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INSIDE

Coenzyme Q_{10} for Neurodegenerative Diseases

By Dónal P. O'Mathúna

NEURODEGENERATIVE DISEASES INCLUDE A VARIETY OF NEUROLOGical disorders such as Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and mitochondrial cytopathies. Although each disease manifests itself differently, a small number of biochemical processes are believed to be involved in all the disorders.[1] Much evidence has accumulated suggesting that mitochondrial defects are involved in the pathogenesis of these diseases.[2] This has led to a search for agents that can prevent or slow disease progression at the mitochondrial level. Coenzyme Q_{10} (also called CoQ_{10}, ubiquinone, or ubidecarenone) is one such agent being investigated for its potential as a neuroprotective agent in a number of diseases.[3] In addition, a committee at the National Institute of Neurological Disorders and Stroke recently identified CoQ_{10} as an agent warranting further clinical investigation for Parkinson's disease.[4]

Biochemistry

Coenzyme Q is the name given to a group of compounds containing a ring structure and a long chain made up of repeating five-carbon sections called isoprenoid units *(see Figure)*.[3] In the Figure, the parentheses enclose one isoprenoid unit, with the subscript indicating the number of isoprenoid units in the particular compound. Human coenzyme Q contains 10 isoprenoid units, hence the name CoQ_{10}. The bacterial form is CoQ_5, whereas the rodent form is CoQ_9. Coenzyme Q is an essential cofactor in the electron transport chain (ETC) and a potent antioxidant.[5] It carries out both roles within mitochondria, the powerhouses of all cells. The cofactor is highly lipid-soluble and lodges within the lipid layers of the inner membranes of mitochondria.

Mechanism of Action

The ETC in mitochondria replenishes the chemical energy molecule called adenosine triphosphate (ATP). The ETC is made up of several complexes, with CoQ_{10} playing a vital role in Complex I and Complex II/III.[3] A group of people using synthetic opiate drugs developed symptoms of Parkinson's disease.[2] The drugs were later

found to be contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which selectively inhibits Complex I of the ETC.[2] The parkinsonism produced by MPTP was reduced significantly when animals were given CoQ_{10} along with MPTP.[3]

These discoveries led to investigations into whether CoQ_{10} levels were changed in patients with Parkinson's disease. Some studies found reduced CoQ_{10} levels, which were increased significantly by oral CoQ_{10} supplements.[3] However, other studies found no significant differences between the CoQ_{10} serum levels in patients with Parkinson's disease compared to controls.[6] CoQ_{10} supplementation in animals also has been found to protect against experimentally induced forms of Huntington's disease and ALS. The potential role of CoQ_{10} in Huntington's disease is more poorly understood, although substantial evidence links impaired energy metabolism to disease development.[7] All these results have led to proposals that CoQ_{10} has a neuroprotective effect both by improving ETC function in mitochondria and acting as an antioxidant.

Clinical Studies

In animal models of ischemia, ALS, Parkinson's disease, and Huntington's disease, CoQ_{10} administration increased animal survival and functionality.[3] Based on these results, a small number of clinical studies have been conducted involving patients with Parkinson's disease or Huntington's disease. A multicenter randomized controlled trial (RCT) enrolled 347 patients in the early stages of Huntington's disease.[8] Subjects were randomized to receive either CoQ_{10} (300 mg bid), remacemide (200 mg tid), both, or neither. Remacemide is an antagonist of a receptor whose activation is suspected to play a role in the development of Huntington's disease. Patients' total functional capacity was evaluated every 4-5 months for 30 months. None of the interventions produced a significant impact on functional capacity. CoQ_{10} did show a 13% slowing of functional decline beginning one year into the trial, but this was not statistically significant ($P = 0.15$).

An open-label pilot study was conducted with 10 patients with Parkinson's disease.[9] All patients were given 100 mg bid CoQ_{10} capsules. After three months, no changes were measured using the Unified Parkinson Disease Rating Scale (UPDRS). However, this study used a relatively low dose of CoQ_{10} and the significance of UPDRS scores not deteriorating could not be evaluated because no control group was used.

A multicenter RCT was conducted with 80 patients with early Parkinson's disease who were not receiving concomitant medications.[5] Subjects were randomly assigned to receive placebo or CoQ_{10} at dosages of 300, 600, or 1200 mg/d. All medications were prepared in capsules containing 300 IU vitamin E and taken four times daily. Subjects were evaluated using the UPDRS every four months for 16 months, or until they required levodopa treatment. All groups taking CoQ_{10} showed slowed deterioration compared to placebo, but the difference was statistically significant only for those taking 1200 mg/d ($P = 0.04$). Slower decline occurred in all three parts of UPDRS: cognitive function, motor skills, and daily activities. Biological analyses showed highly significant increases in serum CoQ_{10} levels that were dose-dependent ($P < 0.001$) and increased mitochondrial ETC activity ($P = 0.04$).

Adverse Effects

Adverse effects in the clinical trials were all mild, primarily GI disturbances. However, in one study of 15 patients with Parkinson's disease given varying CoQ_{10} doses, two patients taking 800 mg/d had abnormal urinalyses.[10] They had 3-5 hyaline casts per low power field and trace protein upon repeat urinalysis. These changes were transient and of unclear clinical significance, but the authors recommended prudent monitoring of renal function on higher CoQ_{10} doses.

