Migraine Prophylaxis: the use of high-dose riboflavin in patients who have failed amitriptyline prophylaxis: A Placebo--controlled, randomized, double-blinded study

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A. Lay Abstract

a. Study Purpose

A wide range of medications has been used to prevent migraines in patients who suffer debilitating attacks > 3 times each month and who have responded poorly to acute migraine treatments. The mechanisms of these preventions are not well understood, despite exhaustive study of the migraine event. A number of physiologic changes have been observed across patient populations:

1) A progressive wave of vasoconstriction travels across the surface of the cerebral cortex, reducing blood flow 25-30%. The resulting pain, however, does not localize to the areas of vasoconstriction, and there is no convincing relationship between pain and reduced blood flow. Successful treatment has been achieved with vasodilatory medications, mainly O-blockers and calcium channel blockers.
2) Serotonin is a hormone and neurotransmitter that regulates many neuromuscular functions. Altered levels are implicated in depression, -and platelet levels (platelets are where most of the body's serotonin is stored) are depleted in migraine attacks. Drugs that deplete serotonin levels have caused migraine attacks in some patients. Successful prophylaxis and treatment of migraines have been achieved by use of drugs that increase levels of serotonin, as well as by drugs that are serotonin agonists. But migraines have also been treated by medications that antagonize serotonin receptors. The connection between migraine pain and serotonin is unclear.
3) Sterile inflammatory response: the trigeminal nucleus in the brainstem is the painprocessing center for head and face. Theoretically, a migraine attack, because of some uncharacterized stimulus, releases neuropeptides that act on blood vessels, causing constriction and/or dilatation. There is also a presumed sterile inflammatory response, with activation of trigeminal nociceptors, with resulting pain. NSAID's and drugs that inhibit inflammatory response have successfully treated migraines.

The success in treating migraines with medications that have such varied physiologic targets suggests that a "migraine" may describe more that one kind of physiologic event; alternately, a migraine may be a single but multistep process that can be blocked any of a number of different stages.

This study will evaluate patients who have failed treatment with one of the standard prophylactic drugs, amitriptyline, that most likely alters serum serotonin levels. Subjects will be treated with riboflavin, a drug found incidentally to reduce migraine frequency and severity; subsequent controlled studies showed riboflavin to have efficacy equal to that of standard prophylactic treatments.

b. Study subjects, recruitment, and procedures

The study will be double-blinded, randomized, placebo-controlled. 172 subjects randomized to a treatment and a placebo arm of 86 patients will be treated for a total of 4 months. Recruitment will take place at the neurology headache clinic. Patients will keep a headache calendar and journal, and return monthly to the clinic for data collection.

B. Introduction

a. Background

Current theories of migraine pathophysiology are still contested, but the following areas of observed physiologic change are perhaps the most consistently cited and form the basis of many migraine treatments.

1) Vasomotor dysfunction: migraine patients, especially those with "classic" auras, have at baseline a "hyperexcitable" cortex.[1] During migraine attacks a progressive wave of vasoconstriction begins at visual cortex (producing the aura) and travels anteriorly, but does not track along the path of cerebral arteries. Vasoconstriction reduces regional blood flow 25-30%. Focal areas of ischemia do not correspond to focal pain SYMPtOMS.[2] Vasoactive medications, 0-blockers and calcium channel blockers, have been among the first line treatments.

2) Serotonin: serum serotonin levels rise during migraine "aura" phase, and platelets (the main storage reservoir of serotonin) have reduced serotonin levels at the onset of migraine HA pain. This complemented the observation that migraine attacks (in some subjects) could be triggered by medications (e.g. reserpine) that deplete serotonin, and that some migraine attacks could be relieved by intravenous injections of 5-Hr. 5-11T agonists, (sumatriptan) and TCA's with proposed 5-HT activity (arnitriptyline) are effective agents in treatment and prophlyaxis. It is noteworthy that ergotamines, 5-HT antagonists and vasoconstrictors, are also effective treatments.

3) Trigeminal Vascular System: an unknown stimulus to the trigerninal nucleus caudalis in the medulla, the pain processing center for head and face, releases substance P and other vasoactive neuropeptides.[3] There is a presumed sterile inflammatory endovascular response, with activation of trigeminal nociceptors.

The broad range of agents that have successfully prevented and treated migraines, many of which were found incidentally, somewhat complicates these hypothetical etiologies. Standard prophylactic treatments-- P-blockers, calcium channel blockers, and 5-HT agonists --have rational mechanisms for their effects in light of the above; valproic acid, gabapentin, and biofeedback, have equal efficacy, but less clear explanations for why they provide relief. Recent trials have tested ACEI [4] magnesium,[5] nitric oxide synthase inhibitor, [6] and cyclandelate [7] both against placebo and against prophylactic mainstays.

