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Dear Healthcare Professionals:

In this edition of *JANA* you will find a one (1) hour approved continuing education program for physicians, pharmacists, and RNs. The CE article is titled:

Magnesium, Feverfew, and Riboflavin: Therapeutic Use in Migraine Prevention

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Editor-in-Chief
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REVIEW ARTICLE

Magnesium, Feverfew, and Riboflavin: Therapeutic Use in Migraine Prevention

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Approximately 28 to 32 million Americans suffer from migraine headaches. The majority of these are women between the ages of 22 and 35 years. Although the causes of migraine headaches are not clearly understood, it is believed to result from interplay between the brain tissue and the circulatory system supplying the central nervous system.

In a survey study of 20,000 individuals, about two-thirds of those who met the criteria for migraine, self-treated with over-the-counter (OTC) drugs to the exclusion of prescription medications.[1] The desirability of prevention is clear to healthcare professionals and patients alike. In addition to obvious financial savings that effective prevention would generate, medical effects of medication leading to rebound headaches could potentially be reduced as well.

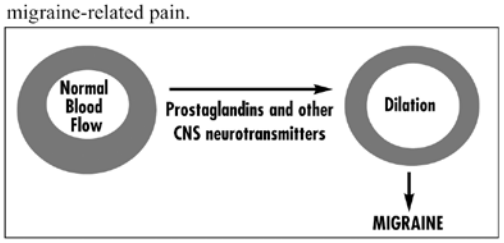
PATHOPHYSIOLOGY OF MIGRAINE

The induction of the migraine appears to be triggered by interactions between precipitating events and specific brain areas. These events appear to induce constriction of the cranial vessels that leads to a decrease in blood flow to the brain, which may induce periods of low oxygenation that can result in neurologic disjunction. Decreased oxygenation may be associated with the aura that is experienced in about 10% of migraine sufferers. Migraine auras manifest as perceptions of flashing lights, partial field of vision loss, unilateral numbness, weakness, or speech difficulty.

About 85% of patients will report migraine without aura. This most common type of migraine lasts about 4–72 hours, and is aggravated by physical activity, occurs unilaterally, and can be of moderate to severe intensity. Nausea, vomiting, photophobia, and or phonophobia may also occur.

The initial vasospasm of the cerebral event is believed to be mediated by the concentration of prostaglandins and other CNS neurotransmitters, including serotonin. In contrast, neurogenic inflammation is mediated by vasoactive neuroproteins. The pain associated with migraine headache usually occurs as a result of cerebral vasodilation and neurogenic inflammation that follows a period of decreased oxygenation. (Figure 1)

Figure 1. Vasodilation of the cerebral vessels may result in migraine-related pain.



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Psychological factors such as stress and depression have been associated with the onset of migraine, as have environmental factors like smoke, light, and weather changes. The consumption of large amounts of alcohol, citrus fruits, aspartame, chocolate, and caffeine may also trigger episodes. A number of medications have also been associated with migraine-related headaches. These include Tagamet, Pondium, Prozac, Premarin, Indocin, nicotine, nitroglycerin, oral contraceptives, reserpine, and ethinyl estradiol.[4]

FEVERFEW

Feverfew, *Tanacetum partheium*, member of the Compositae or daisy family, is native to the Balkan mountains in Europe and can now be found in Australia, China, Japan, North and South American, and North America.[2] Its use as an herbal remedy dates back 2,000 years.[14] Feverfew currently is used for migraine headache prophylaxis and to treat rheumatoid arthritis.[2]

Chemistry

Some components in feverfew are:

- Sesquiterpene lactones: parthenolides, canin, artecanin, santamarin
- Flavonoid glycosides: luteolin, tanetin, apigenin, 6-hydroxy flavonls
- Sesquiterpenes and monoterpenes: camphor, borneol, germacrene, pinenes
- Other: polyacetylenes, pyrethrin, melatonin, tannins, essential oils, chrysanthemum acetate

The leaf is used for medicinal purposes. The most active component of feverfew is parthenolide, the most abundant sesquiterpene lactone.[2]

Mechanism of Action

The exact mechanism of action of feverfew is unknown; however, there are several proposed mechanisms: inhibition of serotonin release, inhibition of prostaglandin synthesis, inhibition of platelet aggregation and secretion, inhibition of polymorphonuclear leukocyte degranulation, inhibition of phagocytosis of human neutrophils, inhibition of mast-cell release of histamine, cytotoxic activity against human tumor cells, and antimicrobial activity; it also has antithrombotic potential.[2]

