



HEADACHE

NEWSLETTER OF THE AHS COMMITTEE FOR HEADACHE EDUCATION

Dear Public and Members of the American Headache Society®:

Welcome to the Spring Edition of the Second Volume of the American Headache Society® Committee on Headache Education (ACHE) Online Newsletter. Our intent remains the same. We ask that medical providers and the public copy this Newsletter for whatever their purpose. Please encourage everyone in need of reliable information on headache to access this online via www.achenet.org under ACHE News 2010 Newsletters. Our pledge to provide commonsense articles we think is met by the contributors to this volume.

In this installment headache experts tell us about critical to know sleep and jaw-related issues for headache sufferers. For parents we offer a plateful of supplement information for prevention of headache in their offspring. And if you suffer headache as does your child, then this information can be a starter course for you as well. Those with chronic migraine or very rapid disability from headache can be benefited by knowing something about the terminator drug known as dihydroergotamine or DHE. Good Reading!

- 1) Sleep, Insomnia and Migraine
- 2) Temporomandibular Disorders and Headache
- 3) Supplements & Nutraceuticals in Pediatric Migraine
- 4) DHE: An Old Dog with New Tricks...Maybe?

The Editors are especially grateful to 1) Drs. Rashmi Halker, Bert Vargas, David Dodick, 2) Steven Graff-Radford, 3) Hope L. O'Brien, 4) Paul G. Mathew and F.M. Cutrer, as authors of these articles and for their time, expertise, their dedication to patients and ACHE. We also note that three of our lead authors are fellows in certified Headache Medicine training programs. We hope they enjoyed their efforts working on behalf of our headache patients.

Every two years a new president of the American Headache Society® takes the lead and the immediate past president takes over as ACHE Chairman. So time has come for good-byes and thanks to our readers. We wish you all the best of health.

Paul Winner, DO, FAHS
ACHE Chairman

Marcy Yonker, MD, FAHS
ACHE Vice-Chair

Frederick R. Taylor, MD, FAHS
Newsletter Editor

Sleep, Insomnia, and Migraine

Rashmi Halker, MD; Bert Vargas, MD; David W. Dodick, MD

Key Points

1. Schedule consistent bedtime that allows 8 hours time in bed.
2. No TV, reading, music in bed.
3. Use visualization techniques to shorten time to sleep onset.
4. Move your last food to at least 4 hours before bedtime; limit fluids within 2 hours of bedtime.
5. Stop naps.

Overview

Medical providers have known for over a century that there is an association between poor sleep and the frequency and intensity of migraine and other pain syndromes. Insomnia, also referred to as psychophysiologic insomnia by many, is one type of poor sleep. The longer word suggests interplay between mind and body factors in insomnia. Other common types of sleep difficulties include sleep apnea, frequent snoring, and excessive daytime sleepiness. Researchers define insomnia as difficulty falling asleep (initiation or onset of sleep) or staying asleep, early morning waking, or waking up feeling un-refreshed. These latter types are sleep maintaining problems. Insomnia, of one or both types, is a common finding amongst individuals with chronic migraine. In many cases, insomnia may stem from other medical problems which cause

Continued on page 2

IN THIS ISSUE

- Sleep, Insomnia, and Migraine
- Temporomandibular Disorders and Headache
- Supplements & Nutraceuticals in Pediatric Migraine
- DHE: An Old Dog with New Tricks...Maybe?

Continued from page 1

chronic pain (making it difficult to sleep comfortably) or which disrupts normal sleeping patterns. Until recently this relationship between insomnia and migraine was not well studied.

Information from Research and a Simple Treatment Plan

At the University of North Carolina (UNC), Chapel Hill, researchers studied this association by interviewing 147 adults with transformed migraine (TM). None of the patients reported feeling “refreshed” upon awaking and four out of five regularly felt “tired” upon waking. This compares to responses of individuals with infrequent migraines – approximately one in four felt “refreshed” upon waking and only about one in three awakened feeling “tired.”

TM has frequently been used for those with migraine who at some earlier time had lower number of headaches including migraines and have “transformed” to higher frequency over 15 days per month. Officially a International Classification system defines chronic migraine as individuals with fifteen or more days of headache for greater than 3 months and 8 or more days of either migraine drug use for headache or migraine descriptive pain symptoms. In this UNC survey insomnia was a complaint of the majority of those who had more than 15 days of headache with migraine with two-thirds having difficulty falling asleep. When asked about their sleep habits, almost 80% watch TV or read in bed, 70% get up in the middle of the night to use the bathroom, approximately 60% regularly nap during the day, and a little over 50% regularly use sleeping pills. Interestingly, less than one in ten used caffeine within 8 hours of bedtime. This poor quality of sleep and the suboptimal sleep habits reported by these researchers represent typical sleep issues for those with frequent, severe migraine needing specialty headache care. Can addressing insomnia positively affect sleep and migraine?

