Hypothesized treatment for migraines using low doses of tryptophan, niacin, calcium, caffeine, and acetylsalicylic acid

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Summary The author hypothesized that existing agents known to influence serotonin blood level, vascular tone, and inflammatory reactions might terminate migraines. The author presented the rationale for using five different agents therapeutically and avoiding two other agents during a migraine. The proposed treatment is to use low doses of tryptophan, niacin, calcium, caffeine, and acetylsalicylic acid (ASA) soon after migraine symptoms are noticed and to avoid during a migraine high-potassium food and magnesium supplements. Preliminary results from 12 migraine patients indicated that 9 of 12 (75%) had significant benefit from this approach. Using these five agents together is a novel combination and a new idea for treating migraines. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Migraine attacks can have debilitating effects that last many hours or a few days. Most affected individuals have a family history of migraines (14), and more women have migraines than men (about 18% vs. 6%) (17). Migraines have been classified according to the appearance of neurological symptoms in relation to the headache (14). Various treatments are available, but some risk a vicious cycle of rebound headaches or serious adverse effects (4,8).

THE HYPOTHESIS

Physiologic events occurring during migraine attacks include but are not limited to the following: (a) falling blood levels of serotonin (1,2); (b) vascular dilatation (6,7); (c), inflammatory response in intracranial structures (18), and in some but not all migraines; (d) an increasing release of histamine still rising 24 hours after onset (1). Histamine is a powerful vasodilator (12). Migraine medications that contain substances that enhance serotonergic functioning might be expected to alleviate sequelae caused by falling serotonin blood levels. Migraine medications that contain substances that affect blood vessel tone, such as vasoconstriction, can be expected to alleviate the migraine feature of vasodilatation and/or irregularities of vascular tone. Some migraine medications individually influence only 1 or 2 of the first 3 physiologic features listed above. Some medications influence all 3 physiologic features, such as sumatriptan/Imitrex (8). Unfortunately, sumatriptan causes rebound headaches in about 40% of migraine patients and, in rare cases, causes serious cardiac effects (8).

The author hypothesized that agents known to influence these 3 physiologic features – falling blood level of serotonin, vascular dilatation, and inflammatory response – might be useful in treating migraines. The rationale for this hypothesis follows.

1. To reverse a falling blood level of serotonin, a low dose of the serotonin precursor L-tryptophan can be used (9).
A 1 gram dose of tryptophan would be the upper limit per intake because single doses higher than 1 gram approach a ‘loading dose’ of tryptophan. Loading doses activate the enzyme tryptophan pyrrolase which routes tryptophan down the kynurenine pathway away from conversion to serotonin (9). Loading doses of tryptophan such as 2 grams per intake actually lower serotonin levels (3,9).

2. To facilitate tryptophan’s conversion to serotonin instead of conversion to kynurenines and nicotinic acid, niacin (also called nicotinic acid) is effective because it is a feedback regulator for the kynurenine pathway of tryptophan metabolism, and it reduces the amount of tryptophan converted to kynurenines (15). Niacin can cause flushing of the skin which is harmless (19).

3. To restore serotonin’s influence in regulating blood vessel tone, reversing the falling blood level of serotonin is required; acetylsalicylic acid can displace tryptophan from binding proteins, thereby freeing up more tryptophan for serotonin synthesis (5, p 61). Using acetylsalicylic acid at the same time as niacin helps reduce the flushing response (21).

4. To reduce vasodilatation, agents with vasoconstricting properties such as caffeine (16) or calcium (12, p 192) are potentially useful.

5. To reduce the inflammatory response, a prostaglandin blocker such as acetylsalicylic acid (ASA) can be useful (4). (The prostaglandin blocker naproxen/Anaprox could be considered as an alternative anti-inflammatory agent (4).)

6. To reduce further vasodilatation, one can avoid during a migraine the consumption of food and drink that are high in potassium, a mineral that causes vasodilatation (12, p 192).

7. Given that the mineral magnesium has vasodilating effects (12, p 192), one can also avoid taking magnesium supplements during a migraine.

In brief, the author hypothesized that taking low doses of tryptophan, niacin, calcium, caffeine, and ASA together would be useful in treating migraines.

The 5 agents being proposed have been in use with humans for decades or much longer, but there are no reports of the 5 being combined therapeutically. Numerous migraine medications mimic the effects of serotonin (11). ASA alone has been used for migraines (11) and it can block plasma extravasation which is associated with migraine pain (10). Another anti-inflammatory drug, naproxen, has also been used alone to treat migraines (20). ASA and/or caffeine are common co-agents in currently available migraine medication. Niacin alone has been mentioned anecdotally for migraines (13, p 60). This is the first report proposing a combination of tryptophan-niacin-calcium-caffeine-ASA for treating migraines.

Vasodilatation can be caused by histamine (12). Research by Anthony and Lance (1) indicated that some, not all, migraines involve a strong release of histamine which is still increasing 24 hours after the onset of the migraine. Therefore, the author reasoned that in episodes where the 5-component approach had little or no effect, it could be because that particular migraine involved a strong histamine release and an anti-histamine would be therapeutic. The author reasoned that a non-sedating histamine type 1 blocker might be useful as an add-on treatment if the other 5 components were ineffective.