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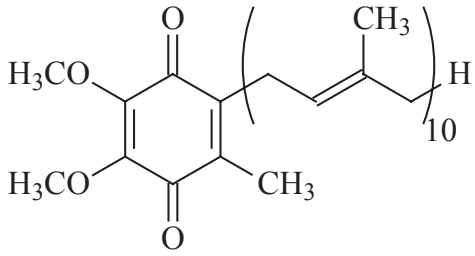
Figure

Coenzyme Q_{10}



Drug Interactions

CoQ_{10} is chemically similar to vitamin K and may have similar pro-coagulant activity, with four cases of decreased effectiveness of warfarin reported and thought to be related to CoQ_{10}.[11] The HMG CoA reductase inhibitors (statins) inhibit cholesterol and CoQ_{10} synthesis, leading to lower CoQ_{10} levels. Whether this is clinically significant is unknown. There are some concerns that CoQ_{10} supplements may interfere with medications for hypertension or diabetes, but these effects are not believed to be widespread.[11]

Formulation

CoQ_{10} supplements are formulated as oil-based capsules, powder-filled capsules, tablets, and soft-gel capsules containing microemulsions.[12] The highly lipophilic nature of CoQ_{10} makes its absorption poor, highly variable, and strongly dependent on the contents of the stomach. It is best taken with food, especially fat-rich foods. Its poor bioavailability has led to the development of solubilized formulations using soy bean oil or emulsifying agents. A bioavailability study of four commercially available products examined three solubilized products and one non-solubilized powder that is found in many OTC products.[13] The three solubilized formulations produced significant and similar increases in plasma CoQ_{10} concentrations, but the powder led to barely detectable increases in plasma concentrations above baseline. Similar bioequivalence results have been produced previously.[14]

Although gel caps have been the favored form of CoQ_{10}, wafers have become widely available. However, no data could be found to demonstrate whether wafers are absorbed as well as gel caps.

Conclusion

Much remains to be understood regarding the causes and treatment of various neurodegenerative diseases. Evidence indicates that mitochondrial defects play an important role. At the same time, CoQ_{10} supplementation is being shown to improve mitochondrial metabolism. CoQ_{10} is also well tolerated. However, the results of clinical trials designed to evaluate whether CoQ_{10} protects against disease progression have been mixed. In Huntington's disease, a small but non-significant benefit was shown. In Parkinson's disease, the highest dose used resulted in significant slowing of deterioration. However, the authors of this Parkinson Study Group trial noted that it is still premature to recommend CoQ_{10} for the treatment of Parkinson's disease before their results are replicated in a larger Phase III study.[5]

Recommendation

Given the lack of significant benefit found to date, CoQ_{10} should not be recommended for patients in the early stages of Huntington's disease. Whether it might be beneficial for those at risk of the disease, or in later stages, remains to be studied. For patients with Parkinson's disease, the data to date are more promising, but the Parkinson Study Group still concluded it was too early to recommend that patients start using CoQ_{10} supplements. With the limitations of current medications, and the relative freedom of CoQ_{10} from adverse effects, CoQ_{10} may be a viable option once patients discuss their proposal with their neurologist.

Given that CoQ_{10} is readily available as a dietary supplement, patients may already be using it or planning to try it. In that case, they should be reminded that dietary supplements are not subject to the same quality and content regulations as pharmaceutical drugs. Patients with neurodegenerative diseases should be cautioned that at a dose of 600-1200 mg/d, CoQ_{10} supplements could easily cost more than $100 per month.[8] Patients will therefore need help evaluating the quality of available brands, and should be actively monitored for potential adverse effects or drug interactions. ❖

Dr. O'Mathúna teaches courses in bioethics and alternative medicine in Dublin, Ireland, and is Visiting Professor of Bioethics at the University of Ulster, Coleraine, Northern Ireland.

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Acupuncture and Pediatric Asthma

By John D. Mark, MD

ASTHMA IS A CHRONIC INFLAMMATORY CONDITION that affects more than 17 million Americans.[1] The prevalence of asthma increased 75% between 1980 and 1994,[2] and has increased 150% over the last 20 years.[3] This increase has occurred in both sexes and in all ethnic groups, primarily in urban, predominately minority, populations.[4] The pediatric group (especially children younger than age 5) has shown the largest increases with a prevalence of more than 5 million diagnoses.

Asthma is responsible for approximately 500,000 hospitalizations, more than 1,997,000 emergency room visits, and at least 5,000 deaths annually.[5,6] Direct health care costs attributed to asthma in the United States total more than $8.1 billion annually; indirect costs represent another $4.6 billion for a total of $12.7 billion.[7] Pharmaceuticals account for the largest direct asthma costs.[8] Reduced productivity due to loss of school days represents the largest indirect cost related to asthma, approaching $1.5 billion.[7] These statistics are all the more concerning because the understanding of asthma has improved, as has the availability of effective medications for its control.[9]

Like many chronic illnesses, the use of complementary and alternative therapies for asthma has been popular. Acupuncture is one type of alternative therapy that health care providers have used in the treatment of asthma, in conjunction with conventional medications. The National Institutes of Health Consensus Statement of 1997 listed acupuncture as an adjunct treatment or an acceptable alternative for asthma, but also said acupuncture should be included in a comprehensive management program.[10]

Acupuncture's growing popularity is reflected in that it is now part of the complementary and alternative medicine (CAM) curricula offered as an elective in most medical schools, and the British Medical Association has approved acupuncture for general practice.[11,12] There are more than 11,000 licensed acupuncturists in the United States and this number is increasing.[13] Acupuncture is one of the CAM therapies most frequently recommended by physicians and is integral to many pain treatment programs (both pediatric and adult) throughout the United States. Although it is infrequently recommended for children, Kemper has shown that many children with chronic pain are willing to try acupuncture.[14]

History and Mechanism of Action

It is important to remember that acupuncture is part of a complex theoretical framework that provides conceptual and therapeutic direction.[15] Although acupuncture may seem to be based in part on conventional perceptions (e.g., trigger points), the approach is based mainly in concepts of yin, yang, dampness, wind, fire, dryness, cold, and earth. *Qi*, the life energy that provides a rationale for explaining change and linking phenomena in traditional Chinese medicine, is gently manipulated to treat the disharmony that may be present.

