism by 3A4.[4]

In the case of Asian ginseng (*Panax ginseng*), 200 mg/d for 14 days of an extract standardized to 4% ginsenosides failed to alter this isozyme's metabolism of

cortisol in 20 humans,[5] and daily doses for 28 days of 1.5 g extract standardized to 5% ginsenosides did not change the metabolism of CYP 3A4 substrate midazolam.[4] However, 200 mg/d of uncharacterized ginseng for 18 days inhibited metabolism by CYP 3A4 of nifedipine, as indicated by increased peak plasma

Table 1

Human studies with botanicals showing metabolic conversion of drug substrates for specific CYP isozymes

CYP 1A2

Inhibitor	Substrate
Echinacea purpurea (echinacea) root extract*	Caffeine[23]

CYP 2C9

Inducers	Substrates
Hypericum perforatum (St. John's wort) extract*	Warfarin[57]
	Phenprocoumon[5]
Panax quinquefolium (American ginseng) root	Warfarin[58]

CYP 2C19

Inducers	Substrates
Ginkgo biloba (ginkgo) leaf extract	Omeprazole[55]
Hypericum perforatum (St. John's wort) extract	Omeprazole[30]
	Amitriptyline[59]
	Mephenytoin[30]

CYP 2D6

Inducers	Substrates
Cimicifuga racemosa (black cohosh) root extract	Debrisoquin[21] (17% change not clinically significant)
Hydrastis canadensis (goldenseal) root extract	Debrisoquin[21]
Panax ginseng (Asian ginseng)	Debrisoquin[35] (7% change not clinically significant)

CYP 2E1

Inhibitors	Substrates
Allium sativum (garlic) cloves, oil*	Chlorzoxazone[4]
Piper methysticum (kava) extract	Chlorzoxazone[21]
Inducers	**Substrates**
Hypericum perforatum (St. John's wort) extract*	Chlorzoxazone[4]

CYP 3A4

Inhibitors	Substrate
Ginkgo biloba (ginkgo) leaf extract*	Nifedipine[6]
Hydrastis canadensis (goldenseal) root extract*	Midazolam[21]
Panax ginseng (Asian ginseng) root*	Nifedipine[6]
Valeriana officinalis (valerian) root extract*	Alprazolam[60]
Inducers	**Substrates**
Allium sativum (garlic) cloves*	Saquinavir[2]
Hypericum perforatum (St. John's wort) tops extract	Alprazolam, cyclosporine, imatinib, indinavir, irinotecan, methadone, midazolam, oral contraceptives, quazepam, simvastatin, tacrolimus,[29] nifedipine, omeprazole,[30] verapamil[31]

* Contrary findings with no effect are found in other studies using different drug substrates and/or other preparations of the botanical; or for St. John's wort and CYP 3A4, with low hyperforin dosage or a duration of less than one week.

Table 2

Botanicals for which all human studies to date show no influence on specific isozymes drug substrates

Herb product	CYP 1A2 Substrates
Allium sativum (garlic) oil	Caffeine[4]
Cimicifuga racemosa (black cohosh) root extract	Caffeine[21]
Ginkgo biloba (ginkgo) leaf standard extract	Caffeine[4,35]
Hydrastis canadensis (goldenseal) root extract	Caffeine[21]
Hypericum perforatum (St. John's wort) extract	Caffeine[4,30,61]
	Theophylline[62]
Panax ginseng (Asian ginseng) 5% ginsenosides	Caffeine[4]
Piper methysticum (kava) extract	Caffeine[21]
Serenoa repens (saw palmetto) liposterolic extract	Caffeine[10]
Silybum marianum (milk thistle) 80% silymarin	Caffeine[10]
Valeriana officinalis (valerian) root extract	Caffeine[21]

Herb product	CYP 2D6 Substrates
Allium sativum (garlic) oil	Debrisoquin[4]
Camellia sinensis (green tea) decaffeinated extract	Dextromethorphan[63]
Echinacea purpurea (echinacea) whole plant extract	Debrisoquin[10]
Ginkgo biloba (ginkgo) leaf standard extract	Debrisoquin[4,35]
Hypericum perforatum (St. John's wort) extract	Debrisoquin[4]
	Dextromethorphan[32,60]
Panax ginseng (Asian ginseng) 5% ginsenosides	Debrisoquin[4]
Piper methysticum (kava) extract	Debrisoquin[21]
Serenoa repens (saw palmetto) liposterolic extract	Debrisoquin[10]
	Dextromethorphan[64]
Silybum marianum (milk thistle) 80% silymarin	Debrisoquin[10]
Valeriana officinalis (valerian) root extract	Debrisoquin[21]
	Dextromethorphan[59]

