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Novel Therapy Series

Beta Blocker Eye Drops For Acute Migraines

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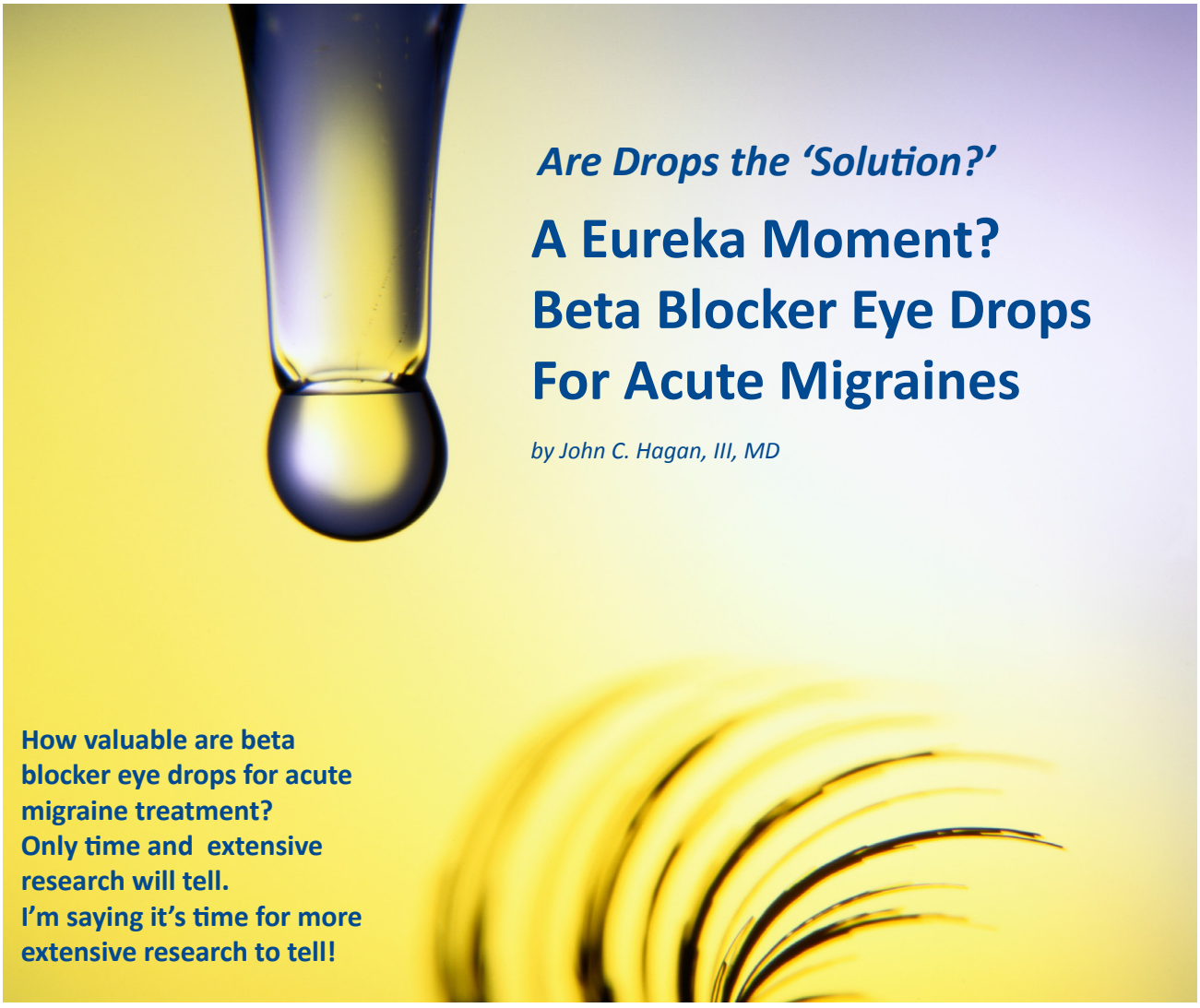

Are Drops the 'Solution?'

A Eureka Moment? Beta Blocker Eye Drops For Acute Migraines

by John C. Hagan, III, MD

How valuable are beta blocker eye drops for acute migraine treatment? Only time and extensive research will tell. I'm saying it's time for more extensive research to tell!

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This issue of *Missouri Medicine* features a novel therapy for acute migraines using inexpensive generic (e.g. $4 for 5 ml. at Walmart), widely-available, relatively safe beta blocker eye drops. The authors are Carl V. Migliazzo, MD, and myself. (See page 283). This is the largest number of successful cases to date; we summarize the previous reports and meager literature.

The first published beta blocker eye drop treatment of headache was in 1980. The author was enthusiastic and called for additional research. So have subsequent papers. Thirty-four years later the promising research has still not been conducted.

Is our enthusiasm warranted? Do beta blocker eye drops deserve to be intensively studied for acute migraine? So far the answer is an enthusiastic "yes." For chronic migraine? Possibly. As editor/co-author I chose to make peer review of our article exceptionally rigorous. The initial reviewers were a clinical neuro-ophthalmologist, an academic professor of neurology, and an academic professor of pharmacology, the latter with masked authorship. All made helpful suggestions and recommended publication. To accompany this expedited manuscript, a second set of experts were given the final version of the paper, copies of referenced

material and asked to write independent editorial critiques. Included are two professors of neurology at the University of Missouri (See page 289); a neuro-ophthalmologist from Saint Louis University (See page 294) and two nationally known headache-migraine specialists from Springfield (See page 292). Please read our article and the three editorial critiques carefully. In this editorial let me flesh out the back story of how our paper initiated and developed.

Our Eureka Moment at Iron Horse

According to popular lore Archimedes jumped out of his bath and shouted, "I have found it!" (Greek = Eureka) after he suddenly conceived of a method of detecting if Hiero II, the King of Syracuse's new gold crown, had been debased by devious goldsmiths. Other select "Eureka Moments" include: special theory of relativity (Einstein), alternating current (Tesla), television (Farnsworth), coordinate geometry (Descartes), Velcro (de Mestral) and Post-Its (Fry).

