Effectiveness of riboflavin in pediatric migraine prevention

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Abstract

Question The rate of migraine diagnosed among children is increasing. Is riboflavin, an alternative to traditional pharmacologic agents, effective and safe for prevention of migraine in children?

Answer Because migraine is a very common condition in childhood and adolescence, often contributing to substantial burden of illness, there is increased interest in alternatives to traditional pharmacologic prevention. The expectation is that over-the-counter alternative medication will be less toxic, better tolerated, and have fewer side effects. A few studies in adults show that riboflavin (vitamin B2) might decrease frequency of migraine headaches. It has become common practice to recommend that children try riboflavin to prevent migraine; however, research on riboflavin use in children is inconclusive.

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More than 11% of children 5 to 15 years old and 28% of adolescents 15 to 19 years old suffer from migraine, and most of them will seek medical consultation at least once during childhood.[1] The prevalence of migraine increases with age; it is slightly higher in boys before puberty and 1.5 times more frequent in girls in adolescence.[2] Childhood migraine might result in increased school absences, compromised academic performance, and decreased participation in extracurricular activities.

Diagnosis of migraine in childhood is challenging and the condition can be classified with or without aura. The *International Classification of Headache Disorders*, 3rd edition, is the current criterion standard for diagnosis.[3] *Migraine* is defined as a recurrent headache disorder with at least 5 attacks that last 4 to 72 hours with at least 2 of the following features: unilaterality, throbbing sensation, moderate to severe intensity, or aggravation by physical activity.[3] Photophobia and phonophobia, as well as nausea with or without vomiting, are also among the diagnostic criteria.[3]

Slight modifications have been made to the criteria for pediatric populations: migraines might be bilateral, they can be shorter in duration, and some autonomic features such as photophobia and phonophobia can be inferred from the child's behaviour. The younger the child, the less characteristic the symptoms; however, by adolescence, presentation should meet adult-based criteria.[3] As in adults, comorbidities such as mood, anxiety, sleep, and eating disorders might occur.[4]

Treating migraine

Acetaminophen, ibuprofen, ergot alkaloids, and intranasal triptans are frequently used to treat acute migraine attacks.[5] To abort the migraine soon after it begins, 15 mg/kg of acetaminophen or 10 mg/kg of ibuprofen have been shown to be equally effective.[6] Of the triptans (5-hydroxytryptamine agonists), sumatriptan nasal spray (5 and 20 mg) has been shown to be most effective for relieving adolescent headaches.[5] Delayed gastric emptying and nausea can accompany migraines, but there are limited studies to support treatment with antiemetics.

Many patients find keeping a headache journal helpful to try and establish a pattern and determine provoking factors.[5] Long-term management of migraine relies on lifestyle changes (eg, adopting sleep hygiene, exercising, avoiding triggers such as caffeine, eating regular meals, maintaining hydration, and managing stress), as well as early treatment to prevent chronicity.[5]

Migraine prevention

With frequent or intense migraines, preventive measures might be necessary to improve quality of life and avoid overuse of medications such as acetaminophen and ibuprofen.[7] Topiramate (100 mg/d) has been shown to be effective in decreasing the frequency of pediatric migraine attacks, but study results with amitriptyline, propranolol, and flunarizine have been contradictory or inconclusive.[4] Other preventive options include cyproheptadine, gabapentin, pregabalin, valproate, amitriptyline, nortriptyline, and verapamil, each with their own efficacies and side effects.[4]

Complementary therapies

With limited effectiveness of current preventive therapies, the use of complementary and alternative medicine has been increasing in headache management.[8] Mitochondrial dysfunction has been postulated to play a role in migraine pathophysiology.[9] Riboflavin is a precursor in the mitochondrial electron transport chain and a cofactor in the Krebs cycle, and has been used in various mitochondrial diseases—hence the hypothesis that increasing riboflavin availability might improve brain mitochondrial function and result in migraine prevention.[10]

Riboflavin in adults

Two randomized controlled trials with high-dose riboflavin (400 mg/d) had conflicting results.[11,12] When riboflavin was compared with placebo in 55 adult patients, riboflavin reduced the frequency of migraine attacks ($P=.005$) and the number of headache days ($P=.012$).[11] When riboflavin was given with magnesium and feverfew to 120 patients (from 2 different suburban hospitals) who were between 18 and 65 years of age and who had had migraine for at least 1 year, there was no difference between the experimental group and the placebo group in reduction of migraines ($P=.87$) or reduction of migraine days ($P=.63$).[12] Of interest, 60% of patients dropped out of the study and there was a very high placebo response, possibly related to the fact that the placebo contained 25 mg of riboflavin.[12]

Riboflavin in children

Evidence for use of riboflavin in children is very limited. One retrospective study reported decreased migraine frequency in younger patients and decreased intensity in male patients.[13] Among 41 Italian children (8 to 18 years of age) who received either 200 or 400 mg/d of riboflavin for 3, 4, or 6 months, riboflavin reduced migraine frequency (21.7 [SD 13.7] vs 13.2 [SD 11.8]; $P<.01$), particularly in children younger than 12 years old, and decreased intensity (2 [SD 0.5] vs 1.6 [SD 0.8]; $P<.01$) predominantly in boys ($P<.05$).[13] Most (77%) patients reported that while taking riboflavin, their regular migraine-relieving medications (primarily nonsteroidal anti-inflammatory drugs, acetaminophen, and triptans) were more effective. The long duration of treatment and the follow-up period were considered the strengths of the study, but the retrospective design and small sample size limited the generalizability of the results.

