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Topical DMSO for Pain

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DMSO (DIMETHYL SULFOXIDE) IS A SMALL ORGANIC COMPOUND originally used for its solvent properties. Prior to the 1960s it was widely used in the wood and paper industry. Dr. Stanley Jacob, an organ transplant surgeon, noticed in 1961 that DMSO could be used to preserve organs,[1] and it continues to be used when storing biological tissues and organs to this day. Dr. Jacob noticed that DMSO penetrated the skin, rapidly leading to a garlic-like taste and odor on people's breath; thus began a life-long research interest for Dr. Jacob. He continues to advocate widespread use of DMSO, which he maintains is as useful as aspirin.[2]

The biological properties of DMSO have been broadly investigated. During the 1970s, many veterinary and human applications were examined, which ultimately gave rise to FDA approval for DMSO as a treatment for at least one clinical entity, that being interstitial cystitis. This condition primarily affects women who typically present with bladder pain and difficulties with urination. Treatment consists of instillation of DMSO into the bladder using a catheter. Treatment, though uncomfortable, is effective.[3] The focus of this review is on the more general use of DMSO in treating various painful conditions. For these, DMSO is primarily used topically.

Biochemistry

Chemically, DMSO is called an amphipathic molecule, meaning it is compatible with both polar and non-polar chemicals.[4] This allows it to both dissolve water-insoluble compounds and mix well with water. For this reason, it is widely used as a solvent in a variety of chemical and pharmaceutical settings. These properties also allow DMSO to readily cross tissue membranes, carrying with it any dissolved compounds.

Mechanism of Action

DMSO reversibly crosses biological membranes without damaging them, including the blood-brain barrier.[3] This property has led to

its use as a vehicle for drug therapy. The absorption of a wide range of drugs and other small molecular weight compounds can thus be facilitated, though not larger molecules like insulin and other proteins.[5] This also underlies concerns about the transfer of undesirable contaminants across these membranes.[4]

A large number of biological studies has been carried out with DMSO. These studies have established that DMSO impacts a wide range of physiological processes, including the inflammatory process, the cell cycle, apoptosis, and lipid metabolism.[4] The precise contribution that each of these makes to a possible analgesic effect is not known. DMSO is also known to be a free radical scavenger, particularly of the hydroxyl radical. It is believed that DMSO may relieve pain by inactivating the toxic oxygen radicals produced by various types of tissue injury.[6]

Clinical Studies

The topical use of DMSO to treat pain is reported to be supported by many studies. However, a highly positive review only cited studies published in the 1960s.[1] A search of PubMed and the Cochrane Library revealed few, high-quality studies. The only painful condition in which DMSO was studied in a number of controlled studies was complex regional pain syndrome type 1 (CRPS I).[7] CRPS I is a heterogeneous syndrome diagnosed after other painful conditions have been excluded. It is characterized by pain originating with an initial noxious event that proceeds to pain disproportionate to the initial injury.[8] This leads to symptoms of diffuse pain, spreading edema, temperature disturbances, and restricted range of motion.[6]

Many different treatments, pharmacological and non-pharmacological, have been recommended for CRPS I.[7] A 1997 review of CRPS therapy found 26 controlled trials involving 17 different treatments.[8] Many of these had no controlled studies to support their use, but topical application of DMSO was found to have "limited support" in relieving pain. This conclusion was based on one clinical trial, which a more systematic review in 2002 evaluated as being of low quality.[9] The trial randomly assigned 26 patients to either 50% aqueous DMSO or a regional intravenous sympathetic block.[10] DMSO was applied four times daily for three weeks. Significant improvements were found for pain and daily activity scores compared to baseline ($P < 0.05$), but no differences were found between the two groups.

The 2002 systematic review located one other study that was evaluated as being of high quality.[9] This double-blind, randomized study assigned 32 subjects to either 50% DMSO cream or placebo cream.[11] Subjects also received physical therapy as pain would allow. After two months, both groups showed significant improvements in pain and overall symptom scores compared to baseline. The overall symptom score was significantly better for the DMSO group ($P < 0.01$).

A 2003 double-blind, randomized study was conducted with 146 subjects.[6] One group applied 50% DMSO cream to the affected area five times daily and took one effervescent placebo tablet three times daily. The second group applied a placebo cream five times daily and took one 600 mg N-acetylcysteine (NAC) effervescent tablet three times daily. NAC is another free radical scavenger used to treat CRPS I. Subjects in both groups also received standard oral analgesics as required, along with standard occupational or physical therapy. Outcome measurements included those for pain, temperature, and range of motion. These were evaluated at baseline and after six, 17, 32, and 52 weeks. Subjects were offered the opportunity to switch groups at 17 weeks. No significant differences were found between the two groups for pain reduction. Both groups had a clinically relevant reduction in an overall impairment level score. This study also referenced an open trial published in Dutch, which found reduced pain in CRPS I patients using 50% DMSO cream.

A small number of additional studies were located in which topical DMSO was used to treat pain. A Cochrane review of nonsteroidal anti-inflammatory drugs for the treatment of tennis elbow identified one study using DMSO. A randomized, double-blind controlled study

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involved 102 subjects with either tennis elbow or rotator cuff tendinitis.[12] For one year, patients used either 70% DMSO aqueous solution or 5% DMSO aqueous solution. The latter was used as a placebo so that patients would still detect the distinctive DMSO taste and odor. Measurements of pain, tenderness, swelling, and range of motion showed no significant differences between the groups.