Herb product	CYP 2E1 Substrates
Echinacea purpurea (echinacea) whole plant extract	Chlorzoxazone[10]
Cimicifuga racemosa (black cohosh) root extract	Chlorzoxazone[21]
Ginkgo biloba (ginkgo) leaf standard extract	Chlorzoxazone[4,35]
Hydrastis canadensis (goldenseal) root extract	Chlorzoxazone[21]
Panax ginseng (Asian ginseng) 5% ginsenosides	Chlorzoxazone[4]
Serenoa repens (saw palmetto) liposterolic extract	Chlorzoxazone[10]
Silybum marianum (milk thistle) 80% silymarin	Chlorzoxazone[10]
Valeriana officinalis (valerian) root extract	Chlorzoxazone[21]

Herb product	CYP 3A4 Substrates
Camellia sinensis (green tea) decaffeinated extract	Alprazolam[62]
Cimicifuga racemosa (black cohosh) root extract	Midazolam[21]
Echinacea purpurea (echinacea) whole plant extract	Midazolam[10]
Glycine max (soy) bean extract 50 mg isoflavones	Cortisol[65]
Glycyrrhiza glabra (licorice) root water extract	Midazolam[66]
Piper methysticum (kava) extract	Midazolam[21]
Serenoa repens (saw palmetto) liposterolic extract	Alprazolam[63]
	Midazolam[10]
Silybum marianum (milk thistle) 80% silymarin	Indinavir[8,9,67]
	Midazolam[10]

concentrations of 29%.[6] In vitro tests found that ginsenoside Rd was a weak inhibitor of CYP 3A4, but Rf increased the activity of this isozyme at 3-4 times the concentration of Rd inhibition.[7]

In two separate studies, milk thistle extract was given to 10 human subjects (153 mg or 173 mg silymarin three times daily for two or three weeks, respectively) and did not inhibit CYP 3A4 metabolism of the substrate indinavir.[8,9] Also, 175 mg milk thistle extract (80% silymarin) twice daily failed to alter bioavailability of midazolam in 12 humans after four weeks.[10] While metabolism of erythromycin by CYP 3A4 was not significantly inhibited by the major component silybin, 3A4 oxidation of denitronifedipine was clearly inhibited in a mostly non-competitive fashion in vitro.[11] The inhibition of CYP 3A4 by silybin, silydianin, and silycristin was shown in vitro to be dose-dependent but not therapeutically relevant due to the concentrations required.[12,13] However, 140 mg/d silymarin did reduce bioavailability after nine days of Pgp/CYP 3A4 substrate metronidazole, either by inducing Pgp or 3A4.[14] Silybin failed to reduce uptake of Pgp substrate ritonavir in vitro (as did hyperforin, paradoxically),[15] but as noted previously, in 16 healthy humans 440 mg silymarin daily for 14 days produced a tendency toward reducing digoxin levels, suggesting potential Pgp induction.[16] The combination of weak inhibition of both Pgp and 3A4 may be responsible.

In the another example, goldenseal tincture and its herb tea were the strongest CYP 3A4 inhibitors tested in vitro of 21 herb extracts and 20 herb and black teas.[17,18] This was believed to be largely due to berberine,[19] generally considered its primary active component.[20] For one extract, inhibition in vitro is due primarily to the alkaloid hydrastine, rather than berberine, that forms a stable adduct with the CYP 3A4 heme iron.[19] In vivo 2.7 g daily for 28 days of goldenseal root extract inhibited midazolam 3A4 metabolism by 40% in 12 men and women.[21] However, 2.28 g of the root given daily to 10 healthy volunteers for 14 days failed to affect the pharmacokinetics of CYP 3A4 substrate indinavir.[22]