China, Japan, and Korea have all developed their own distinct versions of acupuncture and apply other associated therapies, including massage, scarification (body

marking), and cupping in conjunction with acupuncture. Lifestyle counseling on topics such as diet, exercise, and mental health also may be part of therapy. Even the encounter between patient and acupuncturist is felt to be important in the healing process. Biomedically trained acupuncturists use approaches that are based on a Western understanding of myofascial trigger points and the nervous system, and might use a fixed regimen for a patient's symptoms independent of a traditional Chinese medicine diagnosis.

The exact mechanism of how acupuncture might help asthma is unclear. Theories have been proposed about the immune modulating effects of acupuncture and others have postulated that increased levels of circulating endorphins and corticotrophins are involved in treating this chronic inflammatory illness.[16,17]

Systematic Review

Since the 1970s there have been more than 500 randomized controlled trials (RCTs) evaluating the efficacy of acupuncture. Some of these studies had placebo controls, some included conventional therapies, and some looked either at acute symptoms or chronic ongoing symptoms associated with various illnesses or pain. Unfortunately, many problems have been encountered with acupuncture RCTs, such as insufficient sample size, poorly defined illnesses, vague enrollment criteria, and even the type of acupuncture utilized.[18] Many of these studies were investigating asthma and other pulmonary problems, and studies have looked both at chronic and acute treatment of asthma symptoms.

Martin et al attempted to circumvent the problem of small sample sizes by eliminating many studies in previous reviews and combining the results from all relevant randomized clinical trials that compared acupuncture at real and placebo points in asthma patients.[19] They felt that this would be a more objective assessment of sources of conflicting results found in previous trials and might detect moderate treatment effects, which may have been missed in small studies.

Utilizing many of the same studies included in the Cochrane systematic review, Martin et al included nine of 11 trials in the analysis, whereas the Cochrane methodology limited its review to just three of seven trials. The Martin paper identified more than 200 reviewable trials, but only 12 satisfied the inclusion criteria. Only 11 were analyzed due to difficulty with translation.

The authors concluded that there appears to be no clear agreement on the best method of conducting controlled trials of acupuncture in asthma in "relation to the type of design, selected endpoints, and data analysis." All the trials were too small to detect a modest effect of the acupuncture. The shortcomings of the trials were small sample size, effects of prognostic variables, missing information, and the bias against acupuncture introduced by the use of placebo points. Thus, this meta-analysis did not find evidence for the efficacy of acupuncture in the treatment of patients with asthma. This paper, along with the previous reviews, recognized the need for a large randomized clinical trial to address the above limitations.

Clinical Studies

There have been numerous studies investigating the use of acupuncture in a variety of settings, including exercise-induced symptoms in children and adolescents, isocapnic hyperventilation of cold air, and the treatment of dyspnea. In a study using laser acupuncture, Gruber et al found that a single treatment (using real and placebo points in random order) offered no protection against exercise-induced bronchoconstriction in a group of 44 children and adolescents.[20] Malmstrom et al investigated the effect of 15 weeks of acupuncture in 27 asthmatics using a parallel-group, randomized, placebo-controlled trial.[21] They found no significant effects in lung function or bronchial hyperresponsiveness measured by cold air challenge.

Shapira et al attempted to overcome many of the shortcomings of previous acupuncture and asthma studies.[22] They utilized a sham, controlled, crossover design to evaluate the influence of a short and intensive course of personalized acupuncture on patients with moderate persistent asthma. Although their study sample was small (only 20 of 23 finished the study), the design was sophisticated in that it measured pulmonary function, airway reactivity (methacholine challenge), and patient symptoms and medication use. The authors reported no benefit (not even a trend) from the short-term treatment with acupuncture (36 days) in this blinded, placebo-controlled study of patients with moderate persistent asthma. In an accompanying editorial,[23] the study was regarded as an improvement over previous studies of acupuncture and asthma since it provided the rigor of "Western scientific method to an alternative medical therapy." It was concluded that this study placed the benefit of acupuncture in patients with moderate asthma in serious doubt.

However, even this carefully designed study contained methodological shortcomings, including the use of only one acupuncturist who was responsible for the diagnosis and acupuncture treatment of all asthma subjects. Another criticism was that even though personalized, the study design gave treatments on a fixed time schedule despite the differing underlying pathologies

found by traditional Chinese medicine diagnosis. In addition, this study was not sufficiently powered to study asthma, which in traditional Chinese medicine may be part of at least five different syndromes.[24]

Adverse Effects

Acupuncture involves the insertion into the skin of solid needles from 15-50 mm in length (there are some non-needle types of acupuncture, but they will not be discussed here). Depth of insertion can be several millimeters (most often) to centimeters and the tip of the needle may overlie muscles, nerves, and pleura.

Adverse effects of acupuncture include bacterial and viral infection; and trauma of tissues and organs.[25] Often acupuncturists will advise patients that the therapy itself may briefly exacerbate symptoms, especially upon initiation of treatment. As with any CAM therapy, concern arises when delayed diagnosis occurs of a condition that could be treated appropriately with conventional means.