Eureka came to us this year while playing golf at our favorite course - the Iron Horse Golf Club in Leawood, Kansas. For over a decade Carl Migliazzo, myself, and Chuck Lederer, MD, have pursued our golfing muse over various courses in Kansas and Missouri. Midway through a typically less than stellar round, I happened to mention that both my daughters had developed migraines in their late 30s. Carl helpfully suggested they try beta blocker eye drops as quickly as possible when a migraine started. He said he had treated a number of his patients with migraine this way including several scrub nurses and other hospital staff that learned of the novel treatment by word of mouth.

This stopped me in my tracks. "Carl, this is new knowledge; we have to write this up."

Carl and Chuck are glaucoma specialists and I have a large glaucoma segment in my adult/geriatric ophthalmology practice. Collectively the number of patients we've treated with beta blocker eye drops in the last three decades is in the tens of thousands. We knew that systemic absorption occurs and the same contraindications and side effects for beta blocker medication by mouth exist for their eye drop form. We have had many patients, because of their beta blocker eye drops, develop wheezing, chronic cough, profound fatigue, and troublesome bradycardia. We knew that chronic migraines were often treated with oral beta blockers but that they were not used successfully for acute migraine. How could we explain the success of beta blocker eye drops in acute migraine?

At this point the lure of more bad golf intervened. I offered to do a literature search and we would pick the discussion up later. The literature was scant and mostly single case reports dating back to 1980. The neurology-migraine literature confirmed prospective, controlled studies had shown oral beta blockers ineffective against acute migraine. Once again how to reconcile the success of beta blocker eye drops on some acute migraine patients?

Getting the Drop on Acute Migraines

Scores of emails, more discussion interwoven with more bad golf, hours of pondering and speculation led us to what now seems obvious. As ophthalmologists we wanted to get beta blockers into the eye to lower intra-ocular pressure but not in the blood where it might cause unwanted side effects. Research (referenced in our study) had shown that beta blocker eye drops reached therapeutic blood levels within several minutes of installation on the eye. For glaucoma patients this was considered a bad thing. For migraine patients this might be a good thing.

To minimize systemic absorption in glaucoma patients, ophthalmologists instruct patients after instilling their drops to shut their eyelids and not blink for a couple of minutes, dab excess drops away, use finger compression of the lower tear ducts, and sometimes we used drops once a day rather than the standard every 12 hours. The glaucoma pharmaceutical industry developed once daily drops, slow release gel forming drops, select beta blocker and non-beta blocker types of eye drops that had fewer side effects and/or were more effective. Presently laser trabeculoplasty treatment is ideal primary and adjunct therapy. Consequently beta blocker eye drops are used much less now than during previous decades.

Anecdotally, and not reported in our paper, when beta blocker eye drops were approved in 1978 they became the first line glaucoma treatment. Some glaucoma-migraine patients reported fewer migraines. When latanaprost (Xalatan®) was released in 2002 some patients were taken off beta blocker eye drops. Some glaucoma-migraine patients had an increase or re-occurrence of their migraines. This is also described in some of the literature we cite.

So here is where the serendipity starts. One of Dr. Migliazzo's glaucoma patients told him she found if she put in a drop of her beta blocker at the start of her acute migraine it stopped her migraine cascade in its tracks. He tried the beta blocker eye drops on other carefully selected and informed acute migraine patients. For many it worked.

"Eureka! Eureka! Eureka!" *- Archimedes*

"Chance favors the prepared mind." *- Louis Pasteur*

"Carl, this is new knowledge; we have to write this up." *- John C. Hagan, III*

Drops Reach Therapeutic Blood Levels Quickly- Pills Not so Much

So this is the hypothesis we propose: applied to the eye, beta blocker eye drops, passing through the tear ducts, reach therapeutic levels for acute migraine treatment within minutes. This is mainly via trans-nasal mucosal absorption. Theoretically, a beta blocker nasal spray might also be developed and tested. Sublingual use worked for some migrainers.

Oral beta blocker medication takes hours to achieve therapeutic blood levels and is too slow to stop the acute migraine cascade but does work when taken regularly for chronic migraine prevention. Or so it seems.

Beta Blocker Eye Drops For Other Indications

So what about using beta blocker eye drops to try and achieve rapid, therapeutic beta blockade? Attention neurologists and cardiologists.

Involuntary Stress Tremor

It is well known in ophthalmology that beta blocker eye drops instilled on the eye or taken sublingually shortly before ophthalmic microsurgery can dampen the surgeon's involuntary stress tremor. The practice allegedly is *de rigueur* in some ophthalmology training programs. Of course the usual beta blocker contra-indications exist and one well know eye surgeon told me "It works but I was almost too tired to finish my cases so I can't use them."

For non-medical use it is accepted that beta blockers in the blood will dampen stress related tremor. Beta blockers are routinely tested for in some Olympic sports. At the last Olympics a North Korean pistol competitor was disqualified when found to have beta blockers on board to calm his shooting hand.

Essential Tremor

Oral beta blockers are a mainstay in treating essential tremor. How about testing beta blocker eye drops for intermittent treatment or for patients that were helped by oral beta blockers but developed side effects?

This is more than theoretical. I have an elderly essential tremor patient who was well controlled on oral beta blockers. She developed side effects that necessitated discontinuing her medication. I told her about our migraine paper. She asked if she might try eye drops on "bridge day" and when her grandchildren were coming to see her because her shaky hands embarrassed her. At press time her family physician is planning to do a therapeutic trial of beta blocker eye drops during an office visit.

Cardiovascular Indications

What about testing using beta blocker eye drops for conditions where rapid therapeutic levels are needed but intra-venous access not available or possible. Examples: in medical settings where IV cannot be established, first responder use, in patients that cannot swallow, in ambulances. What about having high risk heart patients keep an inexpensive bottle of beta blocker eye drops at home for emergency use with possible myocardia infarct (chew an aspirin, take beta blocker eye drops and call 911), angina, arrhythmia? What about testing beta blockers by eye drop, nasal spray or sublingual as standard therapy for acute or chronic administration of this class of medications?

It's Time for Prospective Studies

Actually its long overdue for prospective, masked, controlled, randomized, adequately statistically powered studies to prove or disprove whether beta blocker eye drops are useful for treating acute, even chronic migraines. It is unlikely that the pharmaceutical industry will invest much money or resources in a generic, inexpensive eye drop. However, the NIH is offering major multi-year funding and soliciting grant proposals for novel treatment of migraine. See http://grants.nih.gov/grants/guide/pa-files/PA-14-069.html. It's also likely that thoughtful applications to foundations or funding sources with interest in migraine might finance research. There may be commercial value in some of the other proposed applications or delivery methods.

