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Role of Lycopene in Prostate Cancer

By Georges Ramalanjaona, MD, DSc, MBA, FACEP

CANCER OF THE PROSTATE RANKS THE SECOND MOST COMMON malignancy in U.S. men, just behind skin cancer. In 2003, there will be 220,900 new cases in the United States, and about 28,900 men will die of this disease, making it the second leading cause of cancer death in men, exceeded only by lung cancer.[1]

High-profile cases of prostate cancer reported in the media have highlighted the importance of a variety of treatment options, as well as preventive measures, including the role of dietary factors. Consumption of saturated fat, especially animal fat, is associated with an increased risk of prostate cancer. Conversely, this risk seems to decrease with a high level of consumption of fruits and dark green and yellow vegetables.[2]

Several epidemiological studies have found an inverse association between lycopene consumption (a major carotenoid found in tomatoes, watermelon, guava, apricots, and pink grapefruit) and prostate cancer risk.[3,4] This article will review the current scientific evidence linking intake of lycopene with a reduced risk of prostate cancer.

Pharmacokinetics

Lycopene is an acyclic carotenoid and potent antioxidant devoid of provitamin A activity that provides the red color of fruits and vegetables like tomatoes. Lycopene content varies significantly with the degree of ripening and variety of tomato: Red tomatoes contain 50 mg/kg of lycopene compared to 5 mg/kg in the yellow varieties.[5] Recent data reveal that watermelon provides on average 40% more lycopene than an equivalent serving of tomatoes.[6]

Lycopene appears to be relatively heat stable, and is actually more readily available from tomatoes that have been cooked. A number of factors influence the initial release and subsequent absorption of lycopene from the physical matrix of food. Heating tomato-based food prior to ingestion improves its bioavailability by dissociating the protein-carotenoid complex. Lycopene also is fat-soluble, so eating tomato-based foods with some fat will enhance absorption. The dual action of bile salts and pancreatic lipases

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facilitates the transfer of lipid micelles containing carotenoids into intestinal mucosal cells via passive diffusion. Chilomicrons then carry lycopene from the intestinal mucosa to the blood stream via lymphatics. Lycopene is stored in the liver and adipose tissue. Under favorable conditions, 30% of ingested lycopene can be absorbed, but the existence of a fat malabsorption syndrome may inhibit lycopene uptake.[7] The presence and concentration of other carotenoids may likewise limit lycopene absorption.

Although data are limited, it seems clear that lycopene is not uniformly distributed in human tissues: Lycopene is highly concentrated in the adrenals, testes, and prostate.[8] Knowledge of the elimination of lycopene is somewhat limited. Furthermore, it is difficult to study the in vivo degradation of lycopene due to the short half-life of intermediate compounds and the very low concentrations of end products.[9]

Mechanism of Action

Lycopene is the most efficient scavenger of singlet oxygen among the common carotenoids.[10] This free radical scavenging property predominates in a lipophilic environment and occurs through both physical and chemical processes; the physical quenching activity of lycopene is primarily responsible and leaves the lycopene intact, in contrast to chemical quenching, which results in the degradation of the carotenoid, known as "bleaching." The number of conjugated double bonds found within lycopene molecules explains its high quenching capacity compared with other carotenoids. Furthermore, lycopene interacts with other reactive oxygen radicals such as hydrogen peroxide and nitrogen dioxide at low oxygen tension.

Recent evidence suggests that lycopene modulates molecular processes related to carcinogenesis, cell differentiation, and proliferation—independent of its role as an antioxidant.[11] Lycopene also increases gap-junctional intercellular communication, which suppresses neoplastic transformation in cell culture systems.[11]

Epidemiological Studies

Several epidemiological studies have reported the inverse association between dietary lycopene intake and prostate cancer. One early prospective trial was conducted in a cohort of 14,000 Seventh-day Adventist men who completed a dietary questionnaire in 1976 and then were followed for development of prostate cancer over six years.[12] During this period, 180 histologically confirmed prostatic cancers were found among 14,000 men. Results showed that a high intake of tomato products (more than five times per week) was associated with significantly decreased prostate cancer risk compared to lower consumption (less than one time per week) (relative risk [RR] = 0.57, 95% confidence interval [CI] 0.35-0.93, P = 0.05).

The largest published study was the Health Professionals Follow-up Study in 1986, which assessed the dietary intake of a cohort of 47,895 men initially free of prostate cancer.[13] Follow-up questionnaires were sent to the entire cohort in 1988, 1990, and 1992. Between 1986 and 1992, 812 new cases of prostate cancer were detected, including 773 non-stage A1 (using the old Whitmore grading system). High quintile lycopene intake (more than 10 servings per week) reduced the overall risk of prostate cancer by 35% and high-grade cancer by 53%. The researchers also found that consumption of tomato sauce, as opposed to tomato juice, displayed the strongest inverse association with prostate cancer risk (RR = 0.66, 95% CI 0.49-0.90, P = 0.001).