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[1] Aurora SK. Ahmad BK. Welch KM. Bhardhwaj P. Ramadan NM. Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Neurology. 50(4):1111-4, 1998 April.

[2] De Benedittis G. Ferrari Da Passano C. Granata G. Lorenzetti A. CBF changes during headache-free periods and spontaneous/induced attacks in migraine with and without aura: a TCD and SPECT comparison study. Journal of Neurosurgical Sciences. 43(2):141-6; discussion 146-7, 1999 June. See also Cutrer FM. O'Donnell A. Sanchez del Rio M. Functional neuroimaging: enhanced understanding of migraine pathophysiology. [Neurology. 55(9 Suppl 2):S36-45, 2000; and Bednarczyk EM. Remler B. Weikart C. Nelson AD. Reed RC. Global cerebral blood flow, blood volume, and oxygen metabolism in patients with migraine headache. Neurology. 50(6):1736-40, 1998 June; Andersson JL. Muhr C. Li1ja A. Valind S. Lundberg PO. Langstrom B. Regional cerebral blood flow and oxygen metabolism during migraine with and without aura. Cephalalgia. 17(5):570-9, 1997 August

[3] Munno 1. Centonze V. Marinaro M. Bassi A. Lacedra G. Causarano V. Nardelli P. Cassiano MA. Albano 0. Cytokines and migraine: increase of IL-5 and EL-4 plasma levels. Headache. 38(6):465-7, 1998 Jun.

[4] Schrader H. Stovner NJ. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomized, placebo-controlled, crossover study. BMJ 322(7277):19-22, 2001 January 6.

[5] Pfaffenrath V. Wessely P. Meyer C. Isler HR. Evers S. Grotemeyer KH. Taneri Z. Soyka D. Gobel H. Fischer M. Magnesium in the prophylaxis of migraine--a double-blind placebo-controlled study. Cephalalgia. 16(6):436-40,1996 October

[6] Lassen LH. Ashina M. Christiansen 1. Ulrich V. Grover R. Donaldson J. Olesen J. Nitric oxide synthase inhibition: a new principle in the treatment of migraine attacks. Cephalalgia. 18(l):27-32, 1998 Jan. See also Gallai V. Floridi A. Mazzotta G. Codini M. Tognoloni M. Vulcano MR. Sartori M. Russo S. Alberti A. Michele F. Sarchielli P. L-arginine/nitric oxide pathway activation in platelets of migraine patients with and without aura. Acta Neurologica Scandinavica. 94(2):151-60, 1996 August.

Riboflavin (vitamin B2) is among the recent prophylactic treatments discovered incidentally. Patients with MELAS syndrome [mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes] have frequent and severe migraine-like headaches. fligh-dose riboflavin was given to patients with MELAS and with other mitochondrial myopathies, with reported improvement in clinical and biochemical outcomes; also reported were improvements in migraine symptoms over months of treatment. Subclinical mitochondrial DNA defects have been implicated in at least one study of migraine patients,[8] though have not been isolated in others. The specific physiologic effect of high dose riboflavin is speculative.[9]

b. Study Purpose and Rationale

Many studies compare, head-to-head, the efficacy of standard migraine prophylactic treatments (e.g. amitriptyline and P-blockers, fluoxetine and 0-blockers),[10] and generally conclude equivalence: between 55 and 60% of trial subjects typically report > 50% reduction in symptoms, a much better result than with placebo. But is a "migraine," despite characteristic features across patient populations, likely to be a single entity if successful prophylaxis can be achieved with so many different classes of drugs with such varied physiologic targets? Characteristic migraine pain may comprise a set of symptoms that look the same but that actually are produced by different physiologic events. Alternately, a migraine headache may be a single disease entity in each patient, but multifactorial or a multistep process, and therefore respond to more than one intervention. Are we treating different headaches with our five or six therapeutic classes, or are we intervening at five or six different steps in the pathogenesis of one disease?

Few studies, including crossover studies,[11] have systematically evaluated patients who fail one of the mainstay therapies and have asked what distinguishes these patients from the successful treatment pool. [12] How would they fare as a group if treated with another therapy from a wholly different drug class? A study of the patients who fail one standard treatment but respond to another may suggest distinct etiologies of headache, and form the basis for more systematic approach to prophylactic treatment.