Conclusion

How valuable are beta blocker eye drops for acute migraine treatment? Only time and more extensive research will tell. I'm saying it's time for more extensive research to tell. **MM**

Case Presentations and Review

Beta Blocker Eye Drops For Treatment of Acute Migraine

by Carl V. Migliazzo, MD & John C. Hagan, III, MD

We report seven cases which describe the successful use of beta blocker eye drops to abort or attenuate acute migraine symptoms. If beta blocker eye drops are effective against acute migraine symptoms, this would be a welcome addition to migraine therapy.

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Abstract

We report seven cases of successful treatment of acute migraine symptoms using beta blocker eye drops. The literature on beta blockers for acute migraine is reviewed. Oral beta blocker medication is not effective for acute migraine treatment. This is likely due to a relatively slow rate of achieving therapeutic plasma levels when taken orally. Topical beta blocker eye drops achieve therapeutic plasma levels within minutes of ocular administration which may explain their apparent effectiveness in relief of acute migraine symptoms.

Introduction

Sporadic case reports have suggested that beta blocker eye drops are effective for acute migraine treatment and chronic prevention of migraine attacks[1-5] (See Table 1 and Figure 1). Although widely prescribed for glaucoma therapy, beta blocker eye drops are rarely used for acute or chronic migraine treatment. Recent comprehensive reviews on migraine therapy do not mention the potential therapeutic value of beta-blocker eye drops.[6, 7, 8, 9]

Oral beta blocker medications are commonly and successfully used for chronic migraine prophylaxis.[7, 8,9] However, beta blocker medications taken orally are not effective in treating acute migraine.[10, 11] Topically applied beta blocker eye drops are systemically absorbed by the nasal mucosa and therapeutic plasma levels are achieved within minutes.[4, 12, 13]

In this paper we report seven cases which describe the successful use of beta blocker eye drops to abort or attenuate acute migraine symptoms. The scant published literature on using beta blocker eye drops to treat migraine is reviewed.[1-5] We present an explanation of why beta blocker medication by topical eye drop, but not by oral administration, may be effective for acute migraine treatment.

Case Presentations

Case 1

CH is a 61-year-old female who has suffered from migraines for approximately 30 years. Her typical migraine is a throbbing, right-sided pain that radiates to her neck and shoulders, occasionally associated with nausea, and a preceding visual aura. Her headache will last one to two days if not treated. Previous trials of oral medications, the names of

which she does not remember, did not give her sufficient relief, so she stopped using them. Approximately 15 years ago she began using at onset of acute migraine levobunolol 0.5% ophthalmic solution one drop in each eye along with ibuprofen 600 to 800 mg orally. She rates her headache relief as a 10 on a scale of 1 (no relief) to 10 (complete relief) since she started using topical beta blocker eye drops. She has had no side effects from the drops and only uses them for acute attacks.

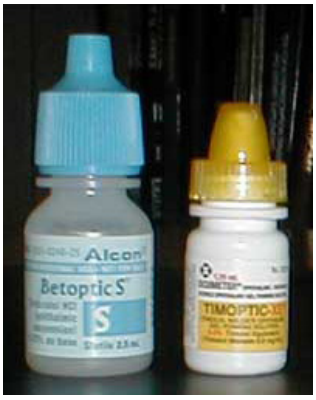


Figure 1
Beta blocker eye drops are inexpensive, available worldwide, and have rapid trans-mucosal systemic absorption when taken topically. Sporadic case reports and the literature collectively [1-12] suggest that the success of beta blocker eye drops in treating acute migraine may be due to the rapidity of eye drops in achieving effective blood levels when instilled shortly after symptom onset.

Case 2

MM is a 66-year-old female who describes the onset of her migraines as throbbing, one-sided, pain sometimes lasting for up to three days. Nausea and sensitivity to light, sounds and smells are often associated with her headaches. Her symptoms began 32 years ago and for the past eight years she has used prophylactic topiramate 50 mg bid and nadolol 40 mg at bedtime. Approximately one year ago she began using topical timolol 0.5% ophthalmic solution one drop in each eye at the onset of her attack. Within 15 to 30 minutes she gets complete relief (10 on a scale of 1-10) of her symptoms. Occasionally, she will take Fioricet® with codeine along with her eye drops; most of the time does not. She has experienced no side effects from the drops and only uses them for an acute attack. She feels that the management of her migraines has been greatly improved with the addition of topical beta blocker eye drops.

Case 3

DW is 38-year-old female who first noticed the onset of her migraines about 25 years ago. She describes an acute attack as a constant pain that begins in her right temple and then radiates to a throbbing vein in her left temple. Associated symptoms include nausea, vomiting, blurred vision, light and noise sensitivity, diaphoresis, and confused mentation. Duration of attacks without treatment is 24 hours or more. She has tried several different oral drugs for the past 14 years and they would take several hours before she had any relief of symptoms. Most of the time she tries to fall asleep. Two years ago she began using topical timolol 0.25% ophthalmic solution one drop in each eye at the onset of a migraine. She noticed some slight shortness of breath and now only uses one drop in one eye and has no side effects. Symptom relief begins in about 10 to 20 minutes and she rates her relief as an 8 on a scale of 1 – 10. Although her symptoms are not completely relieved with one drop, she is at least able to function. If a migraine is particularly severe, she will take oral analgesic medications after instilling an eye drop.

Case 4

EM is a 61-year-old female who describes the onset of her migraines as a visual aura with a classic fortification scotoma that begins with blurred central vision then expands towards the periphery until her central vision clears. This is followed by a one-sided, constant headache associated with nausea, light and sound sensitivity, and pain behind her eyes. Untreated duration of these attacks is 24 hours or more. Prior to using eye drops, oral ibuprofen would give partial relief in about 30 to 60 minutes. Often, she would go to bed and try to fall asleep. About five years ago she began using topical timolol 0.5% ophthalmic solution one drop in each eye at the first onset of a visual aura. Within two minutes she rates her relief of symptoms as 9.5 on a scale of 1 – 10. If she does not instill the drops at the very first visual symptom, relief may take longer, but usually within 10 to 20 minutes. She continues to take ibuprofen along with her topical beta blocker eye drops and has had no systemic or ocular symptoms from the eye drops. She only uses the drops for an acute attack and does not use them prophylactically.