Two other studies have examined the association between serum lycopene levels and risk of prostate cancer.[14,15] The first nested case-control study used serum levels from 25,802 subjects in 1974. A 13-year follow-up of serum lycopene levels from men who developed prostate cancer was compared with those of a matched group (n = 103) of control subjects of the same race and

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age. Results showed a 6.2% lower mean serum lycopene level in subjects developing prostate cancer compared with the control group (RR = 0.50, 95% CI 0.20-1.29). However, this finding did not reach statistical significance.

The other nested case-control study used serum samples from 22,071 healthy men ages 40-84 years who were enrolled in the Physician's Health Study in 1982. Subjects included 578 men who developed prostate cancer within 13 years of follow-up and 1,294 age-matched controls. A statistically significant difference in risk was demonstrated between high quintile and low quintile serum lycopene levels (RR = 0.56, 95% CI 0.34-0.91, P = 0.057).

Clinical Trials

There presently exist only a few randomized, controlled clinical trials (RCT) in the literature addressing the role of lycopene in treating prostate cancer.

In one trial, 26 men ages 51-71 years with newly diagnosed, clinically localized (14 T1, 12 T2) prostate cancer were randomly assigned to receive 15 mg of lycopene (n = 15) or no supplementation for three weeks before radical prostatectomy.[16] Surgical specimens were evaluated for pathological stage, volume of cancer, extent of intra-epithelial neoplasia, involvement of surgical margins, and prostatic tissue lycopene levels. Measurement of serum lycopene levels, prostate-specific antigen (PSA), and IGF-1 was conducted at baseline and after three weeks. Seventy-three percent of the men in the intervention group vs. 18% in the control group (P = 0.02) had no involvement of surgical margins and/or extra-prostatic tissue with cancer. Only 67% of subjects in the lycopene group compared to 100% in the control group displayed diffuse involvement of the prostate by high-grade prostatic intra-epithelial neoplasia; the difference was statistically significant (P = 0.05). Prostatic lycopene levels were significantly elevated (47% higher) in the intervention group vs. controls (0.53 vs. 0.36 ng/g of tissue, P = 0.02). There was a trend toward a beneficial effect on PSA levels, as the PSA decreased by 18% in the intervention group compared to a decrease of 14% in the control group (P = 0.25).

These results suggest that lycopene supplementation slows the growth of prostate cancer. Interestingly, serum levels of IGF-1 significantly decreased in both groups. This finding may have been associated with the decrease in cell proliferation in the lycopene group; in the control group, the reported decline in IGF-1 may be the result of lifestyle and dietary changes initiated during the trial.

A recent pilot, single-blind RCT was conducted to study the biological and clinical effects of lycopene supplementation in subjects with localized prostatic cancer.[17] Twenty-six men with newly diagnosed cancer were randomly assigned to receive either a tomato oleoresin extract with 30 mg of lycopene (n = 15) or no supplementation (n = 11, control group) for three weeks prior to undergoing radical prostatectomy. The investigators used similar biological and clinical parameters to those described in previous trials. Compared to the lycopene group, more subjects in the control group (100% vs. 67%, P = 0.05) had diffuse involvement of the prostate by cancer. Furthermore, the lycopene group displayed less involvement of surgical margins and/or extra-prostatic tissue with cancer compared to the control group (73% vs. 18%, P = 0.05). The authors suggest that lycopene supplementation may have beneficial effects in localized prostatic cancer.

Two clinical trials currently are under way. The first study, sponsored by the National Cancer Institute (NCI), is a Phase I investigation of lycopene for the chemoprevention of prostate cancer. This is a dose-escalating study to determine the presence of dose-limiting toxicity and maximum tolerated dose of dietary lycopene given orally to healthy male subjects. A total of 25 healthy male subjects ages 18-45 years with a baseline serum lycopene level of less than 600 nM will be enrolled.

The second trial, also sponsored by NCI, is a randomized controlled trial comparing the effectiveness of an isoflavone with that of lycopene prior to surgery for the treatment of patients with stage I or II prostate cancer. The primary objective is the measurement of intermediate biomarkers such as indices of cell proliferation and apoptosis. Eligibility criteria include age between 45 and 80 years with histologically confirmed stage I or II prostate cancer, and scheduled prostate surgery within 4-6 weeks of initial biopsy. Patients will be randomized to seven treatment arms: Arms I-III will receive one of three doses of orally administered isoflavones twice daily and a multivitamin once daily; arms IV-VI will receive one of three doses of lycopene orally twice a day and a multivitamin once daily; arm VII will receive only a daily multivitamin. Plans call for a total of 87 patients to be enrolled.

Adverse Effects

No adverse effects have been reported in the published lycopene supplementation trials, and no significant abnormalities were observed in either biological or chemical parameters.

Contraindications and Precautions

There are reports of potential competition between lycopene and other carotenoids, such as beta-carotene,

relative to absorption, distribution, and biological functions.[18]

Lipid malabsorption due to disease processes, surgery, or drug therapy (e.g., olestra, a fat substitute) reduces lycopene absorption and serum lycopene levels.[6] Olestra-induced fat malabsorption inhibits lycopene uptake to a greater extent than other carotenoids such as beta-cryptoxanthin and lutein.