Effects can differ depending on the plant part, its relative component make-up, and the absorption of its active compounds. *Echinacea purpurea* root solid extract at 1.6 g/d for eight days increased the clearance and reduced bioavailability of IV midazolam but did not alter its clearance when the drug was given orally to 12 human subjects. These results suggest that some root compounds inhibit intestinal CYP 3A while others induce liver CYP 3A.[23] When an *E. purpurea* whole plant extract was given in a 1.6 g daily dose to 12 healthy human subjects for 28 days, no significant effect on oral midazolam was detected.[10] *E. purpurea* root tincture is a strong CYP 3A4 inhibitor in vitro, more so than a tincture of its tops.[17] While the tops and root have similar concentrations of the main caffeic acid derivative cichoric acid, the roots contain much greater concentrations of alkamides.[24] The alkamides are systemically available after oral consumption by humans, whereas caffeic acid conjugates are not.[25] These differences in phytochemical content and bioavailability may be reflected in enteric versus hepatic CYP influence.

St. John's Wort Products as Prototypical Inducers of CYP 3A4?

St. John's wort extract LI160 given at 900 mg daily for 14 days increased duodenal P-glycoprotein 1.4-fold, duodenal CYP 3A4 1.5-fold, and hepatic 3A4 1.4-fold in humans.[26] The dual effect on CYP 3A4 and Pgp increases the impact on drugs that are substrates of both. Extract LI160 at 900 mg daily for two weeks prior to administering single doses of simvastatin and pravastatin to eight healthy males each resulted in lower plasma levels of simvastatin and its active metabolite, but pravastatin plasma concentration was not influenced. Simvastatin is a substrate of P-glycoprotein and CYP 3A4 in the intestinal wall and liver, but pravastatin is not a substrate for either.[27]

St. John's wort standardized extract at 900 mg/d given for 14-47 days to four patients on methadone resulted in a 19%-60% (median 47%) decrease in methadone plasma concentration to dose ratios. Methadone is also a substrate of P-glycoprotein and CYP 3A4. Two patients reported opioid withdrawal-like symptoms.[28] The P-glycoprotein and CYP 3A4 substrates indinavir and cyclosporin have their bioavailability significantly reduced in human studies. Several case reports have also been published indicating their reduced efficacy, leading to increased HIV viral load and organ (heart, kidney, liver, pancreas) rejection, respectively, when used with St. John's wort extract.[29] Drugs that are purely CYP 3A4 substrates and have reduced bioavailability in humans taking St. John's wort extract include alprazolam, imatinib, midazolam, nifedipine,[6] omeprazole,[30] oral contraceptives, quazepam, tacrolimus, and verapamil.[29,31]

Studies extended beyond 10 days are necessary to detect effects of induction on Pgp and CYP proteins. For example, the standard research CYP 3A4 drug substrate alprazolam showed increased clearance and decreased bioavailability when 900 mg daily St. John's wort extract LI160 was given for 14 days prior and concurrently to 12 healthy subjects.[32] In an earlier study by the

same research group, seven healthy subjects given 900 mg daily for only four days of an extract standardized to 0.3% hypericin did not show significant changes in pharmacokinetic parameters for alprazolam.[33] When interaction with alprazolam was studied in the context of daily hyperforin dose, it was found in 28 volunteers that 240 mg extract providing 3.5 mg hyperforin daily for 10 days was insufficient to increase alprazolam metabolism,[34] whereas 900 mg of an extract for 28 days that delivered 4.8 mg hyperforin per day induced midazolam metabolism by 141%, when measured as a single time-point phenotypic metabolic ratio.[35]

Hyperforin Key Pgp and CYP 3A4 Inducer

Like other misleading in vitro findings, St. John's wort tincture was one of the most potent herbal tinctures tested in vitro for inhibiting CYP 3A4.[17] However, induction studies correlate with the human effect of the extract and component hyperforin. St. John's wort extracts and hyperforin have been shown to markedly induce CYP 3A4 expression in primary human hepatocytes in vitro. Hyperforin is the extract component that acts as a potent ligand for activating the steroid X receptor (pregnane X receptor) in vitro that in turn regulates expression of CYP 3A4.[36] St. John's wort and its hyperforin also induce Pgp in humans.[37]

In a crossover study with 10 renal transplant patients using cyclosporine, one group received 900 mg/d for 14 days of an extract with 4.7% hyperforin content and the other group received an extract with less than 0.1% hyperforin. The high hyperforin extract led to significantly less cyclosporine bioavailability, peak concentration and plasma concentration at the end of 12 days requiring an increased daily dose, whereas the low hyperforin caused no changes in cyclosporine parameters. Cyclosporine is a substrate for both Pgp and CYP 3A4.[38]