Case 5

JW is a 63-year-old female who had the onset of migraines 27 years ago. She describes a sudden, left-sided, pounding and throbbing temple pain that radiates into her left ear and jaw. Associated nausea, vomiting, and sound sensitivity will occasionally occur. She had previously tried many different oral medications and alternative treatments for her migraines including acupuncture, chiropractic manipulation, various diets, and a nasal-palatine block. Oral medications would take

Table 1

Topical Beta-blockers Commonly Used for Glaucoma Treatment

Generic Name	Trade Name	Receptors	Concentration	Dose	Clinical Pearl
Timolol	Timoptic®	Beta 1 and 2	0.25%, 0.50%	BID	Former gold standard
Timolol	Timpotic XE®	Beta 1 and 2	0.25%, 0.50%	QD	XE is gel form
Timolol	Betimol®	Beta 1 and 2	0.25%, 0.50%	BID	Hemihydrate
Betaxolol	Betoptic®	Beta 1	0.50%	BID	Betaxon (newer)
Betaxolol	Betoptic S®	Beta 1	0.25% (susp)	BID	More selective
Levobunolol	Betagan®	Beta 1 and 2	0.25%, 0.50%	BID or QD	Longest half-life
Meti-pranolol	Optipranolol®	Beta 1 and 2	0.30%	BID	Rare uveitis risk
Carteolol	Ocupress®	Beta 1 and 2	1.0%	BID	Intrinsic sympathomimetic activity

up to 60 minutes to obtain partial or complete relief of symptoms. She is currently taking duloxetine and topiramate for migraine prophylaxis which has reduced the frequency of her attacks. Approximately six years ago she began using topical levobunolol 0.5% ophthalmic solution two drops in each eye at the first onset of symptoms. She will repeat the drops in 15 minutes if she doesn't get meaningful relief after the first set. She gets complete relief of symptoms in about 70 – 80 % of acute migraine attacks with levobunolol eye drops alone. If she obtained no relief, she would use oral medication. She tried using daily, topical levobunolol prophylactically, but it did not eliminate her attacks, so daily use was discontinued. No systemic or ocular side effects have been noted with topical beta blocker use.

Case 6

VB is a 57-year-old female with onset of frequent migraines at age five. She describes sparkling light aura lasting 10-20 minutes followed by severe right-sided pain above the eye, radiating into the temple and head. She had photophobia, nausea and difficulty with thinking clearly. The migraine would often last four to six hours followed by a "migraine hang-over" lasting a day or two. She treated these with Excedrin and lying quietly in a dark room. In her mid 30s she began using timolol 0.5% ophthalmic solution one or two drops sublingually at the first onset of her aura. She experienced improvement of her symptoms in about 10 minutes with complete relief in 30 to 45 minutes. Although she has asthma, she experienced no breathing problems or other side effects. She used the beta blocker eye drops till her mid to late 40s when she ceased to have further migraines.

Case 7

SW is a 76-year-old female whose migraines began in high school. Her typical attack begins with a visual aura of a "broken glass/mirror" followed by a left temporal pain that increases in intensity and radiates to both sides of her head. Nausea, vomiting, garbled speech, and post-migraine fatigue are often associated with her headaches. Symptoms would typically last from 24 to 72 hours. She began using topical timolol 0.5%, one drop in each eye, approximately five years ago. If she instills the drops within a few minutes from the onset of an aura, her symptom relief is immediate and complete. If there is a delay in eye drop instillation, she rates her relief as an 8 on a scale of 1 – 10. She does not take any oral medications along with her drops and she has not had any side effects.

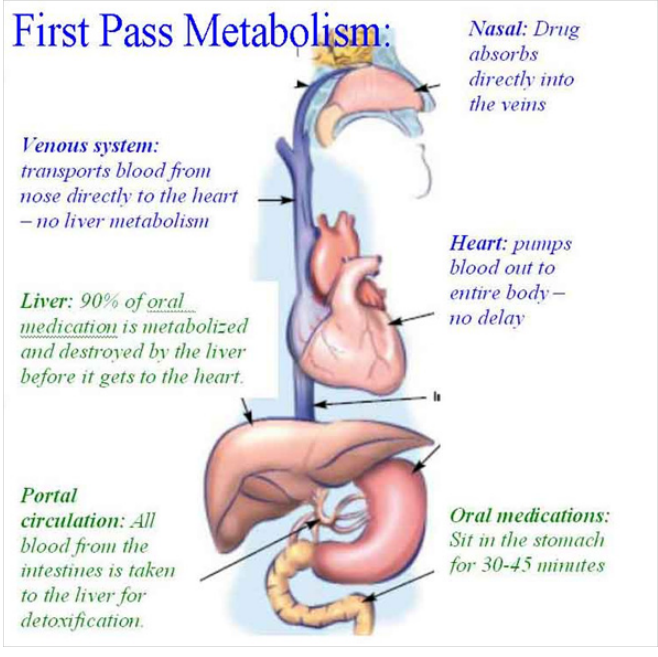
Discussion

The literature on using beta blocker eye drops to treat migraine is sparse. A 1980 report stated that topical timolol 0.5% relieved symptoms of Horton cluster headaches compared with placebo in four patients.[1] In 1999, a 59-year-old female with migraine and glaucoma had no improvement in migraine over 10 years on timolol drops although it controlled her glaucoma. She had a dramatic improvement of her migraines when carteolol beta blocker eye drops were substituted for timolol for better glaucoma control.[2] In 2000, a 4-year-old girl with ophthalmoplegic migraine was treated successfully with 0.25% timolol maleate bid.[3] A 64-year-old woman with classic migraine resistant to standard oral therapy was started on timolol maleate 0.5% eye drops to both eyes. She had been migraine free for 18 years when the case

was reported in 2004.[4] Lastly, a 52-year-old male with "normal tension glaucoma" and migraines had relief from his headaches when placed on Timoptol-LA once per day for glaucoma therapy.[5]