A German study examined topical DMSO in another painful condition, gonarthrosis (knee joint damage that is not advanced).[13] This double-blind controlled study randomized 112 patients to either 25% DMSO gel or a placebo gel. After three weeks, patients using DMSO had significantly improved scores over placebo for pain during everyday activities (P = 0.019), pain at rest (P = 0.015), and pain on palpation (P = 0.029). Pain diaries also reflected significant improvements.

Adverse Effects

Topical application of DMSO is generally well tolerated, although mild transient local burning, rash, and pruritis have been reported.[4] The most frequently reported adverse effect with topical DMSO is the distinctive garlic-like taste and breath odor. This arises within minutes of applying DMSO and is caused by sulfur metabolites. Much of the controversy surrounding DMSO arose after a woman in Ireland died from an allergic reaction to DMSO in 1965.[1] Headache, drowsiness, and other flu-like symptoms have also been reported occasionally.[14]

Drug Interactions

Evidence from animal studies has raised concerns about drug interactions, but specific reports were not found. DMSO enhances the topical absorption of many drugs. Use of DMSO along with other topical drugs will likely increase their systemic concentrations.

Formulation

DMSO is available as aqueous solutions, gels, or creams. Most studies were conducted with 50% preparations, although formulations are available in various concentrations.

Conclusion

Although widely recommended as a topical analgesic for humans and animals, relatively few studies supporting this indication were located. These studies in general revealed some effectiveness in relieving the pain of CRPS I. However, some of the studies did not use a placebo, but found DMSO to be as effective as other treatments of uncertain effectiveness. DMSO was not found to be effective with all forms of pain for which it has been tested. Studies reported few adverse effects, other than the disagreeable taste and breath odor.

Recommendation

Some generalized pain conditions do not respond well to conventional analgesics. Given that topical DMSO has been somewhat effective in treating CRPS I, and that it is generally well tolerated, use on a trial basis can be suggested. However, patients should be warned of the taste and odor on their breath, which may make its use intolerable. Patients should be alerted to the importance of using pharmaceutical grade DMSO. Although less expensive, industrial grade DMSO can contain impurities that will be rapidly absorbed into the body and may cause adverse reactions.[14] Similarly, the skin should be cleaned thoroughly before applying DMSO to prevent absorption of skin contaminants. Patients should also be given information about other pain-relieving strategies that may complement the use of DMSO or other analgesics. ❖

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Wild Chamomile Mouth Rinse and Oral Glutamine Suspension for Chemotherapy-Induced Mucositis

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ORAL MUCOSITIS IS A SIGNIFICANT NON-HEMATOLOGIC complication of chemotherapy and radiation therapy for cancer patients. Forty percent of patients undergoing conventional chemotherapy and up to 70% of patients undergoing conditioning therapy in preparation for bone marrow transplantation are affected.[1,2] In addition to the desired effects on malignant cells, both cytotoxic therapies adversely impact the homeostasis of the rapidly dividing normal cells of the mouth, gastrointestinal tract, and bone marrow. Within the oral cavity, the loss of rapidly dividing mucosal cells results in atrophy, necrosis, and ulceration. There is significant morbidity including pain, diminished taste sensation, and breached mucosal integrity, which compromises nutritional status and provides a systemic portal of entry for bacterial, viral, and fungal pathogens, especially in neutropenic patients. Such complications can delay or limit a patient's total chemotherapy dosage, ultimately compromising the treatment of their underlying malignancies and increasing therapeutic costs.

Predisposing Factors for Oral Mucositis

Treatment factors relevant to chemotherapy and radiation therapy that affect mucosal toxicity include the dose, duration, and intensity of specific regimens, concomitant medication, and previous mucosatoxic treatments. In an individual with successive bouts of mucositis, the oral lesions tend to occur in the same locations, especially the vulnerable non-keratinized surfaces such as the lips, cheeks, floor of the mouth, soft palate, and ventral surface of the tongue.[3] Prolonged, repetitive cycles of cytotoxic agents, such as the antimetabolites (particularly the folic acid antagonist methotrexate) and the anthracyclines, produce the most pronounced stomatotoxicity. Table 1 lists several of the most mucosatoxic antineoplastic agents; however, virtually all patients with head and neck malignancies who receive simultaneous radiochemotherapy are affected by severe stomatotoxicity.[4]

Host factors that affect the response of the oral cavity to stomatotoxins include genetic predisposition, baseline dental and periodontal health, medication- or illness-induced xerostomia, defects of DNA repair mechanisms, folic acid or vitamin B_{12} deficiencies, delayed elimination of antineoplastic agents due to renal or hepatic functional impairment, the presence of pleural and peritoneal effusions, and the administration of certain antidotes such as leucovorin.[4]

Table 1

Selected markedly mucosatoxic antineoplastic agents

Actinomycin D
Amsacrin
Bleomycin
Chlorambucil
Cisplatin
Cytarabine
Daunorubicin
Docetaxel
Doxorubicin
Etoposide
5-Fluorouracil
Methotrexate
Mitoxantrone
Plicamycin
Thioguanine
Vinblastine

Adapted from: Kostler WJ, et al. Oral mucositis complicating chemotherapy and/or radiotherapy: Options for prevention and treatment. *CA Cancer J Clin* 2001;51:290-315.