Inhibition of serotonin release

The active moiety in feverfew (parthenolide) inhibits the release of serotonin from blood platelets, similar to the action of methysergide, an ergot alkaloid.[3] This mechanism explains the therapeutic benefit of feverfew for migraine.[5,12]

Inhibition of prostaglandin synthesis

The interference of phospholipase A by the plant causes inhibition of prostaglandin biosynthesis.[10] In a study reported in 1985, feverfew decreased prostaglandin production by 86–88%, but cyclooxygenase inhibition was unaffected.[4]

Inhibition of platelet aggregation and secretion

Feverfew has been found to inhibit platelet aggregation by inhibiting thromboxane synthesis, which occurs via inactivation of cellular phospholipases.[6-8] Numerous studies have shown that feverfew extract inhibits aggregation and secretion of intracellular granules caused by aggregating agents such as adrenalin, collagen, and adenosine diphosphate.[8]

Inhibition of polymorphonuclear leukocytes

Feverfew extract inhibits the secretory activity of polymorphonuclear leukocytes (PMN), showing a much greater inhibition of PMNs granule release than do high concentration NSAIDs.[8]

Smooth muscle

Sesquiterpene lactones, particularly parthenolide, have spasmolytic properties that cause smooth muscle to become less responsive to endogenous substances such as acetylcholine, noradrenaline, bradykinin, prostaglandins, histamine, and serotonin. These findings can be linked to an anti-migraine effect through inhibition of the influx of calcium in the vascular smooth muscle.[13]

Contraindication

Feverfew is contraindicated in people who may be allergic to other members of the Compositae or daisy family, such as chamomile, ragweed, or yarrow. It should not be used during pregnancy or by lactating mothers, or by children under two years old. Because parthenolide affects platelet aggregation in some in vitro studies, caution may be appropriate for patients with bleeding disorders or those anticipating surgery.[2-3]

Drug Interactions

NSAIDs may alter the efficacy of feverfew. The plants' mechanism of action (mainly inhibition of platelet aggregation) may interact with anticoagulants and antiplatelets such as warfarin and aspirin.[2-3]

Adverse Effects

The most common reported side effects of feverfew consumption are GI disturbances after oral ingestion including diarrhea, heartburn, bloating and flatulence. Mouth ulcers, lip swelling, and tongue irritation can occur when one chews fresh leaves.[2] When feverfew is discontinued after use of six months or more, people may experience rebound headache, stiffness in joints and muscles, nervousness, anxiety and insomnia, responses known as "post-feverfew syndrome."[10]

Dosing

Currently there are no precise dosing recommendations, and doses vary. However, the Canadian Health Protection Branch recommends 125 mg of feverfew daily, containing at least 0.2% parthenolide (the active component) in each dosage unit.[2,3,5] Feverfew dosage is generally based on the weight of the leaves. Commonly-used doses

in herbal practice are:

- Feverfew leaves: 2–3 daily
- Dried powdered leaves: 50–250 mg daily or 125–250 mg daily in two divided doses for migraine prophaylaxis
- In the UK and Canada, feverfew products are standardized to contain at least 0.2% parthenolide

Clinical Evidence

Various studies have shown positive therapeutic outcomes of feverfew monotherapy for migraine prophylaxis; however, a few studies have shown no clinical benefit. In the table below are data collected from five different clinical trials obtained from a systematic review conducted in 1998.[10]

MAGNESIUM

Magnesium is the second most abundant intracellular cation in the body and the most common intracellular divalent cation and a cofactor in hundreds of enzymatic processes; its central role in smooth muscle activity and peripheral vascular resistance is well known.[15] About 65–70% of serum magnesium is ionized, while the rest is protein-bound and complexed to small anion ligands.[2] Many studies of the role that magnesium plays in the pathogenesis of migraines have examined the total body supply of intracellular magnesium. these conflicting results may be due to the fact that even though total intracellular magnesium content is relatively stable, there are wide fluctations in serum ionized magnesium. It is this ionized portion that affects the physiological component of a migraine. Migraine research found multiple relationships between magnesium deficit and migraine attacks.[16]

Pharmacology

Magnesium is an electrolyte necessary in a number of enzymatic processes, phosphate transfer, muscular contraction, and nerve conduction. Deficiencies have been documented in malabsorption syndromes, prolonged diarrhea, vomiting, pancreatitis, aldosteronism, kidney dysfunction, chronic alcoholism, and diuretic therapies.