Physicians often consider migraine prophylaxis when three or more attacks occur per month. Other indications include intolerable migrainous side effects that may constitute a danger to the patient or unsuccessful acute migraine therapy.[6, 7] Two of the four FDA approved oral drugs for migraine prophylaxis are beta blockers (timolol and propranolol).[7] The non-beta blockers are topiramate and divalproex.[7] Three other beta blockers are often used 'off label' (atenolol, metroprolol and nadalol) for chronic migraine prevention. Neurologists and general practitioners preferentially used oral beta blockers for migraine prophylaxis in a European study.[8] However, two double-blind, and placebo controlled studies have shown that oral propranolol has no significant effect in aborting acute attacks of migraine when compared with placebo.[10, 11]

Figure 2



The success of beta blocker eye drops in treating acute migraine may be due to the rapidity of eye drops in achieving effective blood levels. Eye drops pass directly into circulation. Therapeutic blood levels occur in 4-10 minutes. Oral beta blocker medication is subject to first pass metabolism and takes several hours to reach therapeutic blood levels.
Source: http://intranasal.net

Timolol ophthalmic solution was the first topical beta blocker approved by the FDA for the treatment of glaucoma in 1978.[9] It is a highly effective glaucoma medication with few ocular side effects and was for years the first line treatment for glaucoma world-wide. Several other ophthalmic beta blocking eye drops were subsequently approved. All of them have been used extensively (See Table 1). Beta blocker eye drops achieve pharmacologically active concentrations in the plasma.[4] Ophthalmic beta blocker solutions applied topically to the eye are rapidly absorbed into the systemic circulation primarily by lacrimal duct transit into nasopharyngeal mucosa and, to a lesser extent, the conjunctival epithelium and the gastro-intestinal tract.[12] Pharmacokinetic analysis has shown that one drop of timolol ophthalmic solution 0.5% in each eye will reach a plasma concentration of 2 ng/ml within 10-15 minutes.[10] Beta 1 and beta 2 receptor blockade has been calculated to be approximately 80% with this plasma concentration.[10] Our case reports support these observations with acute migraine symptom relief within minutes of beta blocker eye drop instillation especially if the drops are instilled as soon as possible after symptom onset.

Our cases and the literature collectively[1-12] suggest that the success of beta blocker eye drops in treating acute migraine may be due to the rapidity of eye drops in achieving effective blood levels. Oral beta blocker medication is subject to the "one pass effect,"[16] i.e. inactivation of alimentary beta blocker by bacterial, gut and gut wall enzymes and hepatic metabolism (See Figure 2). In chronic migraine therapy, daily oral beta blocker medication attains effective blood levels for migraine prevention within hours to days. This would also explain the effectiveness of oral beta blockers on chronic migraine prevention.

Beta Blocker Eye Drops Therapy for Acute Migraine

A migraine patient reported to one of the authors (CVM) that instilling a drop of beta blocker eye drop at the earliest onset of her aura aborted the migraine attack. Subsequently other acute migraine patients have been successfully treated with beta blocker eye drops taken as early as possible at migraine symptom onset. Seven of them filled out a questionnaire which is used as the basis for these case reports. The others

Table 2
Case Summaries

Case	Typical Symptoms	Duration	Concurrent oral meds	Eye drops	Rated symptom relief with eye drops (1-10)	Side effects
61 y/o female	Visual aura, right sided pain, nausea	1 – 2 days	Ibuprofen	Levobunolol 0.5% both eyes	10	none
66 y/o female	Unilateral headache, light, sound, and smell sensitivity	1 – 3 days	Topiramate and nadolol daily	Timolol 0.5% both eyes	10	none
38 y/o female	Right-sided headache, nausea, vomiting, light and sound sensitivity, confused mentation	24 hrs or more	Occasional analgesics	Timolol 0.25% one eye	8	Shortness of breath if drops in both eyes
61 y/o female	Visual aura, unilateral headache, nausea, light and sound sensitivity	24 hrs or more	Ibuprofen	Timolol 0.5% both eyes	9.5	none
63 y/o female	Unilateral headache, nausea, vomiting, sound sensitivity	Unknown	Duloxetine, topiramate	Levobunolol 0.5% both eyes	8 - 10	none
57 y/o female	Visual aura, unilateral headache, nausea, photophobia, confused mentation	4 – 6 hrs or more	none	Timolol 0.5% one or two drops sublingual	10	none
76 yo female	Visual aura, unilateral radiating headache, nausea, vomiting, garbled speech	24 – 72 hrs	None	Timolol 0.5% both eyes	10	none

did not complete the form or could not be specifically identified. Table 2 summarizes our case reports described in detail above.

Patients undergo a medical history and ophthalmic examination prior to advising this method of treatment to ensure that they do not have contra-indications to beta blocker use.[14, 15] As in glaucoma patients, the potential pulmonary and cardiovascular side-effects are discussed especially slowing of the pulse, wheezing and/or difficulty breathing. Patients are told that the eye drops are typically used in glaucoma patients and have been helpful in some patients who suffer from

acute migraine attacks. They are advised to read the package insert and call if they have any questions or if symptoms develop. Treated patients have had an established, usually longstanding, diagnosis of migraine. Their physicians are informed of their acute migraine beta blocker eye drop use. New cases with symptoms suggestive of migraine are referred to their physicians for appropriate work-up to confirm the diagnosis.

Migraine patients typically put one drop of timolol ophthalmic solution 0.5% or a comparable beta blocker in each eye as early as possible in the aura or migraine evolution. Patients are advised to blink vigorously several times which encourages drop passage into the lacrimal drainage duct for enhanced systemic absorption. If no relief or partial relief of migraine symptoms occurs after 10 minutes, patients are instructed to instill another drop in each eye. If the drops do not work at this point, they are discontinued and other acute migraine medications previously prescribed by their physicians are utilized.

All of our reported cases had a complete eye examination by an ophthalmologist before therapy was started. Ideally before starting beta blocker eye drop therapy physicians should refer their patients to an ophthalmologist for a comprehensive eye examination. It is important to exclude glaucoma, lacrimal stenosis, punctal occlusion or external ocular disease.

Conclusion

Beta blocker eye drops (See Figure 1) are inexpensive, available worldwide, and have rapid trans-mucosal systemic absorption when taken topically. Used acutely at the start of a migraine, they would be expected to cause fewer side effects than oral beta blockers and other potent prescription migraine medication. If beta blocker eye drops are effective against acute migraine symptoms, this would be a welcome addition to migraine therapy.