The effects of lycopene in pregnant women and pediatric populations are unknown.

Dosage

The lycopene supplements used in the clinical trials presented were in the form of soft-gel capsules containing 15 mg lycopene, 2.5 mg phytoene/phytofluene, and minor carotenoids.

Average dietary intake of lycopene in the United States is 5 mg daily, mostly consumed from tomato products.

Conclusion

Epidemiological data strongly suggest an inverse relationship between lycopene intake and prostate cancer risk.

Preliminary results from randomized controlled trials advocate for lycopene supplementation as a safe and useful adjunct to the standard treatment of prostate cancer. Lycopene significantly reduced the degree of diffuse involvement of the prostate by cancer, arguing for a potential role in chemoprevention. The small sample size of some of these studies precludes a definitive conclusion regarding the preventive or therapeutic benefit of lycopene supplementation for patients with prostate cancer, but results are promising, and the results of further trials are eagerly awaited.

Recommendation

Clinicians certainly should encourage patients to increase consumption of vegetables and fruits, but we also should specifically point out the potential benefits of increased exposure to watermelon and tomato-based foods rich in lycopene to reduce the risk of prostate cancer. Future clinical trials should clarify the effectiveness, and appropriate dose and duration of administration, of lycopene supplementation for the chemoprevention of prostate cancer, and as a complement to conventional care in patients with advanced stages of the disease. ❖

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Prickly Pear for Diabetes

By Astrid Pujari, MD

THE COMMON NAME, PRICKLY PEAR, APPLIES TO SEVERAL different species of cacti that belong to the genus *Opuntia* sp. These plants are characterized by their flat, fleshy pads, known as *nopales* in Spanish, which look like leaves but actually are modified stems. Like all cacti, most species have long spines on the surface. However, the *Opuntia* sp. are unique in that they also have short, fine spines called glochids, which are difficult to see but can detach and lodge in the skin, causing irritation.

Prickly pear has beautiful flowers that develop in the fall into edible fruit, known as "tuna." Both the fruit and the immature pads are traditional Mexican foods, although they now are more widely consumed—particularly in the southwest United States. Although most species of prickly pear are edible, *Opuntia streptacantha*, a species native to Mexico, is considered the best for consumption because of its taste. This also is the species that has been studied most extensively as a possible treatment for diabetes.

Pharmacology and Mechanism of Action

Prickly pear is high in fiber, in particular, a form of soluble fiber called pectin. Like all soluble fibers, the pectin found in prickly pear has been associated with lipid- and glucose-lowering effects because it slows carbohydrate and fat absorption from the gut.[1] However, research also suggests that prickly pear may increase insulin sensitivity and hepatic cholesterol metabolism.[1,2] The constituents responsible for the latter effect are unknown, although extracts of the whole broiled stem are thought to be more effective than those made from the raw stem, or from isolated components of the stem.[3] Prickly pear also is a good source of vitamin C, calcium, potassium, and iron.[4]

Animal Studies

In animals, consumption of prickly pear prior to glucose tolerance testing has been shown to decrease both the area under the curve and the hyperglycemic peak resulting from glucose ingestion.[5] Furthermore, one study of experimentally induced diabetes found that animals ingesting *Opuntia* sp. achieved a normal hemoglobin A1c at 15 weeks, and that treatment with both *Opuntia* sp. and insulin was superior to insulin alone.[6]

Clinical Studies

Current studies assessing the effect of prickly pear on diabetes are limited by short duration and small sample size. At present, the study of longest duration in which the effect of prickly pear on blood sugar was assessed in diabetic patients occurred over a one-week period;[7] the remainder of the research has assessed the effect of *Opuntia* sp. on blood sugar only in the acute setting, within a three- to six-hour time period. Thus, although preliminary data suggest that opuntia may lower blood sugar in Type 2 diabetics, further research is necessary to evaluate prickly pear's potential role in the long-term management of diabetes.

Several studies have been published demonstrating that broiled whole opuntia stems acutely lower serum glucose in patients with diabetes. One trial of 32 Type 2 diabetics found that in comparison to water or a broiled-squash control, subjects who ingested broiled whole opuntia stems had a statistically significant mean reduction in serum glucose (-16.2%) and insulin (-40.3%) at 180 minutes.[8]

Another study of eight people with Type 2 diabetes found that in comparison to both a water control and crude raw extracts of opuntia, only broiled whole stems caused a statistically significant decrease in serum glucose over three hours, with a maximum decrease of 48.3 mg/dL from basal values at 180 minutes.[3] A third trial of eight Type 2 diabetics found that in comparison to a water control, 500 g of broiled opuntia stems resulted in a statistically significant 46.7 mg/dL decrease in serum glucose from basal value at 180 minutes.[9]

Interestingly, however, when opuntia was given to 14 healthy individuals and 14 Type 2 diabetics in another study, healthy individuals did not demonstrate a statistically significant change in serum glucose and insulin levels over a three-hour period.[10] In contrast, a statistically significant reduction in serum glucose (-40.8 mg/dL) and serum insulin (-7.8 μU/mL) was noted in the diabetics in this study. These results suggest that prickly pear may work via a different mechanism than current hypoglycemic agents. All of these trials are limited by small sample size and short duration, and most of the trials on prickly pear were published by the same author. Ideally, these results should be confirmed by other investigators.