These UNC researchers attempted to see if making changes in sleep patterns

could have an effect on migraine frequency and intensity. Forty-three women with chronic migraine were randomly placed into one of two groups. The first group received formal instructions on how to improve their sleep habits. The other received placebo instructions. They were asked to keep a diary of their headaches. Six weeks later at follow-up women who changed their sleep behavior saw a significant improvement in headache frequency and intensity. Dramatic improvement was seen in one of three, to the extent that they no longer met criteria for chronic migraine. None of the placebo group had such a dramatic change. However, this placebo group was then given the formal teaching that the other group received and followed for another six weeks. At the final visit, six weeks later, almost 50% of all subjects who followed the sleep suggestion experienced headache improvement so that they no longer met criteria for chronic migraine. The sleep plans given to the patients to improve their sleep quality were listed in recommendations 1-5 in italics at the top of this article. Since they are so important read them again here:

1. Schedule consistent bedtime that allows 8 hours time in bed.
2. No TV, reading, music in bed.
3. Use visualization techniques to shorten time to sleep onset.
4. Move your last food to at least 4 hours before bedtime; limit fluids within 2 hours of bedtime.
5. Stop naps.

Risk Factors for a Sleep Disorder

Since poor sleep can be associated with more frequent and severe migraine, it is only natural to ask what factors place people at risk for developing a sleep disorder. Changing behaviors as suggested in the sleep plan address factors that can disturb sound sleep. Other potential risk factors for insomnia include:

- Stressful life events, such as death of a loved one, divorce, or the loss of a job.
- Day-to-day life stresses such as

concerns about school, work, family, and finances may lead to disruptive sleep.

- Depression, anxiety and other mental health disorders can lead to fragmented sleep patterns, and these individuals can have trouble sleeping or may even sleep too much.
- Medications including prescription drugs and medications available over-the-counter. Many prescription drugs, including antidepressants, corticosteroids, allergy medications, pain medications, and blood pressure medications can interfere with sleep patterns. Other over-the-counter medications, including those for allergies, cough and cold, pain, and weight loss can also disrupt sleep. Many can leave you feeling groggy; others contain caffeine and other stimulants that prevent you from getting a good night’s sleep.
- Using caffeine, nicotine, alcohol – especially before bed. Caffeine and nicotine contain stimulants that can keep you up at night. Alcohol can initially lead to sedation, but it prevents you from reaching deeper stages of sleep, can lead to waking in the middle of the night, and a feeling of not being refreshed in the morning.
- Medical conditions associated with chronic pain, breathing difficulties, or frequent urination can lead to sleeping difficulties. Medical conditions that have been linked with insomnia include arthritis, gastro-esophageal reflux disease (GERD), cancer, lung diseases, congestive heart failure, overactive thyroid, obstructive sleep apnea, and Parkinson’s disease. Treating these conditions can lead to better sleep.
- Change in environment or work schedule, such as jet lag from changing time zones, working nights, or shift work, can lead to insomnia.
- Eating too much or too late in the evening can lead to trouble sleeping due to heartburn. Many people experience heartburn after meals, and this can be worsened by lying flat.

Continued on page 3

Continued from page 2

- Poor sleep habits, including irregular sleep times, stimulating activities before bed, and reading, watching TV, or studying/working in bed can all contribute to insomnia.
- Female gender – women can experience hormonal shifts during their menstrual cycle and during menopause that can lead to trouble sleeping. Lack of estrogen is thought to play a role.
- Age over 60 – As sleeping patterns change with age, insomnia often becomes more common. It is estimated that nearly half of elderly individuals suffer from sleep problems.

More on Sleep Plans

Several lifestyle modifications, particularly changes to your daytime and bedtime routine, can help with insomnia. Try to include the following in your sleep plan:

- Stick to a regular sleep schedule. Keeping your sleep times consistent, even on weekends, can help maintain your body's natural sleep rhythm.
- Get out of bed when you're not sleeping. In the mornings, allow yourself to sleep as much as you need to feel rested, and then get out of bed. At night, if you are unable to fall asleep after 15 minutes, get out of bed and try to do something relaxing, such as reading. Try to wait until you become drowsy before getting back in bed and attempting to sleep.
- Use your bed and bedroom only for sleeping and intimate relations. Don't eat, read, work, or watch TV in bed.
- Find ways to relax before bed. Creating a relaxing bedtime ritual, such as a warm bath, reading, soft music, yoga, or prayer can all be helpful techniques.
- Avoid napping, as taking naps can make it more difficult to sleep at night. If you cannot avoid a nap,

limit it to no more than 30 minutes, and don't nap after 3 PM.

- Make your bedroom conducive to sleep. Close the door or run a fan to create a soft background noise to shut out other noise, adjust the temperature so that it's comfortable, and keep the bedroom dark. Don't keep a TV or computer in the bedroom.
- Exercise and stay active. At least 30 minutes of vigorous exercise daily, 5-6 hours before bedtime, can be helpful.
- Avoid or limit caffeine, nicotine, and alcohol.
- Avoid large meals or beverages before bed.
- Check your medications to see if they have possible side effects which may be contributing to sleep problems.
- Adequately treat your pain so that it's not keeping you up at night.
- Set your alarm so that you know when it's time to get up in the morning, but otherwise hide the clocks from view. The less often you know what time it is at night, the better you'll likely sleep.