Two randomized double-blind placebo-controlled trials reported no difference in reduction of migraines with use of riboflavin.[14,15] Among 48 Australian children (5 to 15 years old) who were treated daily for 12 weeks with 200 mg of riboflavin, there was no significant difference in the number of migraine attacks over 4 weeks when compared with those receiving placebo.[14] Severity of migraines (self-rating) was also similar between groups.

In a 2010 randomized double-blind placebo-controlled trial, 42 children from the Netherlands who were 6 to 13 years old received 50 mg/d of riboflavin for 16 weeks, followed by a 4-week break and 16 weeks of placebo or vice versa.[15] The investigators found no significant difference in the mean frequency ($P=.44$), duration ($P=.15$), or severity ($P=.18$) of migraines between groups.[15] Interestingly, there was a significant reduction in tension headaches ($P<.04$) reported by those in the riboflavin group.

Safety considerations of riboflavin

Riboflavin was well tolerated in all studies and there were no reports of serious toxicity.[13] Riboflavin absorption has been shown to reach saturation at 30 to 50 mg and the half-life is approximately 1 to 2 hours.[16] Dosing of 100 to 400 mg/d of riboflavin in the pediatric studies has been based on previous adult studies and doses used in mitochondrial diseases.[10,13] This is approximately 100-fold higher than normal dietary intake.[13] In both adult and pediatric riboflavin studies, there have been only limited reports of diarrhea, orange-coloured urine, and vomiting.

Conclusion

Despite being safe, well tolerated, and inexpensive, riboflavin does not show effectiveness in preventing migraine in children, and is not currently recommended for that indication. There seem to be sex and age differences in response to riboflavin,[13] possibly owing to differences in pharmacokinetics and riboflavin serum levels.[17] Research with a larger sample size is needed in order to control for placebo response. Administering riboflavin with food or in multiple daily dosing was previously suggested.[17] Pharmacogenetic studies are ongoing, and there might be certain haplotypes of mitochondria that respond to riboflavin more readily.[18]

If a provider decides that the child should try riboflavin, the recommended dose should be 50 to 400 mg/d for a minimum of 4 months. If there is no improvement, riboflavin should be discontinued and pharmacologic prevention should be considered. Providers should ensure that children continue to receive appropriate migraine treatment, suggest the use of a headache journal, and advise patients and families about lifestyle changes.

Competing interests
None declared

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References

1. Split W, Neuman W. Epidemiology of migraine among students from randomly selected secondary schools in Lodz. *Headache* 1999;39(7):494-501.

2. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. *Dev Med Child Neurol* 2010;52(12):1088–97. Epub 2010 Sep 28.
3. International Headache Society. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013;33(9):629-808.
4. Jacobs H, Gladstein J. Pediatric headache: a clinical review. *Headache* 2012;52(3):333-9. Epub 2012 Jan 30. Erratum in: *Headache* 2012;52(3):527.
5. Lewis DW, Yonker M, Winner P, Sowell M. The treatment of pediatric migraine. *Pediatr Ann* 2005;34(6):448-60.
6. Hämäläinen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. *Neurology* 1997;48(1):103-7.
7. Gaul C, Eismann R, Schmidt T, May A, Leinisch E, Wieser T, et al. Use of complementary and alternative medicine in patients suffering from primary headache disorders. *Cephalalgia* 2009;29(10):1069-78. Epub 2009 Apr 2.
8. Schetzek S, Heinen F, Kruse S, Borggraefe I, Bonfert M, Gaul C, et al. Headache in children: update on complementary treatments. *Neuropediatrics* 2013;44(1):25-33. Epub 2013 Jan 11.
9. Montagna P, Cortelli P, Monari L, Pierangeli G, Parchi P, Lodi R, et al. 31P-magnetic resonance spectroscopy in migraine without aura. *Neurology* 1994;44(4):666-9.
10. Sparaco M, Feleppa M, Lipton RB, Rapoport AM, Bigal ME. Mitochondrial dysfunction and migraine: evidence and hypotheses. *Cephalalgia* 2006;26(4):361-72.
11. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50(2):466-70.
12. Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004;44(9):885-90.
13. Condò M, Posar A, Arbizzani A, Parmeggiani A. Riboflavin prophylaxis in pediatric and adolescent migraine. *J Headache Pain* 2009;10(5):361-5. Epub 2009 Aug 1.
14. MacLennan SC, Wade FM, Forrest KM, Ratanayake PD, Fagan E, Antony J. High-dose riboflavin for migraine prophylaxis in children: a double-blind, randomized, placebo-controlled trial. *J Child Neurol* 2008;23(11):1300-4.
15. Bruijn J, Duivenvoorden H, Passchier J, Locher H, Dijkstra N, Arts WF. Medium-dose riboflavin as a prophylactic agent in children with migraine: a preliminary placebo-controlled, randomised, double-blind, crossover trial. *Cephalalgia* 2010;30(12):1426-34. Epub 2010 Mar 26.
16. Zempleni J, Galloway JR, McCormick BD. Pharmacokinetics of orally and intravenously administered riboflavin in healthy humans. *Am J Clin Nutr* 1996;63(1):54-66.
17. O'Brien HL, Hershey AD. Vitamins and paediatric migraine: riboflavin as a preventative medication. *Cephalalgia* 2010;30(12):1417-8. Epub 2010 Jul 27.
18. Di Lorenzo C, Pierelli F, Coppola G, Grieco GS, Rengo C, Ciccolella M, et al. Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. *Neurology* 2009;72(18):1588-94.

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