The longest study of prickly pear was a crossover, single-blind study of 14 Type 2 diabetics who withdrew their oral hypoglycemic agent and received either 30 opuntia capsules or 30 placebo capsules three times per day for one week.[7] Serum glucose, triglycerides, and cholesterol increased from baseline while patients were on the placebo, but remained stable in those taking opuntia. However, the overall quality of this study was poor, with concerns including the lack of double-blinding, small sample size, and short duration. Furthermore, this formulation required patients to take a large number of capsules, which would make this method of administration impractical over a long period of time.

Prickly pear is thought to decrease cholesterol via its high soluble fiber content. One study, conducted in 24 otherwise healthy, hyperlipidemic males on a step I diet, found that replacing 625 kJ with 250 g of prickly pear decreased total cholesterol by 12%, LDL by 15%, and triglycerides by 11% over eight weeks.[1] Interestingly, the authors also noted that subjects demonstrated improved insulin sensitivity, which could not be accounted for by the increase in dietary soluble fiber. Again, this study is limited by its small sample size, short duration, and lack of blinding.

Prickly pear also may be beneficial simply as a food for diabetic patients. The glycemic index for prickly pear in comparison to white bread was 10 in one study,[11] suggesting that substituting prickly pear for carbohydrates with a higher glycemic index in the diabetic menu may help to control postprandial spikes in blood sugar.

Adverse Effects

Hypoglycemia may be possible in diabetics using nopal, particularly in combination with other agents. Monitoring serum glucose is advisable. Appropriate precautions should be taken when handling and preparing the cactus, since dermal exposure to the glochids has been associated with skin reactions.

Dose and Preparation

There have been several studies evaluating the effect of different doses, preparations, and duration of effect for prickly pear on serum glucose levels in Type 2 diabetics. Broiled whole prickly pear stems were superior to raw preparations or dehydrated extract in two separate studies.[3,12] Furthermore, there appears to be a significant dose response: At 100 g, the maximal decrease in serum glucose was 2.3 mg/dL from baseline in comparison to the 46.7 mg/dL drop noted with 500 g of broiled whole prickly pear stems.[9] The peak hypoglycemic effect with a 500 g dose is thought to occur at three hours, while the duration of action is approximately six hours.[13] In general, the immature stems are the best for consumption, as mature stems are often tough and fibrous.

Traditionally, both the fruit and stems have been used for diabetes, though research has primarily focused on the hypoglycemic action of the stems of *Opuntia streptacantha*. They are available in specialty stores, particularly those carrying traditional Mexican fare. Most studies use a dose of 500 g of broiled stem three times per day, taken with meals. Bulk powders or capsules are not thought to be as effective.

The ripe fruit of the plant can be eaten fresh or cooked. If eaten fresh, the glochids must be removed, either by peeling the fruit carefully or by passing it through an open flame. The fruit also can be made into a juice, by simmering it for about half an hour and pressing it through a strainer. Juice can be bought ready made as well, although because the taste is otherwise tart, the juice often contains added sugar, limiting its appropriateness for diabetics. Traditionally, one glass of juice is recommended three times per day with meals.

Conclusion

The whole broiled stems of prickly pear have been shown to decrease blood sugar over a three-hour time period in Type 2 diabetics. It remains unclear whether prickly pear is beneficial for the long-term management of blood sugar in Type 2 diabetics. However, prickly pear may be beneficial when substituted for other carbohydrates as part of a diabetic meal plan because of its low glycemic index.

Recommendation

Prickly pear should not be recommended as a substitute for standard hypoglycemic agents, but ultimately it may prove to be a useful adjunct to conventional care for people with Type 2 diabetes. It may be useful when substituted for other carbohydrates in a diabetic meal plan because of its low glycemic index. Traditionally used as a food for hundreds of years, it appears to be safe. Careful monitoring of serum glucose is advisable if this food is introduced to diabetic patients on hypoglycemic agents. ❖

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Guafenesin and SAM-e for Fibromyalgia

By Sharon L. Kolasinski, MD, FACP, FACR

Fibromyalgia is a common disorder of unknown etiology characterized by chronic fatigue, diffuse pain throughout the body, and the presence, on physical examination, of multiple points that are tender to the touch.[1] In addition, patients may suffer from irritable bowel syndrome, irritable bladder syndrome, headaches, and other symptoms related to altered sensory perception.[2] The severity of symptoms varies considerably between patients, but constant pain and fatigue are typical.

There is no known cure for fibromyalgia and no one medication treats every aspect of the disorder, nor is any given therapy helpful in all patients. This has led patients with fibromyalgia to explore many types of treatments, including alternative therapies. A number of epidemiological surveys have shown that more than 90% of those with fibromyalgia use alternative therapies.[3] Recently, this has come to include the use of guafenesin and S-adenosylmethionine (SAM-e), both readily available over the counter products.