First author reference	Patients entered/ dropouts	Medication	Main outcome measures	Result
Johnson et al.	17/2	2 capsules (25 mg) powdered feverfew	Frequency of headache. Incidence of nausea and vomiting.	Frequency of headache increased significantly ($p<0.02$) in patients receiving placebo compared to baseline values.
Murphy et al.	72/12	1 capsule (82 mg) powdered feverfew	Frequency, duration and severity of headache. Incidence of nausea and vomiting.	24% reduction ($p<0.005$) in attack frequency, significant reduction ($p<0.002$) of N/V. No change in duration and severity of headache.
Kuritzky et al.	20/nr	100 mg feverfew	Effect of feverfew on 5-HT uptake and platelet activity.	No effect
Weerdt et al.	50/6	1 capsule (143 mg) granulated feverfew	Severity of headache attacks. # work days lost.	No significant effect in either outcome.
Palevitch et al.	57/nr	2 capsule (50 mg) powdered feverfew	Pain intensity. Severity of nausea and vomiting, sensitivity to noise & light.	Significant reduction ($p<0.01$) in each outcome measure.

nr: not reported

MECHANISMS OF ACTION

Inhibition of platelet aggregation / Serotonin levels

Platelet aggregation and serotonin release have been shown to be present during migraine attacks. Magnesium has been shown to cause a dose-dependent inhibition of platelet aggregation. Decreased magnesium levels may contribute to thrombin-induced platelet aggregation, which can lead to serotonin release from platelets.[16]

Vascular dilating effect

Magnesium has a strong vascular dilating effect lending support to the vascular theory of migraine.[2] Ionized magnesium levels are known to affect entry of calcium and release of intracellular calcium from the sacroplasmic and endoplasmic reticulum in vascular smooth muscle and vascular endothelial cells, and to control vascular tone and reactivity to endogenous hormones and neurotransmitters. Cerebral blood vessel muscle cells are particularly sensitive to ionized magnesium; magnesium deficiency results in contraction and potentiation of vasoconstrictors and excess magnesium results in vasodilation and inhibition of vasoconstrictors.[16]

NMDA receptor antagonist

Magnesium is intimately involved in the control of N-methyl-D-aspartate (NMDA) glutamate receptors, which play an important role in pain transmission in the nervous system and in the regulation of cerebral blood flow. Magnesium ions plug the NMDA receptors and prevent calcium ions from entering the cell. Lowering magnesium concentration facilitates activation of the NMDA receptor, which allows calcium to enter the cell and exert its effects on both neurons and cerebral vascular muscle.[16] Blocking the receptor renders calcium unable to exert its vasodilatory effects.

Results of clinical studies

- Many clinical studies have researched the use of magnesium in migraine treatment and prophylaxis. The following data is from selected published clinical studies.
- Bigal et al. found that the relief of pain with IV magnesium sulfate ($MgSo_4$) was not different from treatment with placebo in the migraine without aura (MO) group, and was better than placebo in the migraine with aura group (MA). Magnesium sulfate was highly effective in relieving photophobia and phonophobia in both MO and MA groups. There was a greater response observed, in all symptoms, in the MA group than in the MO group.[17]
- In a study by Peikert et al., high oral doses of magnesium lowered the frequency of migraine attacks within 12 weeks of therapy. Compared to placebo, the therapeutic effects were already significant by the second therapy phase (weeks 5–8) and were confirmed by a significant reduction in the number of migraine days as well as the per patient consumption of acute medication. The duration and intensity of the attacks also declined without being statistically significant in comparison with the placebo group.[18]
- In a study by Mauskop et al., of the 40 patients to whom IV $MgSO_4$ was administered, 32 (80%) had at least a 50% initial reduction of pain intensity. In most patients, headaches began to improve before the end of infusion. Complete elimination of pain was observed in 80% of the 32 patients within 15 minutes of infusion. Of these 32 patients, 18 had persistent headache relief beyond 24 hours. Long-term responses to $MgSO_4$ varied in the different diagnostic categories.[19]
- Findings from a study by Mauskop et al. indicate that serum ionized magnesium levels can be used as a marker for detection of patients with migraine and cluster headaches who can benefit from magnesium infusions.[20]
- In a double-blind, placebo-controlled trial of oral magnesium supplementation in 24 women with menstrual migraine, positive results were noted. Taken at a dose of 360 mg/day taken in 3 divided doses for 4 months, there was a 50% reduction in the number of days with headache. Patients receiving active treatment also showed improvement according to the Menstrual Distress Questionnaire score. Four patients dropped out of the study, but only one did so because of adverse effects (magnesium-induced diarrhea). In a larger double-blind, placebo-controlled study involving 81 patients with migraine headaches, a significant improvement in patients receiving magnesium therapy was demonstrated. The frequency of migraine attacks was reduced by 41.6% in the magnesium group compared with only 15.8% in the placebo group; 3 patients receiving magnesium therapy dropped out of the study.[21]