It appears that St. John's wort with low-hyperforin content is safe, but is it effective? A randomized, double-blind, placebo-controlled multi-clinic trial compared 900 mg daily of extracts containing 0.5% (WS 5573) and 5% (WS 5572) hyperforin that were otherwise identical. These were used in treating 147 patients with mild-to-moderate depression (initial Hamilton Depression Rating Scale [HAMD] average > 20) for six weeks. The group receiving the 5% hyperforin extract had the largest reduction in the HAMD from the beginning of the study (-10.3), followed by WS 5573 (-8.5) and then the placebo (-7.9). Only the 5% hyperforin extract significantly improved the score in comparison with placebo.[39] In another study it was determined that those who were more severely depressed (HAMD > 22) benefited even more from the 5% hyperforin extract, but not with the 0.5% hyperforin WS 5573.[40] In contrast, ZE117 is a 5:1 strength 50% ethanolic extract low in hyperforin,[37] and it has been effective in randomized, placebo-controlled, double-blind, multicenter clinical trials for depression,[41] comparable to imipramine[42] and fluoxetine.[43,44]

Other CYP450 Influences in Humans with Popular Botanical Preparations

In 16 subjects given 10 mL of aged garlic (*Allium sativum*) extract daily for 12 weeks, no effect on CYP 2E1 metabolism of acetaminophen was detected.[45] The extract used minced garlic incubated in 15-20% alcohol for 8-12 months and had as its major constituent S-allyl-cyseine, but very little diallyl sulfide. Diallyl sulfone, a metabolite of the main aromatic garlic component diallyl sulfide, given in doses as low as 25 mg/kg prevented hepatotoxicity in mice from bioactivation of CYP 2E1 substrate acetaminophen.[46] Aged garlic alcoholic extract does not prevent acetaminophen hepatotoxicity in vitro, though its component S-allyl-cysteine can reduce it.[47] Non-aged garlic extracts consistently inhibit CYP 2E1 in vitro and in vivo.[48-50] Consumption of 1,500 mg/d of garlic oil for 28 days in 12 healthy subjects inhibited chlorzoxazone metabolism by CYP 2E1 and enhanced sedation from the drug.[4]

When 1 g kava root extract was given twice daily for 28 days to 12 healthy volunteers, it inhibited metabolism of the CYP 2E1 substrate chlorzoxazone by 40%, though not substrates for CYP 1A2, 2D6, or 3A4.[21] In another contrast between human and in vitro results, kava root preparations and its various isolated kavalactones have been shown to be in vitro inhibitors of CYP 1A2, 2C9, 2C19, 2D6, and 3A4 substrate metabolism,[18,51-53] though 2E1 was unaffected.[51]

E. purpurea root extract at 1.6 g/d for eight days increased bioavailability of caffeine when the drug was given orally to 12 subjects, suggesting the root inhibits CYP 1A2.[23] However, when an *E. purpurea* whole plant extract was given in a 1.6 g daily dose to 12 healthy subjects for 28 days, no significant effect on caffeine was detected.[10] Again, this may reflect the greater alkamide content of the root[54] and its systemic bioavailability.[26]

Ginkgo (*Ginkgo biloba*) leaf concentrated extract EGb761 at 280 mg/d in 12 Chinese subjects significantly decreased omeprazole bioavailability, likely inducing its metabolism by CYP 2C19, but also reducing urinary excretion of its major metabolite.[55] This may be a consequence, as previously noted, of CYP 2C19 being subject to genetic polymorphism in 15-20% of Asians.[56] So, depending on the specific isozyme makeup of the

subpopulation studied, this result may not be typical of most responses.

Conclusion

Alterations in drug pharmacokinetics are a fact of life for everyone who takes medications. Inhibiting and inducing influences on drug absorption and metabolism commonly occur via the use of other drugs and consumption of common beverages and foods. Medicinal herbs are no exception in their potential to alter the bioavailability of certain medications. An important aspect in evaluating their influence is the understanding of the relative merit of different types of herb-drug interaction studies. Research done in vitro to screen a variety of plant preparations for CYP450 inhibition is suggestive at best, with numerous false-positive results documented. These misleading outcomes may be explained by exceedingly high concentrations of phytochemicals that are not achieved in vivo, polyphenolic binding and interference with CYP isozymes, and/or a disproportionate exposure to phytochemical mixtures that does not occur systemically due to variable botanical component pharmacokinetics. Animal studies have severe limitations for predicting human outcomes, due to distinct and unique species expression of CYP isozyme profiles.