Guafenesin: Rationale for Use

R. Paul St. Amand, MD, an endocrinologist in private practice for almost 40 years and clinical assistant professor of medicine at the University of California at Los Angeles Harbor campus, has championed the use of guafenesin for fibromyalgia. St. Amand has not authored any peer-reviewed publications regarding his observations of treatment with guafenesin, but his views are readily available for review on his web site, www.guaidoc.com. St. Amand was interviewed for this article. He has treated more than 2,000 patients with his guafenesin regimen.

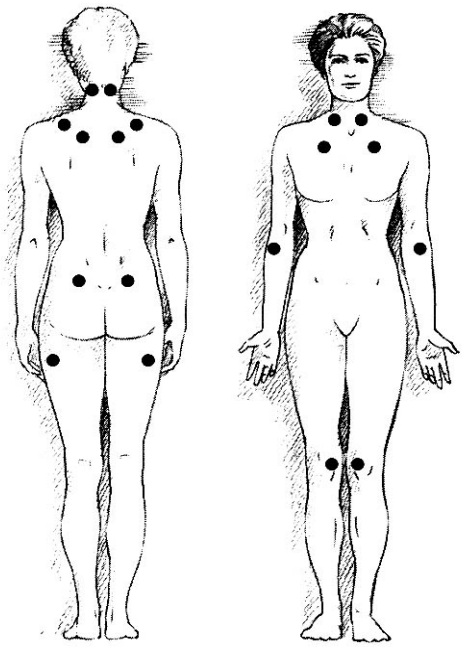
Occasionally, palpable muscle spasm can occur along with the signs and symptoms of fibromyalgia. Sometimes a patient will complain of the sensation of a "knot" under the skin with or without the presence of palpable spasm. Using an approach that is not standard in the rheumatology community, St. Amand focuses heavily on the presence of "distinct, swollen lesions" that he feels arise as a result of these muscular contractions in virtually all fibromyalgia patients. Although the standard evaluation of patients with fibromyalgia includes a determination of whether any of 18 predefined tender points *(see Figure)* are present, St. Amand favors mapping the palpable lesions. He uses these maps as one of his most important outcome measures in gauging the response to guafenesin therapy.

St. Amand believes that fibromyalgia is an inherited disorder in which renal tubular resorption of phosphate is impaired. He hypothesizes that a cellular accumulation of phosphate occurs in patients with this defect and that ATP-dependent sarcomeric calcium pumps malfunction as a result. This, in turn, results in muscular contraction.

A further, nonstandard observation St. Amand claims to have made is that fibromyalgia symptoms improve when patients are treated with uricosurics. He further states that guafenesin is weakly uricosuric and, without

Figure

Nine paired tender points of the American College of Rheumatology's criteria for fibromyalgia



Source: Daniel J. Clauw musculoskeletal signs and symptoms E. Fibromyalgia and diffuse pain syndromes. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*. 12th ed. Lanham, MD: National Book Network; 2001:190.

laboratory evidence, that this is the basis of its beneficial effects. He claims that guafenesin is more effective and has fewer side effects than agents he previously tried, including probenecid and sulfinpyrazone. However, he does not feel that the benefit derives directly from being uricosuric, because he does not think uric acid is the etiologic factor in fibromyalgia. Rather, he feels that inorganic phosphate is at least partially to blame. No direct experimental evidence supports this contention. However, St. Amand states that he has collected 24-hour urine specimens that reveal increased excretion of phosphate, calcium, and oxalate from guafenesin-treated patients. He also cites work by others that showed modestly decreased ATP levels in the biopsied muscles of fibromyalgia patients[4] as evidence that phosphate metabolism may be involved in the pathogenesis.

St. Amand begins patients on a dose of 300 mg PO bid and works up to doses as high as 600 mg PO tid. He reports that the symptoms of fibromyalgia are exacerbated when guafenesin therapy is initiated and that this represents the beginning of the therapeutic response. Palpable painful areas are mapped and doses are adjusted according to response. St. Amand describes guafenesin as innocuous and claims that lesions eventually are cleared and the disease is reversed. The time to reversal is proportional to the time that the patient has had the disease.

A final hypothetical point that St. Amand stresses is that exposure to salicylates in virtually any form can interfere with the effectiveness of guafenesin. He cautions that use of aspirin or salicylate-containing drugs or use of topical salicylate-containing compounds can block completely the uricosuric effects of guafenesin. Again, this is without experimental evidence. In addition, St. Amand lists on his web site numerous brand name products and commercially available herbal preparations that should not, theoretically, be used in combination with guafenesin.

Pharmacology

There is little in the medical literature detailing the pharmacology of guafenesin. One animal study suggested that guafenesin could potentiate the effect of aspirin in reducing inflammation.[5] The outcome variable reported was rat paw edema induced by subcutaneous injection of a 5% bentonite solution, not a commonly used outcome measure in animal arthritis research. The author did not report on the number of animals used in the experiments, how many times each experiment was repeated, or what statistical analysis was used. No clinically relevant conclusions can be drawn from this work.