You might consider crossing out or putting an X before those activities you have mastered or accomplished, circling or placing an O before those you consider an Opportunity or not accomplished and then star or * in front of a priority that you believe you can accomplish. When you succeed with that goal star another opportunity and so on and so on until all are marked with a finished X. When you achieve this you will be sleeping more soundly. If not, you are in need of the 33 Sleep Secrets you can locate under the Search option on www.mercola.com or advice at www.sleepfoundation.org. Otherwise, consider a very well trained sleep center/specialist assessment.

Rashmi Halker, MD, Headache Medicine Fellow; Bert Vargas, MD, Assistant Professor of Neurology; and David Dodick, MD, Professor of Neurology, Mayo Clinic Scottsdale, Arizona.

Temporomandibular Disorders and Headache

Steven Graff-Radford, DDS

Key Points

1. A temporomandibular disorder involves the chewing muscles, temporomandibular joint and connected structures.
2. The signs and symptoms of TMD are often transient and self-limiting. Simple and reversible treatments have to be preferred over irreversible procedures.
3. The goals of treatment for TMD are to decrease pain and to restore normal function.
4. Five basic treatment tools include a) patient education and self care, b) cognitive and behavioral intervention, c) pharmacologic management, d) physical medicine techniques, e) surgery.

Overview

Temporomandibular disorders (TMD) are a collective term embracing a number of clinical problems that involve the chewing muscles, the temporomandibular joint (TMJ) and associated structures, or both. This is also called Temporomandibular Pain Disorder Syndrome by at least some. The syndrome is described by pain and tenderness of the chewing muscles, joint sounds with jaw opening and limited jaw movement. Pain in the TMJ may occur in 1 in 10 of the population and TMD has been reported in nearly one-half of the US population. Work in this field has not specifically sorted headache from facial pain. In non-patient population studies, 3 out of 4 have at least one joint dysfunction sign (clicking, limited range of motion) and about 1 in 3 have at least one symptom (pain, pain on palpation). Out of those with a sign or symptom, fewer than 1 in 20 require treatment and even fewer have headache as the primary pain. Because both headache and TMD are so common they may be one and the same or separate entities. The TMJ and associated face and mouth structures should be considered as triggering or persisting factors for migraine. Scientific study has described the pathways and mechanisms for pain referral from the

Continued on page 4

Continued from page 3

head to the temporomandibular joint and vice versa. Headache may result from temporomandibular structures or pain may be referred to the temporomandibular joint, secondary to a primary headache diagnosis. It is essential not to confuse the issue and suggest a cause and effect relationship because both are present or based on treatment responses.

Longitudinal studies suggest that TMD is a disorder usually effecting females between 15 and 30. It is suggested the disorder is self limiting and takes about 7-10 years to resolve and rarely are TMD's a problem later in life. This is possibly due to the nature of the lining of the TMJ with its ability to remodel.

Classification Criteria by the International Classification of Headache Disorders 2

Criteria exist for use by headache specialists to diagnose TMD created by the classification committee of the International Headache Society. TMD are listed as: Headache or facial pain attributed to temporomandibular joint (TMJ) disorder criteria:

- A. Recurrent pain in one or more regions of the head and/or face
- B. X-ray, MRI and/or bone scintigraphy demonstrate TMJ disorder
- C. Evidence that pain can be attributed to the TMD, based on at least one of:
 1. pain is precipitated by jaw movements and/or chewing of hard or tough food
 2. reduced range of or irregular jaw opening
 3. noise from one or both TMJs during jaw movements
 4. tenderness of the joint capsule(s) of one or both TMJs
- D. Headache resolves within 3 months, and does not recur, after successful treatment

Comment: Pain from the temporomandibular joint or related tissues is common. It is due to the so-called temporomandibular joint disorders (e.g., disk displacements, osteoarthritis, and joint hypermobility) or rheumatoid arthritis, and may be associated with myofascial

pain and headache.

Etiology

It is not clear what triggers a TMD. Perhaps it is arthritis, or perhaps associated with trauma to the joint. This does not need to be a major trauma, as in a direct assault on the joint, but possible due to smaller traumas such as perpetual grinding or clenching of the teeth.

The TMJ is made up of two bones, the temporal bone and condyle, which are separated by a fibrous disk, and surrounded by a capsule. The TMJ is lined by fibrocartilage, which is cartilage largely composed of fibers like those in ordinary connective tissue. This gives the joint the tendency to remodel.

Inflammation within the joint accounts for TMD pain and the dysfunction (abnormal movement) is due to a disk, condyle incoordination. When the disk, which separates the two bones making up the TMJ, slips forward a noise or clicking can be heard, as the condyle rides over the disk. This may progress to locking, where the mouth does not open more than 25 mm (normal 45mm). This is due to anterior movement of the disk where the condyle can't ride over the forward located disk.