Dosage

For migraine prophylaxis: oral intake of 300 to 600 mg/day.[21,22]

Adverse reactions

Diarrhea and gastric complaints are the most commonly reported adverse drug reactions. In one study, tolerability of magnesium was assessed. Sixteen (45.6%) of 35 patients in the magnesium group reported 35 adverse events during the course of treatment, mainly soft stools (5 patients), diarrhea (5 patients), and heart palpitations (3 patients). Altogether 17 episodes of adverse events occurred in 8 (23.5%) of the 34 patients on placebo.[22]

At higher doses of magnesium, low blood pressure, nausea, vomiting, urinary retention, decreased heart rate, and dilation of blood vessels have been documented. Coma and cardiac arrest are known to occur with toxic doses of magnesium. Magnesium may accumulate in patients who have decreased renal function; therefore, one must be cautious when consuming magnesium as a dietary supplement.

In addition, use of magnesium in pregnant women should be approached with caution due to its dilating properties.[23] Patients taking potassium-sparing diuretics or with renal failure should not use magnesium supplements.

Drug Interactions

Before beginning therapy with magnesium or any over-the-counter supplement, a complete medication review should be conducted by a pharmacist or physician since magnesium may interfere with the absorption of many other medications. Lanoxin,® Macrodantin,® penicillamine, and tetracycline drugs such as Sumycin,® and Vibramycin® may be less well absorbed in the presence of magnesium, decreasing their effectiveness. This is especially important with Lanoxin since its therapeutic concentration must be monitored closely for clinical effectiveness. Antimicrobials like nitrofurantoin and tetracyclines may not be effective against bacterial pathogens due to less-than-anticipated serum concentrations. Concomitant use with excretion-reducing drugs can increase the effects of supplemental magnesium and magnesium serum levels. These drugs include calcitonin, glucagons, and potassium-sparing diuretics.[23]

Family history

A strong family history is present in up to 80% of patients with migraines.[21] This fact, along with the identification of a gene for familial hemiplegic migraine, suggests that genetic factors are present in a majority of migraine patients. Cellular magnesium content and magnesium metabolism are also under genetic control. Possibly there is an overlap between these two genetic mechanisms.[21]

Migraine management

Another important aspect of migraine management is identifying and avoiding triggers. Many migraine headaches can be triggered by certain foods, especially those containing tyramine. Caffeine or caffeine withdrawal and strong odors, such as perfume, are other common triggers. It is often helpful for patients to keep a headache diary to record possible triggers. Typically, removing identified triggers significantly reduces the frequency of headaches.[22]

Riboflavin

Riboflavin, also known as the water-soluble vitamin B_2, is essential for the body's conversion of food to energy. It enables carbohydrates, proteins and fats to release energy, and is also needed for normal reproduction, growth and repair of skin, hair, nails, and joints. The riboflavin requirement in humans is often related to energy intake, but it appears more closely related to resting metabolic requirements. Differing amounts are recommended for infants, children, and pregnant women based on differences in their caloric intakes. The recommended daily intake for adults is 1.1 mg for women and 1/3 mg/day for men. Rich sources of riboflavin are liver, kidney, eggs, milk, cheese, yeast, broccoli and spinach.[24]

Indications: Riboflavin deficiency prophylaxis.[24] Possibly effective in migraine prophylxis.[24-27]

Chemistry

The active, phosphorylated forms of riboflavin, flavine mononucleotide and flavine adenine dinucleotide, are involved as coenzymes in oxidative-reductive metabolic reactions. These two coenzymes are necessary for normal tissue respiration. Riboflavin is also necessary for the functioning of pyridoxine and nicotinic acid.