As with this paper, all previous publications describing the beneficial effects of beta blocker eye drops for the treatment of migraine headaches are small case reports. No controlled, prospective or retrospective study has been done on acute migraine treatment by beta blocker eye drops; such a study was first called for in 1999.[2] A prospective, masked, placebo controlled study, perhaps with a cross-over design, is both feasible and warranted.

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Disclosure

None reported.

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EDITORIAL CRITIQUE: NEUROLOGY

Beta Blocking Eye Drops in Acute Migraine: A Novel Use of an Old Drug

by Brandi R. French, MD & Niranjan N. Singh, MD

The NIH has issued a call for research on migraine. Beta blocker eye drops and could pose an attractive and feasible area for study of a new use of an old medication.

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Migraine affects 29.5 million Americans and according to the American Migraine Prevalence and Prevention study (AMPP), the largest study of migraine sufferers, approximately 12% American have migraines with higher prevalence in woman than man, 17% vs. 6% respectively.[1] Migraine is usually characterized by one-sided pulsating pain with nausea, vomiting and sensitivity to light and noise. A minority of the migraine sufferers have aura, visual displays before or during attack. Estimates vary anywhere from 2-61 working days lost per patient per year due to migraine, depending on the population studied.[2] Numerous print and online resources are dedicated to those seeking permanent disability due to migraine. From these data, it is clear that both long term preventive and acute abortive therapy must continue to advance, and novel therapies must be sought.

In this issue of *Missouri Medicine*, Migliazzo and Hagan (See page 283) present a series of seven of their own patients who were treated with topical beta blocker eye drops for treatment of acute migraine attacks. All patients were long-standing migraine sufferers with well-established patterns of pain and response to standard acute abortive medications. There was rough equivalency of migraine patients with and without aura, with only one patient having additional neurologic deficits (garbled speech) associated with attacks. All patients were screened with a medical history and ophthalmological evaluation prior to instituting therapy, and were advised of the possibility of systemic side effects. Patients reported, via questionnaire, that there was relief of pain within minutes of instilling eye drops, with infrequent need for repeat drops though some used coincident NSAIDS. The authors correctly point out that this is a novel use of beta blocker eye drops with only sporadic reports in the literature of similar use. Of these, only one was a small series of four patients, the rest being case reports.[3, 4, 5]

It is noted in this paper that the use of oral beta blockers is useful in, and FDA approved for, migraine prophylaxis[6], though ineffective in acute abortive treatment.[7, 8] It is postulated that this differing usefulness of beta blockers in migraine treatment depending upon the route of administration is due to the speed by which the medication achieves a therapeutic blood level. It can take hours to days for oral administration though only minutes with the eyedrop route.[8, 9]

Current acute abortive therapy consists of conservative over-the-counter analgesics and NSAIDS, as well as newer caffeine-containing "for migraine" preparations combined with analgesics; these can be associated with unwelcome side-effects, particularly in those with GI illness. Prescription medications such as ergotamine and triptans have several limitations, most important being patients with coronary disease, stroke and peripheral vascular disease. This presents a unique challenge when treating older patients, or those with significant vascular disease, who suffer persistent migraine pain. The abuse potential of some of prescription remedies, or propensity for rebound phenomenon also poses unique challenges in the acute and chronic treatment of migraine. There is an ongoing search for an effective antimigraine treatment which works faster, can be used at home and is devoid of these unwanted side effects.[1, 10]

Off-label rapidly acting intravenous medications include valproate and verapamil. It is postulated that the rapid attainment of therapeutic levels of these medications is responsible for the rapid resolution of migraine pain. Small trials of intravenous valproate provide conflicting results regarding efficacy.[11,12] Case series of verapamil primarily address hemiplegic rather than common or classic migraine, though tend to be supportive.[13,14] We have located no reports thus far regarding the use of intravenous beta blocker agents for acute migraine control. However, the intravenous form of delivery is inconvenient, necessitating office, or more commonly emergency department visits, and by its very nature patients will have suffered hours prior to achieving any form of relief. A fast-acting alternate form of delivery could be ideal.

The authors of this paper emphasize the safety of beta blocker drops, and all patients were given a medical history interview and ophthalmological examination. The only reported side effect in the authors' population was shortness of breath with multiple drops. The literature indicates additional common side effects being generally mild hypotension and bradycardia, which occasionally can be dose-limiting.[9, 15]

There are several strengths of this paper. This is the largest case series review of patients treated with beta blocking eye drops for the indication of acute migraine, with no stronger study designs available in the literature. There is a clear demonstration of efficacy in a well-established migraine population, with documentation of the duration of migraine history and prior response, or importantly lack of response to traditional acute abortive therapies. Compelling argument is made for the efficacy of beta blockers possibly due to route of administration and lack of first pass effect[16], with coincident rapid escalation of plasma level of drug.[9] Further mechanism of action is unknown or unclear, and parallels the lack of clear known mechanism for other off label agents.

The weaknesses of this paper involve study design with it being a case series, with a small number of patients, and lack of an available control. The authors have described seven cases of migraine, five of them are more than 60 years of age. Timolol eye drops has been used in five of them while levobunolol in two patients. Five of seven patients have also used NSAIDs acutely. The frequency of use of the eye drops is not reported. Beta blockers are known to have prophylactic properties for migraine. Additionally, while there was no neurologist's documentation of the migraine diagnosis, the description of symptoms provided for each patient helps the reader draw the diagnostic conclusion of migraine with or without aura.

This therapy is attractive due to its possible efficacy as a novel agent for the acute treatment of migraine. The widespread use of beta blocking eye drops do indicate that it is safe across a broad spectrum of the population.[9, 15] The route of administration is both easy and convenient, with the added benefit of being inexpensive and widely available. Additionally and importantly, it may be more generalizable to the elderly or those with cerebrovascular or cardiovascular disease, a known contraindication to triptans or other sympathomimetics.[10] While migraine tends to wane in the elderly, a significant subset of older patients do continue to have migraine pain.