In a recent survey study of more than 32,000 consultations for acupuncture, vague complaints were reported including nausea, vomiting, fainting, drowsiness, disorientation, lethargy, anxiety, euphoria, headache, and slurred speech (671 minor events per 10,000 consultations). Complications of bleeding and needling pain were the most commonly reported adverse events and all but one case resolved within one week.[26] There were several earlier case reports of pneumothorax in the treatment of bronchial asthma with acupuncture, but this now seems rare with only two cases in nearly a quarter of a million treatments.[27,28]

Conclusion

Acupuncture in the treatment of asthma in both adults and pediatrics has gained popularity over the last decade. It is one of the most commonly prescribed and recommended forms of CAM. Although it is not commonly thought of as a pediatric CAM therapy, it is now being utilized in the majority of pediatric pain clinics in the United States. However, there is still a relative dearth of data supporting a significant role for acupuncture in the treatment of either chronic asthma or the acute symptoms associated with asthma.

Acupuncture studies are difficult to design due to the individualistic nature of acupuncture and traditional Chinese medicine in general. Hammerschlag also called into question designing research for comparing acupuncture to standard care.[29] It may be more important to consider studies that assess whole systems of care rather than specific therapies or modalities.

Clearly, conventional asthma treatment using newer anti-inflammatory medications (controller medications) has helped asthma patients. However, even with these medications and National Asthma Guidelines,[30] asthma prevalence and severity are increasing. Because acupuncture is now utilized more commonly in asthma treatment; more research for its efficacy is needed.

Recommendation

Acupuncture traditionally has been utilized in the care of patients with asthma symptoms. It appears that complications of acupuncture are rare and transient in nature.[31] Studies involving acupuncture are becoming more sophisticated in trying to eliminate the methodological problems many of the previous asthma and acupuncture studies have encountered. Acupuncture cannot be recommended alone as a management therapy for asthma based on studies completed. However, as an adjunct to current therapies as outlined in the National Asthma Guidelines,[30] acupuncture may be useful, and further studies are warranted. ❖

Dr. Mark is Assistant Professor of Pediatrics, Pediatric Pulmonary and Integrative Medicine, Department of Pediatrics, University of Arizona, Tucson.

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Capsaicin and Neuropathic Pain

By Robert Lutz, MD, MPH

NEUROPATHIC PAIN DESCRIBES A DIVERSE GROUP OF chronic pain syndromes that affects up to 1.5% of the U.S. population.[1] Patients experiencing neuropathic pain represent approximately 50% of visits to pain centers, and their clinical conditions present challenges to successful therapeutic management.[2] Examples include: post-herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, HIV polyneuropathy, neuropathic low back pain, post-stroke pain, post-mastectomy pain, phantom limb pain, and complex regional pain syndrome (CRPS), types I and II. The pain is described variably as burning, lancinating, electric, deep, or shooting. The cardinal signs are allodynia (the perception of a non-noxious stimulus as painful) and hyperalgesia (an excessive response to painful stimuli).

People with chronic pain may be unable to identify an antecedent event, and reasons for its persistence may not be readily apparent to either the individual or clinicians. The condition may affect multiple aspects of an individual's life including physical functioning, psychological health, social interactions, and societal functioning. Whereas a number of pharmacological (e.g., tricyclic antidepressants, anticonvulsants, and antiarrhythmics) and non-pharmacological (e.g., nerve stimulation and psychological treatments) interventions currently are available with variable success, capsaicin represents an interesting natural alternative.

Botanical Information and Traditional Use

Chili peppers (*Capsicum frutescens*) are members of the Solanaceae, or nightshade, family. They are native to

South America where they have been cultivated for thousands of years as a perennial. Upon introduction to other parts of the world in the 16th century, they became inappropriately linked to black pepper due their similarity in pungency and were called "red peppers." The substance that gives chili peppers their heat, capsaicin, is believed to have evolved as a protective mechanism against foraging mammals. In contrast, birds do not have an adverse response to capsaicin and probably contributed to their wide distribution throughout northern South America and Central America via seed dispersal.

It is estimated that chilies are regularly consumed by more than a quarter of the world's population. Their medicinal and non-culinary uses have included: the relief of toothaches by Native Americans; as an aphrodisiac, a digestive aid, a cough expectorant, and a stimulant; and for rheumatism, dyspepsia, and postoperative analgesia.[3] Legend has it that the Incas used burned dried chilies to ward off the invading Spanish.[4] This last use is probably familiar to readers as it is currently used in defensive sprays to ward off criminals as well as animals.

Chemistry and Mechanism of Action

Capsaicin is lipophilic, hydrophobic, and very soluble in alcohol. It was first isolated in the mid-1800s by Thresh and its chemical structure (N-Vanillyl-8-methyl-6-(E)-noneamide) was determined in the early 1900s by Nelson.[5] Its unique ability to "desensitize" afferent pain neurons (nociceptors) with repetitive applications was determined by Jansco,[6] and it is this attribute that has made it of interest to researchers.

The gene for the capsaicin receptor was identified only very recently.[7] This nocireceptor, the vanilloid receptor (TRPV1), has been found on the afferent neuronal membranes of C-fibers (small-diameter, unmyelinated, slow-velocity conduction), a smaller population of Aδ fibers (medium-diameter, partially myelinated, intermediate-velocity conduction), and is sensitive to all three pain modalities (mechanical, chemical, and thermal). It is believed that the primary function of this receptor is to provide integration of chemical and physical stimuli, especially thermal stimulation (> 43° C) and low pH. Capsaicin and acidification lower the threshold for receptor stimulation.[8] These receptors are found in the skin, cornea, and mucus membranes of the mouth, as well as skeletal muscle and joints, and organs of the cardiovascular, respiratory, and genitourinary systems (of note, these visceral receptors function at both a reflex autonomic level as well as a conscious perceptual level).