Human studies likewise suffer limitations in what can be concluded about a particular herb. Varying outcomes with the same plant source can result from using different parts, preparations, doses, and durations. Isolated studies of a single preparation are therefore relatively inconclusive as regards different types of products from the same plant. The advantage of identifying and quantifying particular active phytochemicals in the different preparations is exemplified by hyperforin in St. John's wort products. The pertinent factor thus becomes the relative content and intake of the phytochemical, not the plant per se. Since botanical preparations may contain multiple phytochemicals with different drug metabolism influences, each type of preparation should be separately considered in terms of its own makeup, pharmacokinetics, and potential for influence. An over-simplistic approach for assessing or generalizing these influences is likely to be unreliable.

Recommendation

Where a well-designed human study demonstrates an interaction between a particular botanical preparation and a specific pharmaceutical, this combination should ordinarily be avoided unless it leads to an improved clinical outcome with little or no increased risk of adverse effects. If a single human study indicates no interaction with a particular drug, a similar combination may be cautiously employed. However, it cannot be assumed that all preparations from the same plant will necessarily yield the same result.

When human studies consistently demonstrate that the bioavailability of two or more substrates of the same transport protein or CYP450 isozyme is altered by prior or concurrent use of a particular botanical, combined use of these and other substrates of the same transporters and/or isozymes should not be used together with that botanical unless the modified clearance is taken into account by careful monitoring and dosage adjustments. Even in these cases, such combinations should only be considered when a relatively broad therapeutic index helps assure a safe and effective dosage for the specific drug involved. In cases where patients are consuming multiple medications, further risk of potential interactions by the introduction of pharmacologically active substances, whether pharmaceutical or botanical, should only be considered with great circumspection. ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Sweet Sorrow: Risks of Aspartame

Source: Soffritti M, et al. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006;114:379-385.

Goal: To evaluate the carcinogenicity of aspartame (APM) in a rat model deemed a consistent predictor of human cancer risk.

Design: Long-term (life span) carcinogenicity bioassay.

Subjects: Sprague-Dawley rats from colony CMCRC/ERF.

Methods: Assumed human daily APM intake ranging from 0 to 5,000 mg/kg was simulated by adding APM to standard rat feed in seven specific concentrations. Sprague-Dawley rats were randomized at 4-5 weeks of age and then permitted to ingest feed ad libitum beginning at 8 weeks of age and continuing until natural death, with control rats consuming the same feed without

APM. At death animals underwent complete necropsy and histopathologic evaluation (death of the last animal occurred at the age of 159 weeks).

Results: No significant difference was found in survival or behavior between groups. A significantly positive trend was found for the incidence of malignant tumors in both male and female rats at levels higher than simulated usual human APM intake, but also at levels less than the currently stated acceptable human daily intake. Identified tumors included among others leukemias/lymphomas, brain tumors, and transitional cell carcinomas of the renal pelvis (the latter of which is extremely uncommon in untreated rats).

Conclusion: APM possesses multipotential carcinogenic effects in both male and female Sprague-Dawley rats, a model that has previously predicted human cancer risks.

Study strengths: Large number of animals studied (> 1,800); study continued until natural death of animals (significantly longer duration than prior studies, usually 110 weeks).

Study weakness: Inherent challenge of extrapolating rat data to human experience (though track record of the model seems consistent).

Of note: This study is but one of 32 long-term bioassays assessing carcinogenicity of dietary substances completed at the Cesare Maltoni Cancer Research Center (CMCRC) since 1985, including data on vinyl chloride that led to strict regulation in the United States; FDA approval for limited use of APM occurred in 1981, while approval for use in soft drinks and later as a general sweetener occurred in 1983 and 1996, respectively; APM is the second most commonly used artificial sweetener in the world behind saccharin, with an estimated exposure of > 200 million people; surveys suggest average APM intake in the United States is 2-3 mg/kg/d, slightly higher in children and women of childbearing age (2.5-5.0 mg/kg/d); acceptable daily intake of APM has been set at 50 mg/kg/d; because studies have been ongoing for almost 30 years at CMCRC using specific Sprague-Dawley colonies, significant historical data exist regarding cancer incidence among untreated rats for comparison.