Given substantial prevalence, morbidity and disability, these results are compelling. However, to have more definitive answers, the beta blocker eye drops need to be tried against placebo without any supplemental nonsteroidal anti-inflammatory medications. Their use as a prophylactic agent should also be investigated. Further aspects of this treatment to explore include the possibility of rebound effect with multiple or frequent doses. Additionally, its sustained efficacy in large populations of patients will need to be verified, though the case reports provided by the authors provide preliminary support to efficacy over time. As called for in 1999 further studies are warranted.[4] The NIH has issued a call for research on migraine (http://grants.nih.gov/grants/guide/pa-files/PA-14-069.html) and this could pose an attractive and feasible area for study of a new

use of an old medication to address a pervasive problem throughout the population, particularly in the important subset of those with vascular disease in whom treatment options become more limited. We would anxiously await institution of trials to explore expanding our therapeutic repertoire.

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EDITORIAL CRITIQUE: HEADACHE MEDICINE

Ophthalmic Beta Blockers: Treatment for Acute Migraine?

by J. Kent Dexter, MD and Roger K. Cady, MD

Further large scale randomized placebo controlled studies of beta blocker eye drops for acute migraine are clearly warranted.

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Migraine is the most prevalent neurological disease in the world and a leading cause of medical disability worldwide.[1] While important advances in treating migraine have been made in the last 25 years, migraine continues to be significantly under-diagnosed and under-treated.[2] Unfortunately, available acute treatments for migraine are not always effective. Numerous studies suggest that oral triptans provide sustained pain free outcomes in less than 25% of attacks.[3] In addition nearly 80% of patients are willing to try new treatments, further suggesting the need for better more successful acute treatments for migraine.[4]

In this issue of *Missouri Medicine*, Carl V. Migliazzo, MD, and John C. Hagan, III, MD, present a series of seven case reports of patients successfully treating attacks of acute migraine with beta blocker eye drops. (See page 283). While this is a small case series and as such has numerous limitations, the authors' report is both well organized and compelling. If beta blockers ophthalmic drops are demonstrated to be effective in rigorous clinical trials, this novel approach to acute treatment would add much to the care of migraine patients.

The case reports provided by Migliazzo and Hagan have both strengths and weaknesses. Each of the seven cases discussed in their article provides enough information to confidently assume a correct diagnosis of migraine with or without aura. The outcome of six of the seven patients was provided through use of a questionnaire mailed to patients and measurement of efficacy while confined primarily to pain relief and functional restoration is clinically valuable. There is however, no acknowledgement of the number of unreturned questionnaires or if there were patients who did not respond to topical beta blockers that are not reported in their article. In addition most of the patients are in their 60s which may represent a unique subset of the migraine population which is most prevalent in the third and fourth decade of life. Another confounding factor is that several of the patients are reported to be using topical beta blocker eye drops in conjunction with another NSAID or analgesic. Finally, the number of cases reported is small making any generalization of these observations impossible.

That being said, there is significant positive potential for exploring the role of topical beta-blocker eye drops as acute

treatment for migraine. Inhibitory modulation of peripheral and central neuronal pathways provides the pharmacological basis for several common acute treatments for migraine. Most notable are triptans and ergotamines which are agonists of the inhibitory neurotransmitter serotonin (5-HT). 5-HT 1 b/d receptors are well documented as the principle mechanism by which triptans and ergotamines abort acute migraine.[5] Divalproex sodium is an FDA approved migraine prophylactic medication that has studies demonstrating efficacy for acute migraine when given as a rapid IV infusion.[6] Valproic acid is a GABA agonist and another important inhibitory neurotransmitter. Non-steroidal anti-inflammatory drugs inhibit prostaglandin synthesis and glial recruitment of neurons and are also widely used acute treatments.

Both timolol and propranolol are FDA approved for migraine prophylaxis and numerous other beta blockers are commonly employed in in this role. While the exact mechanism of action of beta blockers in migraine is not fully understood, they are known to rapidly inhibit adrenergic drive, block smooth muscle contraction and prevent arterial dilation and pain. Further, beta blockers inhibit catecholamine-induced platelet aggregation and adhesiveness as well as block catecholamine-induced lipolysis and prostaglandin production. Finally beta blockers inhibit forebrain postsynaptic serotonin receptors.[7] Many of these mechanisms could potentially have a positive benefit in acute treatment of migraine.

Other positive attributes of beta blockers are that they are well tolerated and have a high benefit to risk ratio in numerous therapeutic areas including migraine prophylaxis.[8] Given their use as daily prophylactics over extended periods of time, it is unlikely that beta blockers would lead to Medication Overuse Headache which is a common liability of currently used acute treatments. Topical beta blocker eye drops provide significant blood levels sufficient to provide beta-blockade within minutes of administration; an ideal pharmacokinetic feature of an acute migraine medication.

Given the efficacy reported in this small series of case reports, the mechanistic potential of beta-blockers to be effective as an acute treatment, and the tolerability and safety of this class of medication further large scale randomized placebo controlled studies are clearly warranted.

An interesting historical footnote might be that the use of propranolol as a migraine prophylactic was made by a physician noting improvement of migraine in a patient being treated for angina pectoris.[9] We commend the authors on their astute observations and bring this novel and potentially important concept to the attention of the medical community.

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EDITORIAL CRITIQUE: NEURO-OPHTHALMOLOGY

Can Topical Beta Blockers be Successful for Acute Migraine Management?

by Sophia M. Chung, MD

The authors successfully have contributed an additional seven cases to the literature supporting an alternate treatment for acute migraine.

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I appreciate the opportunity to review the article entitled, "Beta Blocker Eye Drops for Treatment of Acute Migraine: Case Presentations and Review." (See page 283.) The manuscript is a report of seven patients who suffered from migraine headaches that successfully modify their pain with the instillation of topical beta blocker eye drops, traditionally used in the management of chronic open angle glaucoma. This is the only case series using topical ophthalmic beta-blockers to manage acute migraine published in the literature. The encouraging positive response of the acute migraine in these patients supports the need for a prospective, randomized and masked study of a topical beta-blocker.

Migraine is thought to result from cortical spread of depression (CSD), a well-defined wave of cortical neuronal excitation that spreads 2-6 mm/min. A whole host of neurochemical and physiologic changes occur and are beyond the scope of this review. But as a result of this CSD, there is an activation of the trigeminovascular system to stimulate nociceptive neurons on dural blood vessels that releases plasma proteins and a variety of pain-generating substances such as: calcitonin gene-related peptide, substance P, vasoactive intestinal peptide, and neurokinin A.