Numerous publications over the past two decades have evaluated the use of pharmacologic and nonpharmacologic interventions to prevent and treat stomatotoxic effects of antineoplastic therapy. One type of pharmacologic intervention is the use of oral rinses. The ideal oral rinse for immunocompromised patients reduces the oral bacterial load, normalizes the oral fluid pH, promotes re-epithelialization of soft-tissue lesions, has a palatable taste, is nontoxic, and is tolerable. At this time, although no solution meets all of these requirements, two adjunctive treatments that have been studied recently, wild chamomile (*Matricaria recutita* L.) mouthwashes and oral glutamine suspensions, may have clinical benefits.

Constituents and Properties of German Chamomile

Matricaria recutita L., also called wild or Hungarian chamomile, is widely used in teas for its relaxing effect. The flower heads contain all of the pharmacologically active constituents. Apigenin, one of the flavonoids contained in chamomile, interacts with GABA(A)-benzodiazepine receptors and thus can induce anxiolytic and sedative effects.[5]

Anti-inflammatory and anti-ulcerogenic activity has been documented for the primary component of the volatile oil, alpha bisabolol, which constitutes up to 50% of the oil along with azulene and chamazulene. Chamazulene has been found to inhibit leukotriene B4 formation.[6] Antibacterial activity has also been documented for the coumarin constituents.[7]

Glutamine

Glutamine, as the levorotary or L-stereoisomer, is an amino acid that accounts for 60% of the amino acid content of muscle tissue. In humans, it plays a role in interorgan nitrogen transport, renal ammoniagenesis, acid-base balance, hepatic glutathione production, and preservation of mucosal structure and function in the intestine, and acts as an essential substrate for lymphocyte and macrophage proliferation. It is considered conditionally essential because although it can be manufactured in the body, under circumstances of extreme stress demand exceeds synthetic ability.

Typical dietary glutamine intake is approximately 5 g/d and it is supplied by plant and animal proteins such beef, chicken, cottage cheese, ricotta, and spinach.[8] Patients with malignancies such as breast, gastrointestinal, and head and neck tumors have reductions in plasma glutamine; however, it is not clear whether this is the result of reduced muscle mass, tumor uptake of glutamine, or decreased oral glutamine intake.[9]

Glutamine is available as an individual supplement, typically in 500 mg tablets, capsules, or in powdered form. Due to its poor aqueous solubility and biodistribution, only a suspension of glutamine powder, used as a swish and swallow, can achieve a high local concentration in the oropharynx.[8] Such supplementation should be mixed with a cold or room temperature sucrose-containing liquid (not above 22° C, as heat destroys glutamine). Because L-glutamine is unstable in water, fresh solutions should be prepared daily.[10]

Basic Non-Pharmacologic Mucositis Preventive Measures

Pre-therapy dental examination and ongoing daily oral hygiene. Dental evaluation, treatment, and optimization of daily oral hygiene prior to initiation of chemotherapy and radiation therapy are critical, often overlooked aspects of cancer therapy. Poor oral care with concomitant dental and periodontal pathology such as dental caries, ill-fitting prostheses, defective restorations, orthodontic appliances, piercings, periodontitis, and third molar pathology leads to a greater risk for oral complications, especially infection. The pre-existence or development of xerostomia is associated with an increased bacterial colonization on dental surfaces and prostheses and, therefore, a higher incidence of oral

Table 2

Oral self-care and dietary measures for cancer patients

- Eat a mechanically soft, bland diet.
- Maintain oral and lip moisture with sips of water, ice chips, specially formulated OTC toothpastes (Biotene), mouth moisturizing gels (Oral B), and water- or lanolin-based lip balm.
- Avoid acidic, citrus, spicy, salty, coarse, and dry foods, and alcohol or tobacco-containing products.
- Brush with a soft-bristled toothbrush and use waxed or taped floss to minimize trauma after meals and at bedtime.
- If platelet count is below 20K or ANC is below 500, use foam brush and do not floss.
- Rinse with saline several times daily to increase pH and decrease bacterial flora in the oral cavity.

Adapted from: Hicks J, et al. Chemotherapy induced mucositis: Treatments and potential new therapies. *U.S. Pharmacist.* Available at: www.uspharmacist.com/index.asp?show=article&page=8_1122.htm. Accessed Oct. 10, 2005.

mucositis and dental caries during the course of antineoplastic therapy. Amelioration of xerostomia can be accomplished by avoidance of drugs that decrease salivary flow and by the use of non-irritating, mint-free, sugar-free, and cinnamon-free sialogogues such as chewing gum or drops, alkaline saline solutions, or low-dose pilocarpine.[11-13] Table 2 summarizes dietary and oral self-care measures for cancer patients.[14]

Cryotherapy. The use of oral cryotherapy (intraoral ice chips) for 30 minutes just before and during administration of chemotherapy has been shown to be a useful adjunct for attenuation of the mucositis reaction to agents given by bolus infusion, such as 5-fluorouracil.[15]

Studies on chamomile oral rinse. In an uncontrolled study of 98 patients undergoing chemoradiation therapy for head and neck cancers, Carl and Emrich found that the German product, Kamillosan Liquidum oral rinse, and an oral care protocol accelerated the resolution of mucositis in 36 of 46 patients without adverse effects.[16] Subsequently, however, a Phase III, double-blind, placebo-controlled clinical trial by Fidler et al, using cryotherapy and 14 days of chamomile oral rinse three times daily for 14 days in 164 cancer patients on a 5-fluorouracil regimen, failed to show any significant difference between the chamomile and control groups in the severity or duration of stomatitis.[17] No toxicity was reported.