Imaging the TMJ with MRI can help identify the disk position; tomographic imaging is also very helpful in identifying degenerative changes and condyler movement. Muscle pain disorders may include spasm, myositis, muscle splinting and myofascial pain. The most frequent muscle disorder included in TMD classification is myofascial pain.

Myofascial pain is described as dull and/or achy pain associated with the presence of trigger points (tender areas) in muscles, tendons or fascia. A trigger point is identified as a localized spot of tenderness in a palpable taut band of muscle, tendon or ligament, which when pushed replicates the pain sensation. These trigger points may be the hallmark of tension-type headache.

Treating headache by targeting TMD's

The goals of treatment for TMD are to decrease pain, and to restore normal function. Because the signs and

symptoms of TMD can be transient and self-limiting, simple and reversible treatments have to be preferred over complicated and irreversible procedures. These goals may be achieved through a structured, time limited program, which addresses the physical disorder and the perpetuating factors. The five basic areas that should be considered are summarized below and include a) patient education and self care, b) cognitive and behavioral intervention, c) pharmacologic management, d) physical medicine techniques, and e) surgery.

Patient education and self care

Satisfactory management requires an explanation and reassurance. Persistent jaw joint noise may be interpreted as a sign of disease. Understanding that joint noise may occur in otherwise healthy joints may be difficult to accept. Likewise complaints of limited mouth opening and other signs of joint dysfunction must be interpreted and assessed in the context of age, gender and general health. You deserve realistic expectations regarding treatment outcome and must have reasonable goals. Simple modification of lifestyle and oral habits may be sufficient to alter symptom intensity.

Cognitive and behavioral intervention

Behavior modification programs are often accompanied by relaxation training, hypnosis or biofeedback. Muscle relaxation training techniques are varied, and the choice of technique will depend on the skill of the therapist and suitability of the patient. This approach has been shown to be generally effective in reducing or controlling muscle pain.

Pharmacologic management

Drugs are used in the management of TMD to control symptoms. These include anti-inflammatories (both steroidal and non steroidal), muscle relaxants and antidepressants and antiepileptic agents. The antidepressants and antiepileptic agents are used to help the body block pain signals.

Continued from page 4

Physical therapy

Physical therapy modalities provide a popular and safe approach to the management of TMD's. Treatment goals are generally based on physical rehabilitation of the joint by reducing joint inflammation, restoring joint mobility and elimination of muscle pain through heat and stretching. Occlusal appliances have been the mainstay of dental therapies for TMD since Costen first published his report on jaw joint pain in 1934. Typically, occlusal appliances are made from rigid heat cured acrylic which covers the occlusal surfaces of either the upper or lower dentition. The potential benefits of occlusal appliance use have been attributed to removing strain from the joint surface, relaxation of masticatory muscles, and reduction or elimination of teeth clenching and grinding. However, these accepted mechanisms of action are largely unproven by research. A second appliance design called a repositioning device or splint is less commonly used. Its function is to reposition the mandible in a forward or protruded direction, theoretically to aid recovery of the inflamed discs tissues. These devices have significant risk of altering the bite, and therefore are discouraged in most situations. Currently the NTI (Nociceptive Trigeminal Inhibition Tension Suppression System (NTI-tss) is popular and, although these can be effective, negative or adverse events may outweigh their benefit including cases of aspiration into the lungs. Splint therapy is usually necessary and safe only during the day.

Occlusal therapy

The association between occlusion and TMD is one of the most controversial topics in dentistry. Malocclusion or misalignment of the teeth is often suggested to be a cause of headache in susceptible individuals. However, 'occlusal theories' are weakly supported by research. The malocclusions which are seen in adults are probably of little consequence, as

skeletal adaptation has already occurred. However certain dental abnormalities such as missing posterior cross bite in the occlusion, excessive vertical or horizontal discrepancy between the upper and lower anterior teeth may contribute in a small way to the development of TMD.

Surgery

Given the self limiting nature of most TMD surgical intervention is rarely warranted. Joint injection with corticosteroid is frequently part of treatment programs but lacks literature support for its value. Authors have expressed concern regarding the potential for condyler damage due to repeated injection of corticosteroid. As a result, clinicians are urged to limit use of this modality for individual patients. Improvement of jaw mobility and reduced joint pain with irrigation (arthrocentesis) of the joint with lactated Ringer's solution or normal saline may occur. Arthroscopy is a more invasive approach than arthrocentesis but allows for direct viewing of the joint surfaces. Data exists for the usefulness in the restoration of mouth opening for both procedures. The use of open joint surgery is relatively rare but may be justified in cases where circumstances are extreme, and disability associated with joint disease impacts greatly on quality of life.

Conclusion

TMD are a collection of clinical entities that are often very painful and disabling. Yet, they are self limiting and usually respond to conservative therapy. Basic principles of management to reduce pain and restore range of motion will reduce disability and often contribute to reducing primary headache if it co exists.