A human trial assessing pharmacokinetic effects of guafenesin on paracetamol absorption was based on previous observations published in Czechoslovakia that guafenesin had muscle-relaxing and anxiolytic properties in mice.[6] This human study involved seven healthy volunteers who took a single dose of one of three paracetamol-containing preparations: paracetamol and guafenesin; paracetamol, guafenesin, and caffeine; or paracetamol alone. The authors reported that the rate of absorption of paracetamol was increased significantly by a 200 mg combination dose of guafenesin, but not by the 130 mg combination dose of guafenesin with caffeine. This corresponded to the fact that absorption of paracetamol was completed about 20 minutes sooner in the presence of guafenesin, but not when caffeine was present, compared to taking paracetamol alone. Bioavailability of paracetamol was not altered. No published reports are available on the effect of guafenesin on the pharmacokinetics of other analgesics, nor on efficacy of any analgesics.

Currently, in addition to over-the-counter cough and cold preparations, guafenesin commonly is used in

equine anesthesia. Intravenous guafenesin in a dose of 100 mg/kg is given during anesthetic induction in horses as an alternative to the use of benzodiazepines.[7]

Clinical Study

Only one clinical trial has been carried out to assess the efficacy of guafenesin in fibromyalgia. This was reported in abstract form in 1996 and is available for review in its entirety at www.myalgia.com/guaif2.htm.[8]

This double-blind randomized controlled trial enrolled 40 female subjects with fibromyalgia. Subjects were randomly assigned to receive guafenesin 600 mg or placebo tablets twice daily. Outcome measures included Fibromyalgia Impact Questionnaire score, tender point score, and an assessment of renal tubular function. Subjects were treated for 48 weeks.

Eight patients dropped out of the trial. The intention-to-treat analysis revealed no difference in response between the placebo and guafenesin groups. No subjects rated themselves cured and there was no improvement in FIQ or number of tender points. The authors were unable to confirm the purported mechanism of action for guafenesin, since there was no detectable increase in uric acid or phosphate excretion in those who received guafenesin. Toxicity was not reported.

Adverse Effects

As with other widely available, over the counter products, it is easy for consumers and physicians alike to conclude that guafenesin is safe. However, no systematic study has been performed assessing the safety of treating fibromyalgia with guafenesin, and long-term effects are unknown.

SAM-e: Rationale for Use

In contrast to guafenesin, SAM-e is a physiologic molecule, normally present in cells, with known biologic effects. It acts as a methyl group donor and precursor to endogenous sulfated products, including cartilage proteoglycans.[9] These properties have led to its use in the treatment of osteoarthritis, with success in symptom reduction in some clinical trials.[9,10]

Three decades ago, SAM-e was serendipitously observed to alter mood and it has been studied subsequently as an antidepressant in a limited number of trials.[11] Because of the link noted by others between psychological factors and symptoms in fibromyalgia, an Italian group became the first to use SAM-e in a preliminary trial[12] and two additional randomized controlled trials have followed. There also has been interest in investigating the use of SAM-e for the treatment of liver disease since, as a glutathione precursor, SAM-e has been shown to attenuate liver injury caused by alcohol in animal models.

Pharmacology

The development of sensitive and specific assays for SAM-e led to the observation that it is normally present in brain tissue. It is now known to be an important methyl donor in numerous methyltransferase reactions, making it somewhat difficult to isolate a pharmacologic action in any given tissue. Nonetheless, SAM-e interacts with catecholamines, fatty acids and phospholipids, proteins, nucleic acids, polysaccharides, and porphyrins. Interestingly, after demethylation to S-adenosyl-L-homocysteine, it can inhibit methylation reactions, and it subsequently can be metabolized to cysteine and glutathione, both intracellular antioxidants.

Limited pharmacologic studies reveal a 90-minute serum half-life after intravenous administration in humans. Intramuscular bioavailability is about 85%, but oral bioavailability is only 1% in rats. Detectable levels of SAM-e can be found in the brain of rats after IM administration and in the cerebrospinal fluid of humans after large daily IV administration. A number of studies have failed to show clear and consistent changes in monoamine metabolism, although clinical trials have suggested that SAM-e is as efficacious as tricyclic antidepressants in the treatment of depression.[11]

Clinical Studies

Tavoni and colleagues were the first to report on the effects of SAM-e in fibromyalgia patients.[12] Twenty-five patients attending their outpatient clinic, who had at least three tender points, were enrolled in a randomized, double-blind crossover protocol. They received either placebo or SAM-e 200 mg IM once daily for 21 days, underwent a two-week washout, and were switched to the other agent for 21 additional days. Outcome measures included the number of trigger points plus painful anatomic areas (an undefined parameter) and administration of questionnaires assessing depression.

Only 17 subjects completed the trial with six leaving for unexplained reasons and two developing injection site abscesses. Eleven of 17 subjects were depressed at baseline. SAM-e treatment was associated with a significant decrease in the number of trigger points plus painful anatomic areas and with a reduction in scores on the depression scales. Interpretation of these results is limited by the small sample size, the number of dropouts, and the confounding effect of depression on pain symptoms and outcome assessment.