Studies on Glutamine Oral Suspension for Mucositis

In two small randomized studies, prophylactic glutamine mouthwashes significantly reduced the incidence, severity, and duration of oral mucositis in patients undergoing chemotherapy or radiation therapy, respectively.[18,19] Jebb et al, however, in a randomized, double-blind, crossover trial involving 17 patients with metastatic colon cancer treated with two cycles of a 5-fluorouracil-based regimen and leucovorin, found no significant differences between control and glutamine oral suspensions (4 g four times daily) with regard to severity and duration of mucositis.[20]

Aquino et al, in a prospective double-blind, randomized, placebo-controlled study, evaluated the effect of a glutamine oral suspension (2 g/m^2 twice daily to a maximum of 4 g daily) on the development of mucositis in 120 children undergoing hematopoietic stem cell transplant (HSCT).[21] He found a trend toward a reduction in the average mucositis score that was not significant (P = 0.07), but did find a statistically significant decrease in the median number of days of morphine use from 19 in the control (glycine) group to 12 in the glutamine group (P = 0.03) and a reduction in the median number of days of TPN use from 27 days in the placebo group to 17.3 in the glutamine group. There were no statistically significant differences in episodes of bacteremia or total number of hospital days. The 100-day mortality was similar between the groups. No toxicities were reported.

Anderson et al conducted a double-blind, randomized, prospective, placebo-controlled study of oral glutamine suspension for the prevention of mucositis in 193 patients (children and adults) undergoing HSCT.[22] They received either glutamine or glycine at a dosage of 1.0 g/m^2 to swish and swallow four times per day after stratification according to transplant type. They received the glutamine/glycine supplementation during preparative chemotherapy and radiation and continued for 28 days after marrow infusion. Patients undergoing autologous bone marrow transplantation (BMT, n = 87) had significantly less mouth pain and eating difficulty during low-dose oral glutamine supplementation (P = 0.05). The percentage of these patients that had no morphine requirement was significantly greater in the glutamine group compared to the placebo group (53% vs. 31%, P = 0.04). The duration of opiate administration was also significantly less in the autologous BMT glutamine patients compared to placebo (5 days vs. 10 days, P = 0.005). No differences were observed in days of TPN use or use of parenteral antibiotics for infection in any of the transplant groups. Although the early (day 28) mortality was significantly different between the glutamine (0/98) and placebo (7/95) groups (P = 0.006), this difference was no longer significant at day 100. No differences were observed in the development of acute or chronic graft vs. host disease between the glutamine or placebo groups.

Chamomile Dosage

The German Commission E recommends steeping 3 g dried flower heads in 150 cc of boiling water for 5-10 minutes, cooling, straining, and then using it as a rinse-and-spit mouthwash. Because the quality of phytotherapeutic products such as chamomile can be variable, it is important to ascertain that products are from a reliable source.[23]

Standardization of Chamomile

German chamomile products such as Kamillosan, which contains 20 mg of chamomile essential oil per 100 g of cream, are standardized to a minimum value of chamazulene and alpha bisabolol. Tablets and capsules of chamomile are standardized to contain 1.2% apigenin and 0.5% essential oil per dose. Examples of standardized chamomile flower preparations include Nutritional Dynamics German Chamomile which contains 400 mg

chamomile flower per capsule, standardized to 1.25% apigenin and 0.5% essential oil and Nature's Way German Chamomile, which provides 125 mg chamomile flower, standardized to 1.25% apigenin.[7]

Glutamine Dosage

Oral doses of L-glutamine up to 21 g daily appear to be well tolerated. The adverse reactions reported with these high doses are primarily constipation and bloating, and their incidence is uncommon.[10]

Clinical studies of cancer patients with the goal of preventing chemotherapy- or radiation-induced stomatitis, however, have specified doses of 2-4 g twice daily or 2 g four times daily of the swish-and-swallow suspension. This glutamine dosage approximates the amount that would be ingested on a high-protein diet.[22] This dosage of glutamine was chosen because of concern over evidence from in vitro studies demonstrating that glutamine, in addition to providing an energy source for dividing intestinal epithelial cells and lymphocytes, may also function as a growth factor for malignant epithelial cells or alter the pharmacokinetic interactions between malignant tumors and chemotherapeutic agents, thus causing relapse or progression of malignancy.[24,25] The currently available clinical data for glutamine use in cancer patients, however, do not suggest that oral or parenterally supplemented glutamine at this dosage level enhances tumor growth or worsens clinical outcomes.[10,26] Clinical safety of glutamine use in humans has been documented.[27]

The L-glutamine utilized in clinical studies by Anderson et al was pharmaceutical grade crystalline amino acid powder obtained from Ajinomoto USA (Teaneck, NJ; FDA IND No. 36,978) and the swish and swallow can be made by suspension in a vehicle of two parts of Ora-Sweet SF, one part water, and one part Ora-Plus (Paddock Laboratories, Minneapolis, MN).[28]

MGI Pharma recently submitted a New Drug Application to the FDA for an oral glutamine suspension called Saforis for the treatment of chemotherapy-induced oral mucositis. However, this particular preparation is not yet commercially available.[29]

Adverse Reactions: Chamomile

Chamomile is listed on the FDA's Generally Recognized as Safe (GRAS) List; however, persons with known hypersensitivity to plants of the Asteraceae (Compositae) family such as arnica flower, marigold, yarrow, ragweed, tansy, asters, and chrysanthemums should avoid its use.[30] Theoretically, chamomile may act as a uterine stimulant, which could cause abortion. Its use, therefore, should be avoided during pregnancy.