Steven B Graff-Radford, DDS, Director, The Program for Headache and Orofacial Pain, The Pain Center, Cedars-Sinai Medical Center, Los Angeles California.

Supplements & Nutraceuticals in Pediatric Migraine

Hope L. O'Brien, MD

Key Points:

1. *Supplements are popular, but not adequately studied or frequently used in children, although more frequently by adolescents.*
2. *Review and consider magnesium and vitamin D with little concern, as lower cost options and safe in the pregnant adolescent.*
3. *Review and consider use of riboflavin, CoQ10 if blood levels are low or Petadolex™ if cost and long-term safety are not a concern.*
4. *Avoid feverfew until possibly Mig99 becomes available.*

Overview

The use of nutraceuticals is increasing in the general population. Wide-spread popularity exists among patients including those with migraine. Health care providers are often questioned by parents about the use of more "natural" treatments for their child with migraine. The use of nutritional supplements or "nutraceuticals" is considered for several reasons. First, there are "failed" experiences with previously prescribed conventional prophylactic medications with ineffectiveness or intolerance due to adverse side effects. Second, there is often reluctance to start traditional prophylactic treatment due to concern for recognized possible adverse effects. Third, there may be personal preference for a more "holistic" approach. Furthermore, nutraceuticals are often well tolerated and, most importantly in today's economy, often are relatively inexpensive. Despite studies showing some effectiveness in adults, positive nutraceuticals studies in migraine for effectiveness and tolerability in children and adolescents are lacking. In this review, I will summarize the literature and discuss the evidence for using nutraceuticals in children and adolescents with migraine.

Butterbur Root - Petadolex™

Butterbur Root, *Petasites hybridus*, originates as a perennial shrub grown in the riverbanks in Germany. Its purpose in migraine is that it contains a substance that inhibits inflammation and also serves as an antispasmodic and calcium

Continued from page 5

channel blocker resulting in improvement in migraine symptoms. In its raw form, it is a toxic plant, but when purified (patented by a German company and marketed as Petadolex™), it has been used in Europe to treat asthma, allergies and migraine. There has been a small single pediatric trial involving only 58 children, comparing Petadolex™ to placebo. The results showed that Butterbur improved migraine frequency. In a larger study in children ages 6-17 years with episodic migraine treated with Butterbur without controls for 4 months, 75% of children had improvement in headache frequency. The doses used in children ranged from 50 to 150mg, based on age. Side effects seen in these studies were minimal, included burping, it were usually seen at higher doses. Given these positive, yet limited studies, there is some concern in using Butterbur. While brand name Petadolex™ is monitored by the German government's Commission E and considered safe, long-term studies over 3 months are unavailable. Generic butterbur is not monitored or certified to be safe by any governmental authority. Since it is a known carcinogen and its long-term effects are uncertain a "consumer beware" and "you're putting your faith in the seller" warning seems warranted. Safety in pregnancy at any age in unproven.

Magnesium

Magnesium is an important ion that in low levels has been linked to migraine. Magnesium is available in soluble and insoluble forms. The soluble forms are better absorbed and many are amino acid chelates. Chelate means "bonded to" and the amino acid bond helps the intestine absorb the magnesium through a different path which is more effective. Insoluble forms are most readily available, such as magnesium oxide or carbonate.

Low brain magnesium is believed to be involved in increased brain excitability. This excitability is thought to be associated with many of the features of migraine. With limited data there is a belief that the higher the frequency of

headache the more likely brain and total body magnesium is deficient. This cannot be detected by a simple blood test as this only measures 1% of total body magnesium.

There has been a single controlled trial investigating magnesium in children and adolescents ages 3-17 years. The study used magnesium oxide, a non-chelated form or insoluble form of magnesium. Each subject received 9mg per kilogram (20mg per pound) divided into three doses daily. Results were equivocal. One possible reason is that fewer children than expected completed the study because of diarrhea, the main side effect. Another criticism is that those treated with magnesium had less severe migraine. In another study, magnesium pidolate (a chelate form not available in the U.S.) was used with most children responding after 1 month. Headache days improved with less disability in those with tension type headaches. Side effects included an unpleasant taste. The intravenous form of Magnesium has been studied in adults demonstrating improvement in those having acute migraine with aura or perimenstrual migraine.

In general, recommending magnesium as a preventative has its uncertainties. Namely, the dose required for migraine prevention is unclear. While it can be eaten with most nuts, seeds and dark green vegetables loaded with magnesium, each has its lovers and haters among this age group. Practically speaking, it is unlikely that adequate intake by food alone is possible in most eating plans. Diarrhea or soft stools are the limiting factors by mouth in whatever form it is taken, but toxic effects are unknown by this route if kidney function is normal. Transdermal magnesium is available without any adverse effects on bowel function, but it too has its pros and cons. This includes possible skin irritation or discomfort or need for removal due to gumming. Since magnesium may reduce migraine severity and frequency in children, the dose suggested is 9mg/kg/day (20mg per pound) of a soluble form of magnesium for at least 3 months. Ask your provider or pharmacist

if you have questions. Three final notes: 1) no studies have been done investigating magnesium in acute treatment of pediatric migraine; 2) long-term effects of magnesium on improving migraine are uncertain; 3) at common tolerated doses magnesium is safe for pregnant adolescents.