We knew that: APM, the methyl ester of the dipeptide L-aspartyl-L-phenylalanine, is frequently employed as a food additive due to its strong sweet taste (200 times stronger than sucrose); APM is metabolized in the GI tract into three constituents, which are then absorbed into the systemic circulation—aspartate (transformed into alanine + oxaloacetate), phenylalanine (transformed mainly into tyrosine), and methanol (transformed into formaldehyde and then formic acid); a number of APM studies, some supported by the manufacturer of APM, have been reviewed by the FDA over the years and considered negative with regard to carcinogenicity.

Clinical import: Conspiracy theorists have long suspected that APM causes illness in humans, but their quivers have been relatively empty. Health practitioners have had little reason to speak with patients about frequent ingestion of diet soft drinks except to state they would do better to choose beverages with known health benefits. Unfortunately, this well-done animal study brings concerns to light anew. A Feb. 12, 2006, story about this trial published in *The New York Times* raised additional concerns apart from health-related ones, leaving the reader curious if not truly concerned. The topic has been, and continues to be, a contentious one. Until clarity is attained through further research, however, it seems prudent to advise patients to lessen their intake of products containing APM, if not to steer clear of such products altogether.

What to do with this article: Keep a hard copy in your file cabinet. ❖

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

12. Most randomized controlled trials for prolotherapy have been carried out for:
a. athletic injuries.
b. acute low back pain.
c. chronic low back pain.
d. osteoarthritis.

13. The most common type of adverse event associated with prolotherapy is:
a. local pain and stiffness at the site of injection.
b. allergic reactions to the injection solution.
c. extensive bleeding at the site of injection.
d. All of the above.

14. Misleading results from herb-drug interaction research may be a result of:
a. exceedingly high concentrations of phytochemicals not achieved in vivo.
b. polyphenolic binding and interference with CYP isozymes.
c. variable botanical component pharmacokinetics.
d. All of the above

Answers: 12. c, 13. a, 14. d.

Supplement to *Alternative Medicine Alert*
April 2006

ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Reading a Dietary Supplement Label

THE FDA, AS WELL AS HEALTH PROFESSIONALS AND THEIR ORGANIZATIONS, RECEIVE MANY inquiries each year from consumers seeking health-related information about dietary supplements. Clearly, people choosing to supplement their diets with herbs, vitamins, minerals, or other substances want to know more about the products they choose so that they can make informed decisions.

In response to new legislation, dietary supplement labels have changed over the past several years.

Supplement Labeling

Ingredients. Like other foods, dietary supplement products must bear ingredient labeling. This information must include the name and quantity of each dietary ingredient, or for proprietary blends, the total quantity (by weight) of all dietary ingredients in the blend.

Labeling of products containing herbal and botanical ingredients must state the part of the plant from which the ingredient is derived (i.e., root, stem, leaves). Although many herbal products list the binomial name of the herb, herbal supplements are not required to do so. Because it is important to use the same products that have been tested and shown effective in clinical trials, this information can be very important in distinguishing between similarly named products that may have very different effects. Ginseng products offer a good example of this possible confusion: Which ginseng product should you purchase: *Panax ginseng* (Asian ginseng) or *Panax quinquefolius* (American ginseng)?

Supplement Facts. Dietary supplements also are required to include facts about the nutritional content of the product. This information can be found in the "Supplement Facts" box on the label. All ingredients that are present (except inert ingredients) in the product must be listed in this box; ingredients for which the FDA has established a daily consumption recommendation must include the percent daily value they provide.

Claims and Disclaimers. Under the Dietary Supplement and Health Education Act of 1994 (DSHEA) dietary supplement manufacturers can make three types of claims about their products: health claims, structure/function claims, and nutrient content claims.

Health claims describe a relationship between a food substance and a disease or health-related condition. "Diets high in calcium may reduce the risk of osteoporosis" is an example of a health claim. Examples of authorized health claim statements can be found at: www.cfsan.fda.gov/~dms/flg-6c.html.