Chamomile contains natural coumarins, which have the potential to increase anticoagulant effects and inhibit platelets, so it should not be used in patients on chronic anticoagulants such as coumadin, Plavix, or aspirin.[31] Because one of its contents, apigenin, a flavone, has been found to interact with GABA(A)-benzodiazepine receptors in vitro, it also may enhance the effects of sedative and anxiolytic medications.[32]

Adverse Effects: Glutamine

There was a report of exacerbation of manic symptoms in two hypomanic patients following the use of 2-4 g daily of L-glutamine. The symptoms resolved with discontinuation of the L-glutamine.[33]

Because L-glutamine is metabolized by the liver, eliminated by glomerular filtration, and nearly completely resorbed by the renal tubules, it should not be used in patients with impaired hepatic or renal function.[10]

Conclusion

Prior to the initiation of chemotherapy or radiation therapy, all patients with cancer should undergo dental evaluation, treatment, and education regarding daily oral hygiene practices to follow throughout their treatment. Cryotherapy is a simple, inexpensive, and effective prophylaxis against the development of mucositis, especially before and during bolus infusions of antineoplastic drugs. Despite initial promising results from an uncontrolled trial, wild chamomile oral mouthwash did not decrease 5-fluorouracil-induced stomatitis in a subsequent study, and therefore cannot be recommended for general preventive use. Several clinical trials have demonstrated the safety and efficacy of divided doses of up to 8 g daily of glutamine oral suspension in attenuating the development and severity of mucositis in patients undergoing chemotherapy and total body irradiation for bone marrow transplantation.

Recommendation

Careful pre- and intra-procedure dental care, cryotherapy, and glutamine oral suspension can be added to the armentarium of therapies useful to prevent and ameliorate the symptoms and sequelae of chemotherapy- and radiation-induced mucositis. ❖

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1 The most common adverse effect of DMSO is:
a. metallic taste and odor.
b. garlic-like taste and odor.
c. allergic reactions.
d. All of the above

2. The evidence from controlled clinical trials of topical DMSO for pain suggests its use:
a. should be banned.
b. can be recommended as first-line pain therapy.
c. cannot be recommended.
d. warrants a trial in patients refractory to other analgesics.

3. Which areas of oral mucosa are most vulnerable to direct stomatotoxicity of chemotherapeutic agents?
a. The floor of the mouth
b. The lips
c. The soft palate
d. The ventral surface of the tongue
e. All of the above

4. The use of chamomile products is contraindicated in:
a. People who are hypersensitive to plants in the Asteraceae (Compositae) family
b. People taking coumadin or Plavix
c. People on aspirin therapy
d. All of the above

Answers: 1. b, 2. d, 3. e, 4. d.

With Comments from Russell H. Greenfield, MD

Dr. Greenfield is Medical Director, Carolinas Integrative Health, Carolinas HealthCare System, Charlotte, NC, and Clinical Assistant Professor, School of Medicine, University of North Carolina, Chapel Hill, NC.

Something's Fishy—A Supplement for UC?

Source: Seidner DL, et al. An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: A randomized, controlled trial. *Clin Gastroenterol Hepatol* 2005;3: 358-369.

Goal: To assess the efficacy of a balanced nutritional supplement on disease activity and medication use in adults with mild-to-moderate ulcerative colitis (UC).

Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter (five clinical centers) trial over six months in which participants were stratified based on extent of disease and smoking status.

Subjects: Adults older than age 18 (n = 121) with documented UC for at least six months, active inflammation on endoscopic evaluation, and mild-to-moderate symptomatology as determined by a disease activity index (DAI) of 3-9 at time of enrollment.

Methods: Eligible subjects underwent endoscopy and mucosal biopsy to confirm the presence of active disease, as well as a variety of blood tests, at study entry and at three and six months of treatment. Subjects were to maintain their normal diet, but also received a placebo formula (drink containing water, sucrose, flavoring, and color) or the UC nutritional supplement (UCNS) containing a combination of fish oil, fructooligosaccharide, gum Arabic, and a mixture of vitamins and minerals. Subjects maintained a daily diary recording formula intake, bowel movements, and medication use. The primary efficacy endpoint measured was daily dose of medication used, while secondary endpoints included disease severity.

Results: Of the 121 subjects randomized, 86 completed all aspects of the trial. There was no significant difference between the two groups with respect to clinical improvement, including bowel function; however, subjects in the UCNS group were able to decrease the dose of prednisone required to control clinical symptoms at a greater rate, as well as control symptoms with a lower total dose of steroid (35-65% lower), as compared with the placebo group.

Conclusion: A formula containing a mixture of fish oil, fermentable oligosaccharides, and antioxidants provides a corticosteroid sparing effect for patients with mild-to-moderate UC over a period of six months.

Study strengths: Stratification scheme to ensure equal distribution of characteristics among study groups; means of determining compliance; intention-to-treat analysis; duration of trial.

Study weaknesses: Significant withdrawal rate (29%); inequality of groups with respect to DAI (the UCNS group had a higher mean DAI score at baseline compared with the placebo group).