Upon stimulation of the TRPV1, a cascade of neurogenic inflammation occurs that serves to enhance pain and possibly produce hyperalgesia in the affected tissues. This cascade is characterized by excitation, desensitization, and tachyphylaxis.

Excitation. Peripheral topical stimulation of the TRPV1 by capsaicin causes transmission of nerve impulses centrally, where they synapse in the dorsal horn of the spinal cord and produce the pain response, mediated through glutamate. Pro-inflammatory peptides, such as Substance P (SP) and calcitonin gene-related peptide (CGRP), are released peripherally in the efferent element of these neurons, producing the sensation of pain or itch, as well as sometimes producing a flare response seen at a distance from the injury site (SP produces plasma extravasation and edema formation while CGRP triggers vasodilation). Following neuronal activation, there is a period of enhanced sensitivity to noxious stimuli (hyperalgesia and allodynia) mediated through nitrous oxide, the release of glutamate, and the activation of N-methyl-D-aspartate (NMDA) receptors. This initial increased sensitivity to painful stimuli is extinguished with repeated exposure to capsaicin as neurotransmitters are depleted and synthesis is blocked, providing a prolonged analgesic effect (desensitization).

Desensitization and Tachyphylaxis. Following excitation, a refractory period of pain sensitivity of variable duration occurs. Sensitized neurons neither respond to repeated capsaicin challenge nor to other stimuli, such as heat or chemicals. Histological changes have been identified in animal models[9] and in humans.[10] These changes are characterized by a down-regulation of TRPV1s in the epidermis and subepidermis. Additionally, capsaicin down-regulates the release of SP, thereby depleting stores and providing the mechanism for clinical application of cutaneous capsaicin. Repeated applications of gradually increasing doses of capsaicin can prolong this period of desensitization and tachyphylaxis.

Pathophysiology and Clinical Rationale

Capsaicin currently is used topically (for neuropathic pain and other pain disorders, dermatological disorders, and muscle ache), intranasally (for treatment of cluster headaches, vasomotor rhinitis, and perennial allergic rhinitis), and for intravesical infusion (bladder hypersensitivity and spinal detrusor hyperreflexia). The topical application of capsaicin for neuropathic pain will be the focus of the following material.

Neuropathic pain results from a lesion within the peripheral or central nervous systems, or a dysfunction in one or both of these systems. The pathophysiological explanation is complex and continues to be investigated. There is growing appreciation of a role for elements of

the nervous system not previously believed to be involved with pain transmission. Additionally, the autonomic nervous system often is affected, as seen in individuals with CRPS. For example, recruitment of afferent and efferent nerves after insult may explain referred pain patterns, phantom pain, or allodynia. "Central sensitization" (the process by which the nervous system responds to pain more easily following injury[2]) leads to a lowering of the pain threshold, facilitating pain transmission and leading to an increased sensitivity to nociception and actual neurophysiological changes within the central nervous system, especially the spinal cord. Up-regulation of glutamate and increased activation of the NMDA receptor are responsible for this phenomenon.

In normal pain transmission, impulses travel primarily along C-fibers and to a lesser extent along Aδ fibers. These afferent neurons synapse with second-order neurons in the dorsal horn of the spinal cord. Release of glutamate elicits the acute pain response. Glutamate is an excitatory neurotransmitter and may be metabolized to gamma-aminobutyric acid, an inhibitory neurotransmitter. In normal situations, these neurotransmitters exist in balance. This balance is offset in neuropathic pain, however, leading to increased levels of glutamate released into the synaptic cleft with the second-order neuron in the dorsal horn. NMDA receptors, stimulated by glutamate release, in combination with NK1 receptors stimulated by SP, provide an enhanced signal for pain recognition. With neuropathic pain there is an up-regulation of the NMDA receptor as well as enhanced release of SP and glutamate.

For the clinical treatment of neuropathic pain, capsaicin has been delivered primarily as a topically applied cream in concentrations of 0.025% or 0.075%. It is typically applied sparingly 3-4 times per day to the affected area for a period of 4-6 weeks. As described previously, the mechanism by which capsaicin produces its effects elicits initial discomfort with topical application, followed by an eventual decline with repeated use. For this reason, capsaicin has been called a "counter-irritant." Studies have looked at its use in post-mastectomy pain;[11] stump pain;[12] CRPS;[13] periocular pain;[14] trigeminal neuralgia;[15] post-herpetic neuralgia; and diabetic neuropathy. Its efficacy has been challenging to assess in research due the high dropout rates and to an inability to adequately blind participants, in spite of attempts to lessen the discomfort with the co-administration of local anesthetics. Additionally, with the exception of the latter two conditions mentioned above, studies most often have been case reports or only recruited small numbers of participants. The low concentration used in these topical creams also is unlikely to adequately cause desensitization of afferent cutaneous nerve endings. Therefore as a solo agent, capsaicin cream probably has a limited role in the management of neuropathic pain.[16]

However, clinical trials using topical capsaicin cream as an adjuvant therapy in post-herpetic neuralgia have been promising. Peikert et al reported a ~40% reduction in pain intensity in patients using capsaicin cream (0.025%) four times a day for eight weeks in a noncomparative study.[17] Other studies have reported similar findings.[18,19] Although methodological considerations prevent drawing firm conclusions, patients generally reported reduction in pain intensity. It has been suggested that this improvement may be sustained with longer usage.[20] Randomized clinical trials comparing topical capsaicin with other pharmacological agents are not available.