Pharmacokinetics

Riboflavin is readily absorbed in the proximal small intestine by a saturable transport mechanism. It is enzymatically metabolized to two active metabolites in the small intestine: flavin mononucleotide and flavin adenine dinucleotide. Bile salts enhance absorption of riboflavin and people with biliary obstruction have decreased absorption. Approximately 6 to 12% of a dietary dose is excreted in the urine. The amount excreted in the feces can exceed the amount ingested following dietary doses due to the synthesis of riboflavin by intestinal bacteria. The elimination half-life is 1.4 hours with a terminal half-life of 14 hours.

Safety

Problems in humans have not been documented with normal oral intake of daily recommended amounts. Toxicity of high doses of riboflavin has not been reported.[24] Likely safe when used at the recommended dietary allowance (RDA) of 1.4 mg per day. There is insufficient reliable information for using larger amounts during pregnancy.[24]

Drug Interactions

Concomitant use with Probenecid (Benemid) inhibits supplemental riboflavin absorption. Propantheline Bromide (Pro-Banthine) concomitant use delays and increases supplemental riboflavin.[24]

Adverse Effects

Bright yellow-orange discoloration of urine.[24]

Migraine Considerations

A mitochondrial dysfunction resulting in impaired oxygen metabolism may play roles in migraine pathogensis. Migraine headache can be a prominent feature in patients affected by the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Riboflavin is the precursor of flavin mononucleotide and flavin adenine dinucleotide, which are required for the activity of flavoenzymes involved in the electron transport chain. Riboflavin, when given to patients with MELAS or mitochondrial myopathies on the assumption that at large doses it might augment activity of mitochondrial complexes I and II, and improve oxidative metabolism, was able to improve clinical and biochemical abnormalities.[28]

Controlled Trials

Two controlled trials exhibited the benefits of riboflavin in migraine prophylaxis. A randomized placebo-controlled, double-blind trial was conducted by Schoenen et al. to com-

pare the effects of high-dose riboflavin versus placebo on migraine frequency, number of migraine days, duration, and severity of headache. Fifty-five migraine patients were randomized to receive either riboflavin, 400 mg a day, or placebo for a 3-month period. Using an intention-to-treat analysis, riboflavin was superior to placebo in reducing attack frequency (p=0.005) and headache days (p=0.012). In the group of patients who improved by at least 50%, i.e. responders, the attack frequency improved 19% in the placebo group and 56% in the riboflavin group (p=0.01); in the number of migraine days, the placebo group improved 15% as compared to a 59% improvement in the riboflavin group (p=0.002). The authors of the study concluded that because of its high efficacy, excellent tolerability, and low cost, riboflavin is an interesting option for migraine prophylaxis and a candidate for a comparative trial with an established prophylactic drug. Three minor adverse events occurred, two in the riboflavin group (diarrhea and polyuria), and on e in the placebo group (abdominal cramps). No serious side effects were reported and the riboflavin was well tolerated.[28]

An open pilot study was conducted and 49 patients with recurrent migraines were given riboflavin 400 mg/day with breakfast for at least 3 months. The mean number of migraines fell by 67% and mean migraine severity improved by 68%. One patient stopped treatment because of gastric intolerance, but that patient was also taking aspirin. No other side effects were reported and the riboflavin was well tolerated. The study suggests that riboflavin supplements may reduce the recurrence rate of migraines.[29]

Conclusion

The controlled trials are encouraging information for further research. Riboflavin is a promising alternative for preventing migraine headaches because it is safe, well tolerated and inexpensive. However, more research needs to be conducted to prove the efficacy and long-term safety.

COMBINATION PRODUCTS: MAGNESIUM, FEVERFEW, AND RIBOFLAVIN

Since moderate success has been suggested with individual preparations of magnesium, feverfew, and riboflavin, use of these agents in combination may exert a synergistic antagonistic affect on migraine prophylaxis and treatment. Several combination dietary supplement products are currently available, including MigreLief® With Puracol,™ Herbal Migraine Formula,® and MigraHealth.™ [30]

While individual data on these products is limited, information from physicians who are using these combination products in their practices suggest that combination products may assist to maintain proper tone of cerebral blood vessels. By improving tone, blood may flow freely from vessel to vessel and prevent sudden spasms. It may also inhibit platelet aggregation, stabilize membranes, and decrease the inflammatory process.[31] Two case reports from a neurology practice that used a combination product of magnesium, feverfew, and riboflavin to treat migraine follow this review.

Randomized, placebo-controlled studies of the combination products are required to fully evaluate and confirm their benefit in migraine treatment or prophylaxis.

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