Riboflavin

Riboflavin (Vitamin B2) has been the most frequently studied supplement in children and adolescents with migraine. It is a co-factor in mitochondrial metabolism, and low levels have been linked to mitochondrial dysfunction and energy metabolism. Supplementation has proven effective in children with mitochondrial disorders. The first pediatric migraine preventative study published in 2008 used high dose riboflavin. Results did not differ from placebo, although both placebo and riboflavin groups had a high response rate. Another research group studied children with chronic severe migraine on riboflavin. They had failed usual drug prevention, but review of use of high dose showed benefit. A more favorable response was noted in boys. Adverse effects were minimal and included bright yellow urine, diarrhea and frequent urination. Suggested dosing is uncertain as those used in studies ranged from 25 to 400mg per day. All of these doses are high dose compared to recommended adult daily allowances. The drug properties of riboflavin suggest that the maximal amount that the human body can absorb from a single dose is 27mg. The time it takes the body to rid itself of half of the drug, known as half-life, is about 2 hours. These facts suggest there is a need to take riboflavin multiple times per day for best effect. An empty stomach is also less able to absorb riboflavin. Although a vitamin, riboflavin at these doses has not been proven safe in pregnancy at any age.

Coenzyme Q10

Coenzyme Q10 (CoQ10) is the only nutrient discussed that is made in the body. It is a co-factor also involved in mitochondrial metabolism and is known also as an anti-oxidant. When levels are low in the body, it has been associated with abnormal energy metabolism. It has been

Continued on page 7

Continued from page 6

shown to be effective in migraine prevention in adults with rare side effects at high doses which included nausea, anorexia, dyspepsia, diarrhea and rash. Otherwise, it is well tolerated and reported to be safe. A large 2007 study assessed CoQ10 levels in 1400 subjects, ages 3 to 22, who had frequent headaches who and were then provided CoQ10 therapy. The prevalence of a severe insufficiency (deficiency) of CoQ10 was about 33%, with 75% of patients having at least mildly insufficient levels. Use of 1-3mg per kilogram (2-6mg per pound) of CoQ10 resulted in an increase to adequate blood levels. Improvement in headache frequency with less disability resulted. There were no adverse effects recorded. Cost is the primary drawback to CoQ10 therapy. Petadolex™ and Coenzyme Q10 each sell for more than \$30.00 per month at higher doses. While studies have not compared treatment effects, the ubiquinol form of CoQ10 is better absorbed and reaches significantly higher blood levels than ubiquinone. No toxicity issues with pregnancy are known, but safety is also unproven.

Feverfew

Feverfew is sold in the U.S. as dried leaves of a weed plant *Tanacetum parthenium* and has been used for treatment in adults for its anti-inflammatory role in migraine. The active ingredient is believed to be parthenolide. A specially processed and standardized form from Germany is known as MIG-99 (not available in the US). Despite its use in adults, feverfew has not been studied in children or adolescents as a treatment for migraine. Results have been minimal and inconsistent. Reports on evidence of effectiveness do not support its use due to lack of definite benefit. Side effects include gastrointestinal disturbances, mouth ulcers and joint aches. Furthermore, its long-term safety is unknown and currently not a reasonable option for children or adolescents with migraine.

Vitamin D

No controlled studies exist in migraine. There are adult reports linking low vitamin D and migraine. An increasing number of studies reveal benefits of vitamin D for pain conditions. Deficiency is associated with many diseases. Many children and adolescents are deficient, at least in all but the summer months. The best source of Vitamin D is 15-20 minutes of daily direct sunlight during the midday. Some fish products can provide a limited source for vitamin D along with breast feeding by a mother with sufficient Vitamin D stores. Vitamin D typically needs to be taken as a separate supplement. Vitamin D is actually a gene regulator which improves immune function, mood conditions and many additional disorders. Vitamin D should never replace accepted conventional treatments, but for general good health and possibly pain improvement you should consider maintaining a 25-hydroxyvitamin D level at least between 35-60ng/ml with Vitamin D3 replacement. Vitamin D intake during pregnancy appears critical and safe with the levels listed here. A visit to www.vitamindcouncil.org will make issues very clear.

Summary

Although there has been wide spread interest, the use of nutraceuticals in the pediatric population is limited. There are currently no official guidelines as to the use of nutraceuticals in children and adolescents with migraine. Although there have been a small number of studies showing the effectiveness and tolerability for conventional migraine treatment, few of these have been approved by the US Food and Drug Administration or any other government's agency for use in children. More studies are needed to further investigate the role of nutraceuticals in the pediatric population so that guidelines can be developed and recommendations can be made. The use of nutraceuticals has the potential to improve headache outcomes for patients and families of those suffering from migraine who prefer alternatives to conventional therapy.