**CONDITIONS LIKELY TO RENDER THE PROPOSED TREATMENT INEFFECTIVE**

1. Abnormally low serum iron (ferritin) is a condition likely to render this treatment ineffective. Iron is a co-factor in the enzymatic conversion of tryptophan to the serotonin precursor 5-hydroxytryptophan, so insufficient iron would mean less tryptophan can be routed toward conversion to serotonin. Increasing serotonin is a crucial part of this treatment.

2. Delaying taking the treatment by 1–2 hours after noticing migraine symptoms would likely diminish its efficacy.

3. Patients who frequently use medication that causes medication-induced rebound migraines or withdrawal-induced migraines would likely not benefit from this approach. The modest effects of low doses of components found in common foods (a vitamin, mineral, amino acid, caffeine) plus a standard dose of ASA would be comparatively weak against powerful addictive agents like codeine or barbiturates which can cause withdrawal-induced migraines. Therefore, this ‘relatively benign’ approach is unlikely to be effective in people with frequent medication-induced migraines related to frequent use of certain migraine medications.

**AN APPLICATION OF THE HYPOTHESIS**

As an illustration of the application of this hypothesis, results are presented on 8 women and 4 men who tried this approach for 10 migraines. They were kept naive about the main components, but their physicians were aware of all treatment agents. The known safety of the components, lack of serious side effects especially at low doses, and ethical considerations were discussed with all involved. Consent was obtained from participants and their physicians.

The hypothesized treatment involved the following steps. Step 1 was to take the 5 components soon after...
migraine symptoms were noticed. Low doses were used: 500 mg L-tryptophan; 100 mg niacin; 500 mg calcium carbonate; 64 mg caffeine; 650 mg ASA. (Two tablets of Anacin contain 64 mg caffeine and 650 mg ASA (4). A version with 1000 mg L-tryptophan was also tried, but it did not show a reliable advantage over the 500 mg version.) This can be taken with water or with 1/2 cup of milk to protect the stomach. Step 2 was to avoid consuming high-potassium food/drink (e.g., bananas, oranges, dried fruit, nuts, tomato juice) and magnesium supplements during a migraine. Step 3 (if needed) was to take a ‘repeat dose’ after 4 hours only if benefit had been obtained but later the migraine symptoms returned after about 4 hours. Step 4 (optional) was to try a non-sedating anti-histamine (60 mg terfenadine/Seldane) only if the 5-component approach yielded little or no benefit within 90 minutes. (Terfenadine should not be used when taking other medications such as certain antibiotics, antifungal drugs, and grapefruit juice (4).) For their own comfort, participants were to avoid hot fluids and baths for 1 hour after taking the treatment to lessen the minor discomfort from flushing caused by niacin.

Table 1 shows that 9 of 12 (75%) adults were responders to the 5-component approach, obtaining 90–100% relief in about an hour for most or all migraines. With physician consent, some responders continued to use this approach for over 2 years, and no one had rebound headaches or adverse events. (Additional details about the preliminary study are available from the author.) Three of the 12 were nonresponders. One often delayed taking the treatment and she got poor results. Another nonresponder had migraines every second day corresponding to his taking a codeine-barbiturate medication (Fiorinal-C) every other day for years. The third nonresponder had very atypical migraine symptoms and he had no relatives with migraines, whereas all but one of the other participants had a family history of migraines. When the 5 components gave little or no relief, Step 4 was effective in 3 of the 6 people who tried it. These preliminary findings illustrate a practical application of this hypothesis.

SAFETY CONSIDERATIONS

Safety is always a primary consideration. The pharmacological safety of ASA-caffeine at those doses (Anacin) is well established. The safety of vitamin B3/niacin, calcium carbonate, and L-tryptophan individually at those low doses has also been established as these agents are available over the counter or by prescription (L-tryptophan). The proposed treatment is a ‘novel combination’ of 5 components whose safety individually has previously been established. The preliminary evidence indicated no safety concerns and no rebound headaches.

CONCLUSION

The hypothesized treatment is to use low doses of tryptophan, niacin, calcium, caffeine, and ASA soon after migraine symptoms are noticed and to avoid during a migraine high-potassium food and magnesium supplements. The author reasoned that this approach is unlikely to be effective in patients with low serum iron or patients who take powerful barbiturate, codeine, or morphine medication every few days for migraine relief.

The proposed migraine treatment may have certain advantages. It would be relatively inexpensive, which would make it more accessible to low-income patients. It may have a low risk of serious side effects because the safety of ASA-caffeine together and low doses of niacin, calcium, and tryptophan used individually has previously been established. It may have the advantage of not causing rebound headaches, as the preliminary evidence suggests.

Research investigations such as double-blind placebo-controlled studies are the scientifically acceptable way to
test this kind of hypothesis. Preliminary results from a small number of patients indicated that many of them obtained significant benefit from this approach. This hypothesized treatment for migraines may prove to be an approach worth considering by migraine patients and their physicians.

REFERENCES