Of note: Use of antibiotics and nonsteroidal anti-inflammatory drugs was not allowed within two weeks of study entry, while use of immunosuppressive agents was not permitted within four weeks of enrollment (but prednisone and/or mesalamine derivatives were permitted during the course of the study, as were antibiotics, but for no more than 10 days); the DAI is based on four clinical parameters (stool frequency, rectal bleeding, appearance of the rectal mucosa, and physician assessment of disease activity); subjects were instructed to discontinue outside supplementation during the course of the study; almost 50% of participants had stopped smoking before the onset of UC; intolerance rates were similar with both formulas (uncommon); the UCNS contained significantly more calories than the placebo drink, though there was no significant difference in body weight change at study's end between the two groups; levels of arachidonic acid (AA) were significantly decreased only in the UCNS group; bleeding time was not prolonged in the UCNS group, and there was no difference between the two groups in erythrocyte sedimentation rate (a nonspecific measure of inflammation).

We knew that: Corticosteroids are very effective for the treatment of moderate-to-severe UC, but side effects are prominent, and a significant number of patients relapse once treatment is discontinued; fish oils appear to decrease the production of pro-inflammatory eicosanoids; phospholipase A2 causes release of AA, which is metabolized by cyclooxygenase and lipoxygenase into 2-series prostaglandins and thromboxanes, resulting in a variety of processes that can lead to mucosal damage; fructooligosaccharides and gum Arabic are prebiotics that enteric bacteria metabolize into short-chain fatty acids (SCFAs), the primary fuel of the colon; SCFAs do not reach the colon when taken orally due to small bowel absorption and hepatic metabolism; fish oils have shown benefit in animal models of UC; fish oils have been studied previously in the setting of UC with inconsistent results, while studies focusing on the use of SCFAs have shown more consistent benefit; reactive oxygen species are produced by activated neutrophils and macrophages, and contribute to mucosal damage in UC, leading to the hypothesis that antioxidants might ameliorate some pathophysiology seen with UC; the clinical relevance of the dose decrease of steroid employed by those in the UCNS group remains a topic for discussion.

Clinical import: Inflammatory bowel disease can be problematic for the

practitioner aiming to relieve suffering and prevent complication, and maddeningly frustrating for the person with the disease. Treatment options include the use of corticosteroids that, while often effective, are associated with the potential for significant side effects as well as adverse effects on quality of life. An adjunct that could safely lessen the dose of steroid required to control disease activity should prove a welcome addition to the physician armamentarium. Studies addressing Crohn's disease and impact on long-term sequelae will be welcomed, but until such time the unique form of supplementation employed in this study can be considered a viable adjunct in the treatment of people with UC.

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Green Without a Sheen? Organics and Children

Source: Lu C, et al. Organic diets significantly lower children's dietary exposure to organophosphorous pesticides. *Environment Health Perspect* doi:10.1289/ehp.8418, available at: http://dx.doi.org/ [on-line 1 Sept 2005].

Goal: To determine the contribution of daily dietary organophosphorous (OP) pesticide to overall OP pesticide exposure in elementary school-aged children.

Study design: Longitudinal dietary intervention trial over 15 days.

Subjects: Children (n = 23) in the Seattle area aged 3-11 years recruited from public and Montessori schools who partook of conventional diets.

Methods: A letter describing the study was sent home from school with children, and families interested in participating in the trial contacted the research group directly. After further screening, a questionnaire was administered addressing household pesticide use. Children were then enrolled in a 15-consecutive-day sampling period consisting of three phases: conventional diets on days 1-3; organic food items (purchased by research staff from a single grocery store) substituted for most of the children's conventional diet on days 4-8 (parents instructed to exactly replace the items their children would normally have eaten with organics); conventional diets on days 9-15. Parents obtained urine samples from first and last voids of the day, upon which pesticide metabolite analysis was performed.

Results: Frequency of detection of OP pesticide residues differed between initial and terminal conventional diet phases, and markedly between conventional and organic diet phases. All children had pesticide residues detectable at enrollment, but immediately after introduction of the organic diet phase pesticide residues became nondetectable, and remained in that range until reintroduction of conventional food on day 9.

Conclusion: Dietary intake of pesticides represents a major source of exposure for infants and children. An organic diet provides a dramatic and immediate protective effect against exposure to commonly used OP pesticides.

Study strengths: Organic produce was analyzed for pesticide residue through the USDA Pesticide Data Program; trial runs of organic foods offered to children in the same age range to ensure acceptance of taste and appearance; as much as was possible, focus was on organic food as opposed to altering the children's diet.

Study weaknesses: Small sample size; environmental sampling might have provided more intriguing data than a questionnaire on household pesticide use; significant variability in urinary OP metabolite measures; no health outcome data; non-generalizability.

Of note: The study was supported by the U.S. Environmental Protection Agency (EPA); a 1993 report by the National Research Council reported that dietary intake represented the major source of pesticide exposure to infants and children, and may account for the increased pesticide-related health risks noted in children compared with adults; results for pyrethroid pesticides will be published at a later date; organic foods that were substituted for conventional items included fruits and vegetables, wheat- or corn-based products (including popcorn and chips), and juices, all of which are routinely reported to contain OP pesticides; no OP or other pesticide residue was detected in any of the organic food products; two of the metabolites detected were MDA (a metabolite of malathion) and TCPY (a metabolite of chlorpyrifos), representing the common application of these two pesticides on wheat, fruits, and vegetables.