Hope L. O'Brien, MD, Headache Medicine Fellow, Assistant Professor of Pediatrics & Neurology, Children's Hospital, Cincinnati, Ohio.

DHE: An Old Dog with New Tricks...Maybe?

Paul G. Mathew, MD; and F.M. Cutrer, MD

Key Points:

1. In large part due to lack of acute treatment effect greater than 2 out of every 3 migraine sufferers are dissatisfied with their treatment and need to re-treat.
2. Treat Migraine early, whenever possible at mild symptoms with a specific medication for migraine to reduce multiple doses and improve success.
3. Dihydroergotamine (DHE) is available in multiple forms, and of significant benefit except by mouth
4. Ideally use any acute medication 9 days or less per month, but DHE may be used slightly more often with less concern of overuse and rebound.
5. DHE has low return or recurrence of headache once relieved of pain.

Overview

There are many medication choices for acute symptom relief or abortive treatment of migraine. These medications can be sorted into specific and nonspecific types for migraine. Medications with specific actions on migraine pain include non-steroidal anti-inflammatory drugs (NSAID's), triptans, and dihydroergotamine. Nonspecific medications often lack a definite known migraine action or proven effect on the full features of migraine. These include opiates, commonly known as narcotics, and combination analgesics, such as butalbital compounds, isometheptene mucate, and Excedrin.

Nonspecific Group of Acute Treatments

Opiate medications (Tylenol #3,

Continued from page 7

tramadol or Ultram, hydrocodone or Vicodin, oxycodone or Percocet, etc.) are generally avoided by headache providers. At least one guideline directs providers to reserve these medications for those who cannot use other medications. An example is pregnancy. Headache medicine specialists also avoid combination analgesics such as butalbital and Excedrin compounds. Brand names to avoid include Fiorinal, Fioricet, Esgic, Esgic Plus, Phrenelin and Phrenelin Plus. Avoid these due to their high potential for the development of rebound headaches, also known by headache providers as medication overuse headaches. Research shows that as few as 5 days per month of using butalbital compounds, especially in females, can produce progression from episodic to chronic migraine. (See February 2010 ACHE Newsletter by Dr. Cardona on *Acute Therapy: Why Not Over-the-Counter or Other Nonspecific Options?* for further comments and recommendations.)

Specific Group of Acute Treatments

NSAID's, such as over the counter ibuprofen and naproxen, are often the first line of treatment for mild migraine headaches, but are limited by their modest potency. Regular heavy usage can lead to stomach ulcers and kidney damage. An individual's risk varies greatly. Triptans, of which there are seven uniquely different medications, represent a newer class of medications that were specifically designed for the treatment of migraine. Imitrex became available as generic sumatriptan in late 2008. Triptans are available in multiple forms including tablets, orally dissolving tablets, nasal sprays, and injectable types, with or without a needle. Anti-emetic medications, such as metoclopramide (Reglan) prochlorperazine (Compazine) and others are useful for nausea. Metoclopramide makes analgesics it's used with more effective. Given by IV several anti-nausea medications have anti-headache effects including the two mentioned. Anti-nausea drugs should not be used by mouth alone for pain as they are ineffective. Each is often used in

combination with other abortive pain medications.

Satisfaction with Treatment

Although there are many options in abortive medication treatment, it is estimated that about 71% of migraine patients are dissatisfied with the acute treatment of migraine attacks. There are many potential reasons as to why this is so. Multiple doses due to lack of effect is one of the biggest reasons. This lack of effect can take many forms, including failure to reduce intensity, failure to reduce duration, and failure to prevent headache from coming back within 24 hours after relief of the initial headache. This is known as recurrence. Many of these medications also lead to unpleasant side effects such as stomach irritation, chest tightness, tingling, flushing and more. Another reason for dissatisfaction with acute medications may be more specific to the way it is taken. With all oral medications, delays in absorption can lead to delays in pain relief. This is particularly true in the case of migraine as studies have shown that delays in treatment lead to a lower likelihood of complete relief in acute migraine. For the orally dissolving tablet and nasal spray, bad taste can contribute to delay or lack of use. In addition, nasal sprays must rely on variable absorption through the nasal mucus membranes. Injectable medications have the obvious limitations of pain. With one needleless exception using forced air, injections are not an option for patients that have fear of needles. Intravenous medications are probably the most effective, but are also the most inconvenient and costly. They require the establishment of an intravenous line at an emergency room, infusion center, or hospital setting, as well as a nurse to administer the medication. Lastly, rectal suppositories, most often compounded, are available from select pharmacies, but are not commonly considered desirable.