Topical capsaicin likewise has demonstrated potential efficacy in clinical trials looking at diabetic neuropathy. Data from the Capsaicin Study Group found capsaicin cream (0.075%) applied to the affected area four times per day for a period of eight weeks superior to placebo in pain improvement (69.5% vs. 53.4%, P = 0.012), pain intensity (38.1% vs. 27.4%, P = 0.037), and pain relief (58.4% vs. 45.3%, P = 0.004).[21] Improvement in activities of daily living (ADLs) also was noted. A significant placebo response was identified.

A meta-analysis of four clinical trials of subjects with neuropathic pain comparing topical capsaicin cream (0.075%) to placebo demonstrated a significant benefit for capsaicin cream (odds ratio = 2.74, 95% confidence interval 1.73-4.32).[22] A single randomized trial comparing capsaicin cream 0.075% (applied four times daily) with oral amytriptyline (25 mg/d-125 mg/d) for eight weeks found equal improvement in pain severity, pain relief, and ADLs as compared to baseline.[23]

Recently, a novel approach using significantly higher doses of topical capsaicin (7.5%-10%) applied under regional anesthesia has provided promising results. Individuals with CRPS, diabetic neuropathy, HIV-associated neuropathy, and post-herpetic neuralgia have been treated and experienced pain relief for up to several months.[24,25]

Adverse Effects

Other than the aforementioned burning sensation, topical capsaicin is considered a very safe pharmaceutical. Reports of respiratory problems (coughing and sneezing) have been noted.[21]

Whereas concern has been raised that capsaicin may be cancer-causing, as demonstrated in vitro[26] and in animal studies,[27] it is recognized that liver metabolites of

capsaicin are responsible for its mutagenicity. Therefore, topically applied capsaicin is probably safe for use.[4] A case control study has suggested that excessive consumption of chilies may be associated with an increased risk of gastric cancer.[28] Methodological considerations limit the data from this study, however, and conflicting studies have been produced.[29] Therefore, excessive consumption of chilies should probably be discouraged until further data are available.

Conclusion

Chili peppers have a long history of traditional use in medicine. Recent research has elucidated the mechanism of action of capsaicin, the active ingredient in chilies. Although its use in a number of medical conditions, and especially in neuropathic pain, has been limited by its pungency, study of capsaicin has greatly aided the understanding of pain. Continued research may demonstrate increased use for this natural medicine.

Recommendation

Topical capsaicin has a limited role as a primary analgesic for neuropathic pain. It does, however, provide a natural adjunctive therapy for this condition. Topical application of capsaicin, in doses of 0.025%-0.075%, requires frequent administration (3-4 times daily) for a minimum of 4-6 weeks before its therapeutic effects can be assessed adequately. Buffered formulations (e.g., menthol) may lessen the discomfort that occurs during the first few weeks of use. Patients should be advised to use gloves when applying; to avoid application near open wounds; and to avoid rubbing other areas of the body, especially the eyes and mucus membranes. ❖

Dr. Lutz is Assistant Research Professor, College of Medicine and the Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson.

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

59. For which neurodegenerative disease does coenzyme Q_{10} (CoQ_{10}) supplementation show the most potential?
a. Amyotrophic lateral sclerosis (ALS)
b. Huntington's disease
c. Mitochondrial cytopathies
d. Parkinson's disease

60. CoQ_{10} may interfere with the pharmacological effects of:
a. antidiabetic drugs.
b. warfarin.
c. beta-blockers.
d. All of the above

61. Which of the following are the most common adverse effects of acupuncture?
a. Bleeding and needling pain
b. Headache and dizziness
c. Nausea and vomiting
d. Slurred speech and disorientation

62. Capsaicin is a natural adjunct to therapy for neuropathic pain.
a. True
b. False

Answers: 59. d, 60. d, 61. a, 62. a.

Clinical Briefs

With Comments from Russell H. Greenfield, MD

Pollution and Cerebrovascular Disease

Source: Tsai SS, et al. Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. *Stroke* 2003;34:2612-2616.

Goal: To explore the relationship between hospital admissions for stroke and the concentration of specific air pollutants over a four-year period.

Design: Retrospective, case-crossover study.

Subjects: All people admitted for cerebrovascular disorders (CVD) in the region from 1997 to 2000.

Methods: Computerized medical records available through the National Health Insurance Program of Taiwan were reviewed, and those with admission diagnoses of stroke were pulled. For each date of admission, air pollution data were extracted from six air-quality monitoring stations in Kaohsiung and averaged. The pollutants measured were SO_2, PM_{10}, NO_2, CO, and O_3. Air pollution levels on admission dates were compared with levels obtained one week before and one week following hospital admission.

Results: Evaluating single pollutants, admissions for primary intracranial hemorrhage, and ischemic stroke (IS) were significantly associated with all pollutants, except SO_2, on warm days. On cool days, only IS admissions and CO levels were associated significantly. Two-pollutant models again showed an increased rate of admission for CVD with specific combinations of elevated pollutants, except in the case of SO_2.

Conclusion: There is an association between short-term severity of air pollution and hospital admission for stroke (most notably for PM_{10} and NO_2).

Study strengths: Capture of information; multiple sites available for measuring air pollution.

Study weaknesses: Study was performed in a tropical climate, making

generalizability suspect; would have been interesting to note how many people admitted for CVD also smoked; population-based averages of pollutant levels may not equal individual ambient exposure; the limitations of retrospective analysis.