We knew that: OP pesticides are known to cause neurological effects in both animals and humans; there exists a lack of data with which to assess the true nature of pesticide-related health risks in children; the presence of OP pesticide metabolites in the environment as well as food complicates assessment of pesticide absorption; regulatory changes have been instituted since 1998 to lessen household OP pesticide exposure, but fewer agricultural restrictions exist.

Comments: This study suggests that simply by substituting organic food items for conventional ones, parents can minimize exposure to chemicals known to cause untoward neurological effects. A voluntary study involving 23 children who regularly consume fruits, vegetables, and wheat may not be generalizable, and begs corroboration by a larger trial, but the reverberations are both real and complicated. Although few can afford to eat organic produce on a consistent basis, some could afford to lean organic for the fruits and vegetables enjoyed most often by their children, and thus avoid concentrated negative effects from repeated exposure. However, it would be inadequate, if not immoral, for practitioners to recommend organic food items solely to select families with ready access to them should future data continue to point out

potential health benefits. We practitioners will be obligated to demand policy change ensuring that all children have access to such nourishment in their schools, and that lower cost organic options be available to the majority of America's families. If the data bear out, as stewards of community health, we can do no less.

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Placebo Effect: The Brain and Pain

Source: Zubieta J-K, et al. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci* 2005;25: 7754-7762.

Goal: To determine whether introduction of placebo with expectation of analgesia activates endogenous opioid neurotransmission within the human brain.

Design: Randomized, single-blind, counterbalanced trial.

Subjects: Male volunteers (n = 14), 20-30 years of age.

Methods: Each volunteer underwent PET scanning three times with radiolabeled carfentanil. The first scan was performed at baseline, the latter scans associated with either a sustained pain challenge (infusion of 5% hypertonic saline into the left masseter muscle) or sustained pain with placebo with implied analgesic properties. Following initiation of hypertonic saline infusion, subjects were asked to report pain intensity every 15 seconds using an electronic visual analog scale (VAS). Researchers used these data to maintain pain intensity scores throughout the duration of the experiment. The placebo condition utilized intravenous normal saline administered every 4 minutes for 15 seconds following a computer-generated warning and subsequent second-by-second count of the 15-second infusion. Participants, who had been advised they were receiving an agent "that may or may not relieve pain," were asked to estimate the expected analgesic response before and after normal saline administration. Upon completion of the study individual participants completed a battery of questionnaires addressing pain and affect.

Results: The sustained pain stimulus was associated with activation of endogenous opioid transmission and mu-opioid receptors. Data revealed that expectation of analgesia was achieved in participants, and that placebo administration resulted in an increase in the average rate of analgesic stimulus required to maintain pain. The degree of placebo-induced mu-opioid system activation was relatively regionally specific for individual subjects, but directly involved the associative, higher-order brain regions. Significant effects of placebo were noted for ratings of pain intensity and unpleasantness, as well as for affective measures.

Conclusion: Expectation of pain relief, a cognitive factor, is capable of modulating physical and emotional states through site-specific activation of mu-opioid brain receptor signaling in young men.

Study strengths: Use of adaptive system of pain stimulus provision to override systemic antinociceptive responses; compensating for small anatomic variations among subjects.

Study weaknesses: Limited generalizability.

Of note: The study employed a mu-opioid receptor-selective radiotracer, such that activation of the neurotransmitter system was evidenced by reductions in in vivo availability of synaptic mu-opioid receptors to bind the radio-labeled tracer; mu-opioid receptors are thought to primarily mediate the observed effects of placebo and naloxone; researchers often categorize subjects into high or low placebo responders, and this may be the result of individualized blood-flow responses in areas like the rostral anterior cingulate; studies employing functional MRI have shown reductions in activity of pain-specific regions of the brain after placebo administration with expectation of analgesia; both gender- and age-specific effects have been described for mu-opioid receptor concentrations, as well as capacity for their activation, which explains why the authors studied such a restricted sample; at trial's end, nine subjects were classified as high placebo responders, five as low.

We knew that: The authors define the placebo effect as positive physiological or psychological changes associated with administration of inert substances or procedures and positive expectations (in contrast, a nocebo creates negative health expectations); prior studies addressing both clinical and experimentally induced pain have reported reductions in pain ratings after placebo administration with expectation of analgesia that were reversed by administration of naloxone (changes thus mediated through activation of pain-suppressive endogenous opioid neurotransmission); sustained pain induces systemic antinociceptive responses that lower pain ratings over time, thus potentially interfering with studies of the placebo effect.

Clinical import: In this trial, placebo-induced activation of brain neurotransmission correlated strongly with decreased pain intensity and sensory pain qualities. The authors state theirs is the first report to document direct evidence that a placebo with implied analgesic properties regionally activates a specific pain and stress inhibitory neurotransmitter system through direct effects on mu-opioid receptors, and that this activation is associated with real reductions in suffering. The data also suggest that placebo-induced changes in neurochemical signaling represent a graded effect, not an on-off phenomenon. This well-done study lends credence to the existence of the mind/body continuum. Though subjects were healthy volunteers, most practitioners intuit that appropriately engaging a patient's belief in treatment may enhance the therapeutic effect of any clinical intervention. Results of this high-tech trial support that notion.

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Supplement to *Alternative Medicine Alert*
January 2006

ALTERNATIVE MEDICINE ALERT™

A Clinician's Evidence-Based Guide to Alternative Therapies

Sprains & Strains: What They Are and What to Do About Them

WE HAVE ALL TWISTED AN ANKLE OR PULLED A MUSCLE AT SOME TIME. BUT MANY OF US are not sure what to do when this happens. This handout discusses these basic types of injury and information regarding injury first aid and rehabilitation.