DSHEA created the structure/function category of claims. These statements may claim a benefit related to a nutrient deficiency disease (e.g., vitamin C and scurvy), as long as the statement also tells how widespread such a disease is in the United States. Structure/function claims also may describe the role of a nutrient or dietary ingredient intended to affect a structure or function in humans (e.g., "calcium builds strong bones"). In addition, they may characterize the means by which a nutrient or dietary ingredient acts to maintain such structure or function (e.g., "fiber maintains bowel regularity" or "antioxidants maintain cell integrity") or they may describe general well-being from consumption of a nutrient or dietary ingredient.

The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims; they are not approved by the FDA. For this reason, dietary supplement labels that include such a claim must state in a disclaimer that the FDA has not evaluated the claim. The disclaimer also must state that the dietary supplement product is not intended to "diagnose, treat, cure, or prevent any disease"; only a drug can legally make such a claim.

Foods and dietary supplements also can use nutrient content claims. These claims describe the level of a nutrient or dietary substance in the product, using terms such as "good source," "high," or "free." Nutrient content claims may only be made if the FDA has a regulation specifying the criteria that a food must meet in order to use the claim. With few exceptions, nutrient content claims can be made only for nutrients or dietary substances that have an established daily value. The requirements that govern the use of nutrient content claims help ensure that descriptive terms, such as "high" or "low," are used consistently for all types of food products and are meaningful to consumers.

For more information about structure/function and nutrient content claims, go to www.cfsan.fda.gov/~dms/ds-labl.html.

Manufacturer's Information. Manufacturers of dietary supplements are required to include their address and telephone number in the labeling. If you cannot tell whether the product you are purchasing meets the same standards as those used in research studies you read about, contact the manufacturer. It is the manufacturer's responsibility to determine that the supplement it produces or distributes is safe and that there is substantiated evidence that the label claims are truthful and not misleading.

Source: Food and Drug Administration. Available at: www.cfsan.fda.gov/~dms/supplmnt.html. Accessed March 20, 2006.

How to Identify a Problem and What to Do

DIETARY SUPPLEMENTS MAY NOT BE RISK-FREE UNDER CERtain circumstances. If you are pregnant, nursing a baby, or have a chronic medical condition, such as diabetes, hypertension, or heart disease, be sure to consult your doctor or pharmacist before purchasing or taking any supplement. Although vitamin and mineral supplements are widely used and generally considered safe for children, you may wish to check with your doctor or pharmacist before giving these or any other dietary supplements to your child.

If you plan to use a dietary supplement in place of drugs or in combination with any drug, tell your health care provider first. Many supplements contain active ingredients that have strong biological effects and their safety is not always assured in all users. If you have certain health conditions and take these products, you may be placing yourself at risk. Under certain circumstances, taking a combination of supplements or using these products together with medications (whether prescription or over-the-counter [OTC] drugs) could produce adverse effects, some of which could be life-threatening.

Be alert to advisories about these products, whether taken alone or in combination. For example: Coumadin (a prescription medicine), *Ginkgo biloba* (an herbal supplement), aspirin (an OTC drug) and vitamin E (a vitamin supplement) can each thin the blood, and taking any of these products together can increase the potential for internal bleeding. Combining St. John's wort with certain HIV drugs significantly reduces their effectiveness. St. John's wort also may reduce the effectiveness of prescription drugs for heart disease, depression, seizures, and certain cancers, and oral contraceptives.

It is important to fully inform your doctor about the vitamins, minerals, herbs, or any other supplements you are taking, especially before elective surgery. You may be asked to stop taking these products at least 2-3 weeks ahead of the procedure to avoid potentially dangerous supplement/drug interactions—such as changes in heart rate, blood pressure, and increased bleeding—that could adversely affect the outcome of your surgery.

You, your health care provider, or anyone may report a serious adverse event or illness directly to the FDA if you believe it is related to the use of any dietary supplement product, by phone (800) FDA-1088, fax at (800) FDA-0178, or on-line at: www.fda.gov/medwatch/how.htm.

FDA would like to know whenever you think a product caused serious problem, even if you are not sure that the product was the cause, and even if you did not visit a doctor or clinic.

Source: Food and Drug Administration. Available at: www.cfsan.fda.gov/~dms/ds-savvy.html. Accessed March 20, 2006.