Of note: Kaohsiung has a population of almost 1.5 million people, has mild winter temperatures, and is Taiwan's biggest commercial harbor; the number of stroke admissions reportedly varied according to day of the week.

We knew that: Previous studies noted an association between levels of air pollution on a given day and hospitalization or death due to respiratory or cardiovascular events; exposure to specific air pollutants may result in increased coagulability, raised plasma viscosity, and increased heart rate.

Clinical import: Most are aware of existing research pointing to a higher incidence of asthma exacerbation when air quality levels drop. Now come data suggestive of significant cerebrovascular consequences as a result of rising levels of air pollutants. Support of tough clean air initiatives that maintain economic viability, and a push for additional funding for research into the use of clean alternative fuels, would appear to be worthy causes all could get behind. In the meantime, recommending that patients at risk for CVD take measures to limit exposure to air pollution and increase dietary intake of fruits and vegetables makes sense.

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Electric Blankets and Breast Cancer

Source: Kabat GC, et al. Electric blanket use and breast cancer on Long Island. *Epidemiology* 2003;14:514-520.

Goal: To evaluate the relationship between exposure to low-frequency electromagnetic fields (EMFs) and breast cancer risk.

Design: Population-based, case-control study performed in two stages—Part I was the Long Island Breast Cancer Study Project (LIBCSP), which focused primarily on exposure to organochlorines and other environmental pollutants; Part II, the Electromagnetic Fields and Breast Cancer on Long Island Study (EBCLIS), included a subset of LIBCSP participants.

Subjects: Women with first breast cancer diagnosed between August 1996 and July 1997 and matched controls were eligible for entry into LIBCSP. Women who were younger than age 75 and had lived in their current homes for more than 15 years were eligible to participate in EBCLIS (responses from 576/663, 87%, and 585/702, 83%, of available cases and controls, respectively).

Methods: During the LIBCSP, women were asked to participate in a two-hour comprehensive questionnaire and to provide blood and urine specimens. Participants in EBCLIS took part in a 30-minute interview administered at their homes that focused on use of electric blankets, exposure to other appliances, and potential occupational EMF exposure. EMF measurements were determined in two rooms of the home as well as at the front door. Later, electrical wiring configuration was diagramed from outside the home. Some analyses were stratified according to menopausal status.

Results: Analyses of both the LIBCSP and EBCLIS groups showed no association between breast cancer and electric blanket use, frequency of use, duration of use, or other indicators of intense exposure to EMF.

Conclusion: Results of this study do not support an association between use of electric blankets and an increased risk of breast cancer.

Study strengths: Thorough nature of inquiry into possible EMF exposure from electric blankets; sample size (albeit less than was targeted).

Study weaknesses: Inherent limitations of self-reported use of electric blankets; low rate of control participation during LIBCSP, especially among older women; seasonality not addressed.

Of note: Eight prior studies of electric blanket use and breast cancer risk showed either no association or a slight association with continuous use throughout the night; electric blankets purchased before 1989 produce stronger EMF than those purchased at later dates; analysis of household and occupational appliance use in EBCLIS participants has yet to be reported.

We knew that: It has been posited that low-frequency EMF may inhibit the normal nocturnal rise in melatonin, thereby leading to increased estrogen levels and greater risk for development of breast cancer (especially in premenopausal women).

Clinical import: Long Island is one of a few locales that exhibits a high breast cancer rate relative to the rest of the country. For years researchers have been trying to identify environmental factors that might explain the apparent regional disparity in breast cancer risk, including exposure to EMFs. Although prevalence of electric blanket use among today's women is unlikely to be very high, it is conceivably a source of significant exposure to EMFs because the blanket often is applied directly to the body. This study provides welcome respite in that it appears that electric blanket use, in and of itself, does not cause breast cancer.

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In Future Issues:

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Supplement to *Alternative Medicine Alert*
December 2003

ALTERNATIVE MEDICINE ALERT™
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Coenzyme Q_{10}

RESEARCH INTO THE EFFECTS AND POSSIBLE CLINICAL APPLICATION OF COENZYME Q10 (CoQ_{10}) has continued unabated in recent years, building a considerable body of literature. In addition to its possible use in neurodegenerative disease (see *Alternative Medicine Alert* December 2003:133-136), recent investigations have explored many diverse areas of research, including atherosclerosis and asthma.

CoQ_{10} and atherosclerosis

In a randomized, double-blind, controlled trial, the effects of oral treatment with CoQ_{10} (120 mg/d) on the risk factors of atherosclerosis were compared in 73 (CoQ, group A) and 71 (B vitamin, group B) patients after acute myocardial infarction (AMI).[1]

After one year, total cardiac events (24.6% vs. 45.0%, $P < 0.02$) including non-fatal infarction (13.7% vs. 25.3%, $P < 0.05$) and cardiac deaths were significantly lower in the intervention group compared to control group. The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement, previous coronary artery disease, and elapsed time from symptom onset to infarction at entry to study showed no significant differences between the two groups. Plasma levels of vitamin E (32.4 ± 4.3 vs. 22.1 ± 3.6 umol/L) and high-density lipoprotein cholesterol (1.26 ± 0.43 vs. 1.12 ± 0.32 mmol/L) showed significant ($P < 0.05$) increases, whereas thiobarbituric acid reactive substances, malondialdehyde (MDA, 1.9 + 0.31 vs. 3.1 + 0.32 pmol/L), and diene conjugates showed significant reduction respectively, in the CoQ_{10} group compared to the control group. Approximately one-half of the patients in each group (36 vs. 31) were receiving lovastatin (10 mg/d) and both groups had a significant reduction in total and low-density lipoprotein cholesterol compared to baseline levels.