Dihydroergotamine or DHE

What abortive medication can be tried when the prior medications have not been successful? This medication may indeed be the first choice for daily or extremely high frequency headache with migraine features. While the previously mentioned problems exist with this product, the answer may lie in a medication that predates many of the medications that are currently used for the treatment of migraines. Dihydroergotamine (DHE) is part of a class of compounds called ergot alkaloids. The name ergot refers to a group of fungi of the genus *Claviceps*. There are 50 known species of *Claviceps*, and most of them are located in tropical regions. The most prominent member of this genus is *Claviceps purpurea*, which is a fungus that grows on grains. Foods containing the fruiting structure of this fungus in toxic amounts can cause ergotism in humans. Ergotism is a condition that includes symptoms such as painful seizures, muscle spasms, paresthesias, diarrhea, itching, headaches, nausea, vomiting, hallucinations, mania, psychosis, and dry gangrene. Dry gangrene is a condition in which the blood vessels constrict or narrow severely causing weak pulses or loss of pulses and pallor or loss of skin color, peripheral sensory loss, swelling, and eventually cell death. Severe cases of gangrene can lead to amputation of the affected limb. Historically, this was noted in the middle ages, when grains contaminated by *Claviceps Purpurea* caused gangrene. This outbreak was referred to as St. Anthony's Fire, and was named after monks of the order of St. Anthony who treated the disease.

In 1918, ergotamine was isolated from ergot, and later in 1926 ergotamine was introduced as a treatment for migraine. In 1938, Graham and Wolff proposed that the major action of ergotamine was constriction of the blood vessels of the brain. In 1945, ergotamine was modified in the chemistry laboratory and introduced as dihydroergotamine or DHE. DHE is a more potent form of ergotamine with several different

Continued on page 9

Continued from page 8

properties from the original.

When comparing the two compounds, DHE is more effective in aborting headaches, and involves less nausea and vomiting than ergotamine. DHE has a lower risk of headache recurrence after the successful termination of an initial headache. In addition, DHE carries a lower risk for medication overuse headaches. DHE's chemical structure has elements that are similar to many chemicals that occur naturally in the body including epinephrine, norepinephrine, dopamine, and serotonin. These similarities in structure facilitate DHE's ability to terminate headaches.

Due to DHE's structure, it is very poorly absorbed through the gut, so oral forms are not effective. Nasal DHE (Migrainal™) is an effective form of the medication, but can have inconsistent effects. This nasal spray form relies on take up through tissues in the nose, which can lead to variable blood levels, with about 40% or less of the medication getting into the blood stream. In addition, the nasal form has a bad taste for nearly half who use it. Injection of DHE into muscle is effective and consistent with nearly 100% of the medication getting into the blood stream. Unfortunately, intramuscular DHE is inconvenient, because it must be drawn into a syringe by the patient. Once drawn up, the pain associated with the injection limits its use by patients. The intravenous (IV) route is the fastest, most effective method of administering the DHE, but requires establishing IVs and administration or oversight by a nurse. IV DHE is typically administered in intermittent or bolus injections in the emergency room or infusion center, or continuously in inpatient setting for the treatment of

status migraine. Migraine status is defined as a migraine headache that lasts more than 72 hours with or without treatment with either continuous pain or interrupted < 4 hours, not counting relief during sleep. On occasions under the skin infusions with insulin type pumps are used for continuous outpatient treatment. There is very limited information on this technique and your provider is likely not familiar with it.

With DHE's proven benefits, designing a fast, convenient, effective method of administering it could prove to be an important option in the treatment of migraine. As such, a pharmaceutical company is currently performing trials of a new formulation of DHE branded as Levadex. It is not FDA approved as of the publication of this journal. Levadex is an inhaled form of DHE that is absorbed through the lungs directly into the blood stream. A Tempo inhaler, a new type of device, utilizes a breath synchronized, proprietary technology that delivers a 1 mg dose of DHE when the user inhales. This provides more consistent and efficient dosing of medication than conventional inhalers.

Although Levadex is not yet available on the market, trials have shown it to be effective in reducing pain, light sensitivity, sound sensitivity, nausea, and vomiting. In addition, the medication was well tolerated by most patients. Side effects included upper respiratory infection (3%), nasopharyngitis (2%), sinusitis (0.7%), nausea (4.5%), vomiting (2%), coughing (2.5%), and product complaints such as taste (6.4%). Because it stays in the blood stream longer than most of the commonly used triptans, the likelihood of recurrence is also thought to be lower in patients who treat with all forms of dihydroergotamine including Levadex.

Although DHE is an effective medication for headache treatment, there are several limitations in its use. It should be

avoided during pregnancy, with history or suspicion of ischemic heart disease, history of coronary artery disease or a more rare condition called coronary vasospasm or Prinzmetal's angina, severe peripheral vascular disease, uncontrolled high blood pressure, onset of chest pain following test dose of DHE, or previous allergic reaction. It should also be avoided per the FDA PI (package insert) in migraines that involve focal (one sided) weakness known as hemiplegic migraine, use of a triptan medication within 24 hours, or an MAO inhibitors (Nardil) within the preceding 2 weeks.

Paul G. Mathew, MD and F.M. Cutrer, MD, Department of Neurology, Mayo Clinic, Rochester, Minnesota.