Sprains

A sprain is an injury to a joint ligament. Ligaments are the strong bands of tissue that connect one bone to another at a joint. The severity of the injury can be classified by the amount of tissue tearing, joint stability, pain, and swelling. The mildest sprain (first degree) has little tearing, pain, or swelling and joint stability is good. The second-degree sprain has the broadest range of damage, with moderate instability and moderate-to-severe pain and swelling. The most serious sprain is a third-degree sprain. The ligament is completely ruptured and the joint is unstable. There may be no pain. There will be a lot of swelling with this type of sprain, and often other tissues are damaged.

Strains

A strain is damage to muscle fibers and to the fibers that attach the muscle to the bone. Other names for a strain include "torn muscle," "muscle pulls," and "ruptured tendon." Muscle injuries are classified from first- (lease severe) to third- (most severe) degree strains. A first-degree strain has little tissue tearing, mild tenderness, and pain with full range of

Healing Time

HEALING TIME DEPENDS ON SITE, SEVERITY, AND TYPE OF INJURY. FOR EXAMPLE, A MILD ANKLE sprain may heal in 2-4 weeks, while a fracture of the leg may take 8-12 weeks. However, healing usually proceeds in certain stages.

- Swelling and pain decreases or disappears in the first 24-72 hours.
- Discoloration (bruising) usually subsides within 10-14 days.
- Range of motion increases over 7-14 days, although stiffness and weakness may persist.

When an injury occurs, it may result in weakness due to tissue damage and disuse, in addition to decreased control over the damaged body part. Regaining strength and coordination of the injured body part should be considered part of the rehabilitation and healing process, and an injury should not be considered healed until this process is accomplished. Attempting to return to an activity before proper healing of the injury puts you at risk for reinjury or an additional injury. Consultation with a sports medicine professional may aid in the initial treatment and rehabilitation and the determination of when to return to play.

Reprinted with permission from: The American College of Sports Medicine, "Return to Play: A Common Sense Guide for Coaches," written by Lawrence M. Magee, MD, FACSM.

motion. As with the sprains, the second-degree strain has a wide variability. Muscle or tendon tissue have been torn, resulting in very painful, limited motion. There may be some observable swelling or a depression at the spot of the injury with a second-degree strain. The third-degree strain involves complete rupture of a part of the muscle unit. Motion will be severely decreased or absent. Pain will be severe at first, but the muscle may be painless after the initial injury.

Acute Treatment

There are several decisions that you must make when you injure yourself. Among the first of these is how serious the injury is and whether you should go to a health care provider. Look for deformities, swelling, and changes in skin color. If there are deformities, significant swelling, or pain, you should immobilize the area and seek medical help. Many fractures will not cause a deformity; thus, if there is any doubt or concern you should get medical attention.

Stage One

Management of both sprains and strains follows the "PRICE" principle:

P = Protect from further injury
R = Restrict activity
I = Apply ice
C = Apply compression
E = Elevate the injured area

This principle limits the amount of swelling at the injury and improves the healing process. Splints, pads, and crutches will protect a joint or muscle from further injury when appropriately used (usually for more severe sprains or strains). Activity restriction (usually for 48-72 hours) will allow the healing process to begin. During the activity restriction, gentle movement of the muscle or joint should be started. Ice should be applied for 15-20 minutes every hour to hour and a half. Compression, such as an elastic bandage, should be kept on between icing; you may want to remove the bandage while sleeping, though keeping it compressed even during the night is best. Elevating the limb will also keep the swelling to a minimum. Acute treatment is the first stage of rehabilitation.

Important: If you suspect more than a mild injury, cannot put weight on the limb, or it gives way, you should consult a health care provider.

Example: Ankle Rehabilitation

Stage Two (After initial 48-72 hours swelling has stopped increasing and pain decreases.)

Range of Motion
- Towel pull with toes
- Draw the alphabet with ankle

Mild Resistive Exercises
- Foot press—up, down, and each side, against a solid object (no motion of the ankle)
- Tubing exercises in all motions (pain-free)

Joint Position
- Standing with eyes closed—partial squats and shifts from side to side

Stage Three (Pain-free; can walk without a limp.)

Range of Motion
- Stretching with towel

Strengthening
- Toe raises
- Hops—start forward and back, short hops
- Weights—heavy tubing or cuff weights

Joint Position
- One-legged stand with eyes closed

Rehabilitation

Following the first 48-72 hours, it is important to start the next stage of rehabilitation. The second stage of rehabilitation focuses on gentle movement of the muscle or joint, mild resistive exercise, joint position training, and continued icing. When you are able to move without pain, you can progress to the next stage of rehabilitation. During this stage you may gradually return to more strenuous activities, such as strengthening. A simple guide to how much you can do is pain. Pain should remain low during rehabilitation; if pain increases it usually means you have attempted to do too much.

Throughout your recovery you can still maintain an aerobic training program. Options for training include stationary bicycling, swimming, walking, or running in water. If the injury is more than a mild sprain or strain, it is best to consult your health care provider.

Reprinted with permission from: The American College of Sports Medicine, "Sprains & Strains: What They Are and What to Do About Them," written by Lynn Millar, PhD, PT, FACSM.

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Sincerely,

Brenda L. Mooney

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