Danish investigators sought to establish the degree of efficacy of an oral formulation of SAM-e.[13] Subjects

were required to have at least four tender points on physical examination for study entry. Participants were randomly assigned to receive placebo or SAM-e 400 mg bid for six weeks and were "encouraged not to use their usual analgetic [sic], anti-inflammatory, or antidepressant drugs concomitantly." However, eight patients used analgesics during the trial, including six who used narcotics. Five patients withdrew during the trial: Three SAM-e-treated subjects withdrew because of gastrointestinal upset and one for dizziness; one placebo-treated subject withdrew because of headache. The investigators found a significant decrease in visual analog scale measurements for resting pain in the last week of the study and fatigue. However, they found no differences in number of tender points, muscle strength, pain during physical activity, quality of sleep, overall well-being, or Beck Depression Index. The authors noted that poor bioavailability may have limited the effects of the oral preparation and that higher doses might be required.

Several years later, the same Danish group published additional results on the use of SAM-e for fibromyalgia, this time with an intravenous preparation.[14] Subjects in this study met American College of Rheumatology criteria for the diagnosis of fibromyalgia,[1] thus having 11 of 18 tender points. Thirty-four participants were randomized to receive an intravenous injection of either 15 mL of placebo or a solution containing SAM-e 600 mg on the following schedule: daily injection for six days, one day off, daily injection for four days, washout for 11 days, repeat the injection schedule with the other agent. Four actively treated subjects withdrew: three due to gastrointestinal symptoms, one due to anaphylaxis. One placebo-treated subject withdrew because of the travel distance. No statistically significant differences were noted in the number of tender points, the primary outcome measure, nor in severity of fatigue, quality of sleep, morning stiffness, depression assessment scales, or need for rescue medication.

Adverse Effects

The use of injectable SAM-e has been associated with considerable gastrointestinal side effects, including nausea, vomiting, and diarrhea that required hospitalization. Anaphylaxis has been reported after the first injection. The oral preparation also been associated with gastrointestinal side effects severe enough to cause withdrawal from a study, as well as dizziness.

Conclusion

Guafenesin is a readily available, over-the-counter expectorant available in tablet and liquid formulas. It has been promoted for use in fibromyalgia by a practitioner with many years of experience with the medication, but there is little scientific evidence to substantiate its purported mechanism of action or its efficacy. The only trial of use in subjects with fibromyalgia was well-designed and failed to show efficacy.

The rationale for the use of SAM-e in the treatment of fibromyalgia is that benefit might accrue due to neuropsychiatric effects. However, these trials have not demonstrated improvement in either signs or symptoms of fibromyalgia or of depression in fibromyalgia patients. Studies have been inadequately powered to answer the questions posed and appropriate dose-finding studies remain to be carried out. Furthermore, the applicability of the findings to what might be expected in an outpatient population with ready access to oral SAM-e is limited because only one study used an oral preparation. Severe side effects have been reported, including anaphylaxis, nausea, vomiting, and diarrhea requiring hospitalization.

Recommendation

Guafenesin is not recommended for use in patients with fibromyalgia. However, because it is commercially available and its popularity is widespread, treating physicians should be aware that it may be one of many alternative treatments used by fibromyalgia patients. Regular discussion of the use of over-the-counter products with all patients is recommended.

SAM-e is not recommended for use in patients with fibromyalgia. Studies to date do not support its use and side effects may be significant. ❖

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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, you 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 your evaluation is received, a certificate will be mailed to you.

26. In American men, prostate cancer is the second most common malignancy and the second leading cause of cancer death.
a. True
b. False

27. Which of the following statements is *true*?
a. Lycopene is water-soluble, not fat-soluble.
b. Cooked tomatoes provide a higher level of dietary lycopene than do raw tomatoes.
c. Supplementation with lycopene, but not dietary intake, has been associated with health benefits.
d. All of the above

28. Prickly pear is an appropriate substitute for pharmaceutical hypoglycemic agents for people with Type 2 diabetes.
a. True
b. False

29. Which of the following statements is *false*?
a. Use of prickly pear may lower cholesterol levels.
b. The glycemic index for prickly pear is high.
c. Use of prickly pear may decrease serum glucose levels.
d. Handling of prickly pear may result in skin irritation.

30. Which of the following statements is *true*?
a. Guafenesin and SAM-e normally are present in human cells.
b. SAM-e has been used to treat people with depression.
c. A large number of studies addressing the use of guafenesin to relieve symptoms of fibromyalgia have been published.
d. All of the above

Answer key: 26. a; 27. b; 28. b; 29. b; 30. b.

Clinical Briefs

With Comments from Russell H. Greenfield, MD

Multivitamins and Type 2 Diabetes

Source: Barringer TA, et al. Effect of a multivitamin and mineral supplement on infection and quality of life. *Ann Intern Med* 2003; 138:365-371.

Goal: To investigate whether the use of a multivitamin and mineral supplement has a significant clinical impact on well-being and incidence of infection.

Design: Randomized, double-blind, placebo-controlled study.