The present investigation will identify and collect a class of patients who have failed a trial of amitriptyline, and treat them with high-dose riboflavin. The efficacy of riboflavin has not been directly tested against standard prophylaxis in any published study, but in placebo trials it has the same response rate (> 55% of patients with > 50% reduction in symptoms) as amitriptyline, P-blockers, as well as gabapentin, and depakote. Riboflavin is the ideal drug for the study because unlike, say, TCA's and 5-HT agonists, it shares no established or even hypothetical physiologic target with amytryptiline (or with any other prophylactic drug). Indeed, the only comparative study of riboflavin tests its effect on auditory

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[7] Siniatchkin M. Gerber WD. Vein A. Clinical efficacy and central mechanisms of cyclandelate in migraine: a double-blind placebo-controlled study. Functional Neurology. 13(l):47-56, 1998 Jan-Mar

[8] Ojaimi J. Katsabanis S. Bower S. Quigley A. Byrne E. Mitochondrial DNA in stroke and migraine with aura. Ojaimi J. Katsabanis S. Bower S. Quigley A. Byrne E. Mitochondrial DNA in stroke and migraine with aura. Cerebrovascular Diseases. 8(2):102-6, 1998 March-April.

[9] Riboflavin is precursor to two biologically active flavins that bind to flavoenzymes and catalyze various redox reactions. High doses of riboflavin are thought to override mitochondrial energy defects and to increase mitochondrial energy efficiency. Klopstock T. Mitochondrial DNA in migraine with aura. Neurology 46(6):1735-8, 1996 June. See also Neurology 1994;44;2153-2158.

[10] Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Archives of Neurology. 54(9):1141-5, 1997 September.

[11] In 11 cross-over studies surveyed for this project, subjects who failed treatment were not evaluated presumably because the trials were powered and designed to evaluate efficacy, or because the number of failures was too small to provide statistical significance.

[12] Valproate and P-blockers are exceptions: see Ghose K. Niven B. Prophylactic sodium valproate therapy in patients with drug-resistant migraine. Methods & Findings in Experimental & Clinical Pharmacology. 20(4):353-9, 1998 May. See also Whitmarsh TE. When conventional treatment is not enough: a case of migraine without aura responding to homeopathy. Journal of Alternative & Complementary Medicine. 3(2):159-62,1997 Summer.

evoked cortical potentials against that of b-blockers. [13] It concludes that the two drugs act on different physiologic pathways, despite similar efficacy. Riboflavin, furthermore, is an important addition to the migraine prophylaxis arsenal because it is relatively cheap ($8/month vs. $25/month for amitriptyline), and because it has potentially fewer side-effects than the other mainstays (e.g. P-blockers, amitriptyline, valproate). One also suspects that it will have higher patient compliance because it is perceived as a "vitamin" rather than a "medication."

c. Literature Review Riboflavin

Based on the findings in MELAS syndrome treatment, a 1994 open pilot study enrolled 25 patients to evaluate high dose riboflavin as prophylaxis for migraines. [14] The pilot study results were promising (68% reduction in severity index vs. 30% placebo) and led to a larger double-blinded randomized placebo-controlled study. In the larger study 59% of patients given 400 mg PO qd of riboflavin showed a significant reduction in attack frequency (primary outcome) and 56% showed a reduction in headache index (= days of headache/month + severity; secondary outcome) vs. placebo.[15]

i. Amitriptyline

In a double-blinded controlled trial of amitriptyline in migraine prophylaxis, 100 patients received placebo for a four-week baseline period and then were randomized to therapy with amitriptyline (47 subjects) or placebo (53 subjects) for four to eight weeks. Comparing the first and second four-week periods for each patient, the conditions of 55% of amitriptyline subjects as opposed to 34.0% of placebo subjects were greater than or equal to 50% improved and the difference between amitriptyline and placebo response rates was significant ($P < 0.05$). The effect was independent of, antidepressant activity. No difference was found in the treatment response in those with and without aura.

ii. Hypothesis

Riboflavin will reduce migraine frequency and severity in patients who have failed amitriptyline prophylaxis.

d. Methods

i. Study Design

- Subjects will be identified and recruited through the Department of Neurology HA clinic. Approximately 40% of migraine patients can be expected to fail prophylactic treatment with amitriptyline, so enrolling 86 patients for a riboflavin trial is plausible.
- The study will be a placebo-controlled, double-blinded, prospective analysis. Patients will be randomized to two arms, each with an equal number of subjects.
- The study will begin with a one-month lead-in period with symptomatic but no prophylactic medication. Primary and secondary endpoints will be evaluated at the end of the lead-in period, and then at 2, 3, 4 months.
- At the end of the one-month lead-in ann, the treatment arm will receive riboflavin 400 mg PO qd. This was the dose used in the original MELAS studies, and was effective with low toxity. The same dose was used in the pilot study and in the subsequent randomized placebo-controlled study with

[13] Sandor PS. Afra J. Ambrosini A. Schoenen J. Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials. Headache. 40(l):30-5, 2000 January.