The resultant state of sterile inflammation is accompanied by further vasodilation exacerbating pain. Numerous pain centers in the thalamus, cortex, and potentially a "migraine center" in the brainstem are activated to contribute more inflammatory signals to cause vasodilation and additional pain. The changes in neuronal and vascular membranes and release of inflammatory cytokines should allow targeted pharmacotherapy to modulate the response and therefore reduce or hopefully stop migraine pain.

Beyond disease modifying changes in lifestyle, pharmacotherapy has traditionally been used for migraine and can be categorized into abortive therapy and prophylactic therapy. The goal of abortive therapy is to achieve resolution of pain within two hours with one therapeutic choice without significant adverse events. Non-steroidal anti-inflammatory agents such as aspirin, ibuprofen, naproxen, acetaminophen, and diclofenac sodium have been the mainstay of treatment. Triptans are the other most common acute treatment for migraines. There are seven triptan tablets, two fast-melt tablets, two nasal sprays, and three types of injection. While the oral treatments are most commonly used,

the nasal sprays and subcutaneous injections offer quicker onset for many patients bypassing the slow gastrointestinal absorption.[1]

When patients suffer more than two to three migraines/month, prophylactic therapy should be strongly considered. Four drugs are approved by the Federal Drug Administration (FDA) in the preventative management of migraines: timolol and propranolol, the only beta blockers and topiramate and divalproex sodium, both originally designed as anti-epileptics. But a whole host of medications are used off-label including a number of other beta-blockers, antidepressants (e.g., amitriptyline, nortriptyline), calcium channel blockers (e.g., verapamil and flunarizine), and commonly anticonvulsants (e.g., gabapentin and lamotrigine).[2]

Beta blockers were discovered to be beneficial in migraine by serendipitous happenstance. A patient enrolled in a study of propranolol to prevent angina reported improvement not only in his angina but also his migraines while on propranolol but recurrence after crossover to the placebo.[3] Since that report, beta-blockers have become first line prophylactic therapy for migraines. In additional to timolol and propranolol, a large meta-analysis showed acebutolol, atenolol, nadolol, and metoprolol were all better than placebo in the prophylactic management of migraine.[4]

Beta-blockers were initially thought to be effective solely by its vasodilation benefits. We now recognize multiple mechanisms including inhibition of Na+ release and tyrosine hydroxylase, reduction of neuronal firing rate of noradrenergic neurons of the locus coeruleus, modulation of the serotonin receptors, and action at the ventroposteromedial thalamic nucleus and inhibition of the cortical spread of depression.[5] Hence the successful benefit of beta-blockers in the newly accepted context of CSD as the cause of migraines. However, beta blockers are considered beneficial only as a prophylactic agent and not in the acute management.

Topical timolol was the first FDA approved beta-blocker to be used in glaucoma in 1978. It acts by reducing the formation of aqueous humor and therefore lowers the intraocular pressure. When applied to the eye, not only are there local ocular effects but it is also absorbed systemically via mucosal membranes primarily in the nasopharynx. As Migliazzo and Hagan have discussed, pharmacologically active levels in the blood are quickly achieved after topical administration,[6] but may cause side effects in the heart and lungs including bronchospasm, bradycardia, and hypotension. Therefore, reactive airway disease and bradycardia are considered relative contraindications in patients whom topical beta-blockers are being considered.

Conversely, potential systemic benefits could result from the same attained pharmacologically active concentrations of beta-blockers such as management of migraines. As detailed by the authors, there are several prior case reports of beneficial effect of using topical beta-blockers in the eye in the acute management of their recurrent migraine. Herein, the authors add an additional seven patients, the first case series of patients, to the literature. All of these cases are women who reported longstanding history of migraine (with the exception of case 4 whose duration is not recorded) three of whom had consistent visual aura preceding the headache and pain. Six of the seven women instilled topical levobunolol 0.5% or timolol 0.25-0.50% into one or both eyes while one woman used it sublingually within minutes of onset of migraine. Six of the seven patients achieved complete or near complete relief within 45 minutes. The seventh patient achieved complete relief in 70-80% of acute attacks. Five of the seven supplemented the topical beta-blocker with oral analgesics at least some of the events. One case tried using the topical beta-blocker daily as a preventative measure but she continued to have break-through-migraine attacks. One woman suffered some shortness of breath with two drops of beta-blocker ophthalmic solution but when she lowered her dose to only one drop, her side effects resolved. And finally, one patient with known asthma did not suffer exacerbation of bronchospasm with sublingual ophthalmic solution of beta-blocker.

The proposed mechanisms of beta-blockers are discussed above. As the authors have proposed, immediate instillation and rapidity of systemic absorption of topical ophthalmic solution through mucosal membranes may indeed explain the benefit in the acute management of migraine. Immediate access and treatment is important in nearly all migraine patients to attenuate the symptoms before CSD has advanced significantly. The dosing of topical beta-blockers remains uncertain; the fact that such a dilute solution and small quantity would be so effective is remarkable.

The report is certainly encouraging but there are weaknesses of the case presentations that may inadvertently favorably alter the patients' responses. As the authors have acknowledged, this paper reports the results of a retrospective, unmasked, questionnaire. We are not told the number of questionnaires nor to whom the questionnaires were distributed. Details about the patients' past medical history and medication lists are not provided. Concurrent diseases such as renal insufficiency or failure will alter drug availability. Systemic medications similarly

may affect bioavailability of the topical agent. Parallel use of beta-blockers for systemic hypertension or nonsteroidals for arthritis may potentiate effects of topical agents. The average age of the patients reported in this study is 61 years of age, older than most studies report for migraine. Migraines typically peak between 35 and 45 years of age.[7] As a result, this group of older patients, all women and most are likely post-menopausal, may have different responses to medication than the typically younger patient. Finally, generalizations cannot be made from the observations of seven patients.

Nonetheless, I agree with Drs. Migliazzo and Hagan that the seven reported cases should stimulate us to consider a prospective, randomized, masked, and controlled study examining the role of topical beta-blockers in the treatment of acute migraine. The low cost, wide availability and relatively successful tolerance of this medication all favorably support its use. The immediacy of systemic absorption and therapeutic benefits seemingly outweigh the risks. The authors successfully have contributed an additional seven cases to the literature supporting an alternate treatment for acute migraine.

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