Subjects: One hundred fifty-eight subjects older than age 45 who had not used a multivitamin and mineral supplement during the previous month were recruited from two academic primary care clinics (130 available for final analysis).

Methods: Subjects were randomized to receive either placebo or a suitably representative multivitamin and mineral supplement to be taken every day for one year. Subjects were to maintain a daily diary tracking infections and sick days, the contents of which were reviewed at each quarterly visit. Evaluable data included self-reported symptoms of infection, infection-associated absenteeism, and quality of life using results

from completed Medical Outcomes Study 12-Item Short Forms. Subjects were stratified by age (45-64, and ≥ 65 years) and presence of Type 2 diabetes.

Results: Only 43% of those people using a multivitamin reported an infectious illness, while 73% of those taking the placebo experienced an infection. Illness-related absenteeism was higher in the placebo group. Of note, however, is that subjects with Type 2 diabetes accounted for the majority of positive findings, with only 17% of those taking a multivitamin reporting an infection compared to 93% in the placebo group. Not one diabetic subject receiving a multivitamin missed work due to infection, compared with 89% of those in the placebo group. Healthy individuals experienced no significant benefit from use of the supplement. No differences in quality of life were detected per short form responses.

Conclusion: Perhaps due to correction of underlying micronutrient deficiencies, the use of a multivitamin and mineral supplement appears to decrease the incidence of infection in Type 2 diabetics.

Study strengths: Overall design; statistical analysis; efforts to make the placebo and multivitamin indistinguishable from one another.

Study weaknesses: Overall low incidence of infection (54/130 subjects reported no infections over the course of a year); significant dropout rate (likely due to duration of study and daily diary requirement); relatively small sample size with all patients older than age 45, and only a small number older than age 65, limiting generalizability; difficult to gauge compliance with heavy reliance upon self-reporting.

Of note: Subjects with diabetes were more likely to be indigent, obese, less-educated, and poorly nourished than those without diabetes.

Did you know? The normal immune response can be significantly impaired in the presence of even mild nutritional deficiencies.

Clinical import: This well-done trial strongly suggests that patients older than age 45 with Type 2 diabetes benefit (decreased infection rate) from using a daily multivitamin and mineral supplement.

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

Common Sage for Alzheimer's Disease

Source: Akhondzadeh S, et al. *Salvia officinalis* extract in the treatment of patients with mild to moderate Alzheimer's disease: A double blind, randomized and placebo-controlled trial. *J Clin Pharm Ther* 2003;28: 53-59.

Goal: To assess the safety and efficacy of an extract of *Salvia officinalis* for people with Alzheimer's disease (AD).

Design: Double-blind, randomized, placebo-controlled parallel study.

Subjects: Thirty-nine Iranian subjects (aged 65-80 years) randomized to trial intervention over four months (30 included in final analysis); all met criteria for the diagnosis of AD and had experienced a gradual decline in cognitive function over at least six months. All subjects had a score of ≥ 12 on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and ≤ 2 on the Clinical Dementia Rating Sum of Boxes scale (CDR-SB).

Methods: All medications being used to treat dementia were discontinued. Subjects were randomized to receive 60 drops per day of either an extract of *S. officinalis* (1 kg dried leaf to 1 L of alcohol) or placebo. ADAS-cog and CDR-SB were administered to patients at baseline and every two weeks by a neurologist.

Results: There were no significant differences between the two groups at baseline. At trial's end, those who received *S. officinalis* had significantly better scores on ADAS-cog and CDR-SB than subjects in the placebo group. While not objectively measured, agitation appeared to be more prevalent in those receiving placebo. Side effects related to use of *S. officinalis* were related to cholinergic stimulation.

Conclusion: An extract of *S. officinalis* may benefit people with mild-to-moderate AD.

Study strengths: Statistics employed; close follow-up; the study was coordinated by and the herb obtained from The Institute of Medicinal Plants.

Study weaknesses: The alcoholic extract and volatile oil of *S. officinalis* both contain thujones, ingestion of which can be associated with significant side effects (including tachycardia, confusion, and seizures), a point not made in the article; small number of subjects with significant dropout rate (9/39); 103 patients were initially screened for entrance into the study, but it is unclear why the other 64 people were not enrolled; unknown whether subjects had been exposed to agents like donepezil in the past and for how long; inexact reporting of method of administration (60 drops per day—all at once or divided doses?); short trial duration.

Of note: Five people dropped out of the placebo arm, and four dropped out of the active arm of the trial.

Did you know? AD affects close to 20 million people worldwide and is the leading cause of disability in the elderly. The incidence of AD increases from 0.5% at age 65 to 8.0% by age 85. *Salvia officinalis* also is known as common sage.

Clinical import: This study, although intriguing, has significant methodologic shortcomings that limit applicability. Most importantly, it does little to quell concerns over the safety of taking an extract of sage internally for a prolonged period of time. It is far too early to recommend the use of *S. officinalis* to patients with mild-to-moderate AD either alone or in combination with other agents.

An increase in the prevalence of AD can be expected in our aging population, and although any intervention that offers hope for slowing the disease process merits further study, safety must first be established.

What to do with this article: Remember that you read the abstract. ❖