[14] High-dose riboflavin as a prophylactic treatment of migraine: results of an open pilot study. Shoenen J. Lenaerts M, Bastings E. Cephalalgia 1994;14;328-329

[15] Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. Schoenen J. Jacquy J. Neurology 50 1998 466-70.

established efficacy in migraine prophylaxis. Placebo arm will receive standard placebo prepared to be indistinguishable from the treatment capsule.

ii. Outcomes

- Primary outcome will be the frequency of migraine attacks. In previous studies statistical significance vs. placebo was achieved in the third month of treatment with riboflavin.
- Secondary outcome: duration and severity of attacks in the third and fourth month of treatment, a calculated headache index, and number of medications for acute migraine required.

iii. Data Collection

- Patients will record the number of migraine attacks per week in a headache calendar. Frequency in month 4 will be compared to frequency in month 1 (no prophylaxis).
- A headache journal will be used to record duration with the date and time of HA starting and stopping; number of headache days; severity of HA; and acute medications used. Duration will be measured in hours. Severity will be measured on a five-point scale. Amounts and names of acute medications will be recorded. Secondary outcomes in month 4 will be compared to secondary outcomes in month 1 (no prophylaxis).
- Patients will have monthly clinic appointments to collect calendar and journal results.
- A headache index will be calculated from number of headache days/month plus severity of each headache.
- Compliance will be determined by counting returned capsules at each monthly visit.

e. Statistical Analysis

Sample size

The study predicts that those who have failed amitriptyline will respond to riboflavin and to placebo according to published data.

The effect of treatment on the frequency of HA in each group will be evaluated by chisquare. To achieve 80% power and p-value of < 0.05, 81 subjects will need to be enrolled.

Previous studies on amitriptyline and riboflavin report about 5% dropout rate; therefore an extra 5 patients (for a total of 86 subjects) will be added to each arm.

P riboflavin group, 56% of patients with > 50% improvement in symptoms. Q placebo, 34% of patients with more than 50% improvement in symptoms.

N 8 (0.56 x 0.34) + (0.44 x 0.66)/ 0.22 2 +2/0.22+2 N 81 patients in each an-n

f. Subject Selection

- Subjects must meet International Headache Society 1988 criteria for migraine with or without aura.

Migraine without aura: IHS 1988 Diagnostic Criteria

=* Idiopathic, with other causes ruled out.

=> At least 5 attacks with the following features

- Lasting 4-72 hours
- Two of the following characteristics
- Unilateral
- Pulsating
- Severity that inhibits or prohibits daily activity
- Aggravated by routing physical activity

At least one of the following Nausea and/or vomiting Photophobia or phonophobia

Migraine with Aura: HIS 1988 Diagnostic Criteria

Idiopathic, with other causes ruled out.

At least two attacks with at least 3 of the following 4 characteristics
- One or more aura symptoms At least one aura symptom develops gradually over more than 4 minutes or 2 or more occur in succession.
- Aura symptoms last less than 60 minutes
- Headache begins before, simultaneous with, or after aura, but with any free interval less than 60 minutes.

- Subjects must meet criteria for prophylaxis

  The current standard of care consists of symptomatic treatment for patients with fewer than 3 episodes per month. Prophylaxis is reserved for patients with > 3 totally or partially disabling attacks/month that do not respond to symptomatic treatment.
- Subjects must have had responded no better than placebo group for reduction in
- HA frequency and index after a 3 month trial of arnitriptyline.
- Age 18-65
- Subjects must have > 2 months of only symptomatic treatment prior to study
- Subjects must be willing to stay in the trial for 4 months.

g. Exclusion Criteria
- History of prophylactic treatment with riboflavin
- More than 6 migraine episodes/month.
- Menstrual migraines: criteria are not well standardized, and there are likely to be significant differences in pathophysiology.

h. Safety

Patients will have a contact phone number to call for any adverse outcomes during the trial. No serious side effects have been reported in previous trials of riboflavin, chiefly mild diarrhea, and no extraordinary measures for medical treatment will likely be needed.

i. Potential Risks and Benefits

No significant risks from taking riboflavin have been reported in any of the trials. 1-2% of subjects complained of mild diarrhea by the third month of treatment. Symptomatic treatment of diarrhea will be allowed within the study.

Benefits may be significant for patients who are successfully treated with riboflavin: they will have a low-cost, low side-effect treatment for a debilitating illness.

j. Costs and Compensations
- Patients will not bear any additional cost as a result of participating in the study. They will receive no compensation.