It is possible that treatment with CoQ_{10} in patients with recent AMI may be beneficial in patients with high risk of atherothrombosis, despite optimal lipid-lowering therapy during a follow-up of one year. Adverse effect of treatments showed that fatigue (40.8% vs. 6.8%, $P < 0.01$) was more common in the control group than the CoQ_{10} group.

CoQ_{10}, *Ginkgo biloba*, and warfarin

Twenty-four outpatients on stable, long-term warfarin treatment were included in a randomized, double-blind, placebo-controlled crossover trial to determine the clinical effect of CoQ_{10} and *Ginkgo biloba* on warfarin therapy.[2] CoQ_{10} 100 mg daily, *G. biloba* 100 mg daily, and placebo were given in random order over treatment periods of four weeks, each followed by a two-week wash-out period. The international normalized ratio (INR) was kept between 2.0-4.0 by appropriate adjustment of the warfarin dosage.

Fourteen women and 10 men, median age 64.5 years (range 33-79 years) were included. Three patients withdrew from the study for personal reasons. The INR was stable during all treatment periods. The geometric mean dosage of warfarin did not change during the treatment periods: *G. biloba*, 36.7 mg/week (95% confidence interval [CI] 29.2-46.0); CoQ_{10}, 36.5 mg/week (95% CI 29.1-45.8); placebo, 36.0 mg/week (95% CI 28.6-45.1).

The study indicated that CoQ_{10} and *G. biloba* do not influence the clinical effect of warfarin.

CoQ_{10} and Prader-Willi syndrome

To determine if CoQ_{10} levels are decreased in Prader-Willi syndrome (PWS), plasma CoQ_{10} levels were studied in 16 subjects with PWS—13 with obesity of unknown cause, and 15 subjects without obesity, but of similar age and compared with body composition.[3]

CoQ_{10} is an essential component of the mitochondrial respiratory chain and an important scavenger of reactive oxygen species. Low levels are found in individuals with reduced energy expenditure, cardiac and skeletal muscle dysfunction, and mitochondrial disorders; many of these same manifestations are seen in individuals with PWS. In addition, CoQ_{10} supplementation frequently is given to individuals with this syndrome.

Plasma CoQ_{10} levels were significantly decreased ($P < 0.05$), using several statistical approaches in subjects with PWS (0.45 ± 0.16 microg/mL), compared to subjects without obesity (0.93 ± 0.56 microg/mL), but not different from subjects with obesity (0.73 ± 0.53 microg/mL). When plasma CoQ_{10} was normalized relative to cholesterol, triglyceride, and creatinine levels, and fat and lean mass (determined by dual energy X-ray absorptiometry) in the subjects with either PWS or obesity, no significant differences were observed. However, a lower muscle mass was found in the PWS subjects.

CoQ_{10} and asthma

The aim of this study was to assess the levels of CoQ_{10}, alpha-tocopherol, beta-carotene, and malondialdehyde in asthmatics.[4] Fifty-six asthmatics (15 males and 41 females) age 19-72 years (mean age 46 years) were enrolled in the study. The control group included 25 healthy volunteers (16 males, 9 females) age 25-50 years.

Concentrations of CoQ_{10} and alpha-tocopherol decreased significantly both in plasma and whole blood compared with healthy volunteers ($P < 0.009$, $P < 0.004$; $P < 0.035$, $P < 0.001$, respectively). The level of MDA was elevated, but not statistically significantly. No changes were seen in beta-carotene levels. Positive correlation was found between concentrations of CoQ_{10} and alpha-tocopherol.

These results suggest possible contribution of suboptimal concentrations of CoQ_{10} on antioxidative imbalance in asthmatics and provide rationale for its supplementation with clinical evaluation.

CoQ_{10}, blood pressure, and glycemic control

The objective of this study was to assess effects of dietary supplementation with CoQ_{10} on blood pressure and glycemic control in subjects with Type 2 diabetes, and to consider oxidative stress as a potential mechanism for any effects.[5] The study was performed at the University of Western Australia, Department of Medicine at Royal Perth Hospital, Australia.

Seventy-four subjects with uncomplicated Type 2 diabetes and dyslipidemia were involved in a randomized, double-blind, placebo-controlled 2 × 2 factorial intervention. Subjects were randomly assigned to receive an oral dose of 100 mg CoQ_{10} twice daily (200 mg/d), 200 mg fenofibrate each morning, both, or neither for 12 weeks.

Fenofibrate did not alter blood pressure, HbA(1c), or plasma F2-isoprostanes. There was a three-fold increase in plasma CoQ_{10} concentration (3.4 ± 0.3 micro mol/L, $P < 0.001$) as a result of CoQ_{10} supplementation. The main effect of CoQ_{10} was to significantly decrease systolic (-6.1 ± 2.6 mmHg, $P = 0.021$) and diastolic (-2.9 ± 1.4 mmHg, $P = 0.048$) blood pressure and HbA(1c) (-0.37 ± 0.17%, $P = 0.032$). Plasma F2-isoprostane concentrations were not altered by CoQ_{10} (0.14 ± 0.15 nmol/L, $P = 0.345$).

These results show that CoQ_{10} supplementation may improve blood pressure and long-term glycemic control in subjects with Type 2 diabetes, but these improvements were not associated with reduced oxidative stress, as assessed by F2-isoprostanes.

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