Compounded Beta-blocker Nasal Spray for Treatment of Acute Migraine: A New Therapeutic Modality

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Abstract

Beta blockers (timolol 0.5% ophthalmic solution) delivered topically to the eyes or sublingually have recently been reported in case series and small placebo-controlled studies to be effective in some cases of acute migraine. Rapid systemic absorption to achieve therapeutic levels of beta blockers is extremely important in the treatment of acute migraine. Nasal-delivered beta blockers have been shown to be absorbed as fast as intravenous administration and seem ideal for acute migraine treatment. A nasal delivered beta-blocker spray has not been available. In 2019, O'Brien Pharmacy prepared a compounded timolol nasal spray that is now available to authorized prescribers. The theoretical basis for using nasal beta-blocker spray is presented and research on fast-acting beta-blocker solutions for acute migraine is reviewed.

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Migraine, an idiopathic headache disorder, is the third most common disease, the most prevalent neurological disorder in the world, and a leading cause of medical disability.[1] Migraine is estimated to affect 6% to 8% of males, 12% to 14% of females, and about 50 to 60 million Americans. Migraine therapy is generally divided into those drugs used intermittently to abort an acute attack and chronic therapy taken daily for prophylaxis to prevent an attack from developing in individuals having 10 or more headache days per month.[2] In spite of a wide variety of medications available for acute migraine, 60% of surveyed migraineurs indicate dissatisfaction with their migraine treatment and would try an additional medication.[3]

This paper will summarize and reference author JH's experience with using timolol 0.5% eye drops for treating acute migraine and discuss the possibility of improved success now that a compounding pharmacy (O'Brien Pharmacy, Mission, Kansas) has prepared a nasal spray device delivering 0.125% timolol solution that is available to authorized practitioners (see Figure). Authors EE and TC describe how the product is compounded. JH describes how he prescribes it.

FIGURE.

A 0.125% TIMOLOL NASAL SPRAY WITH 15% MUCOLOX DELIVERING A 0.125-MG/0.1-ML SPRAY.

(WITH A PROPER PRESCRIPTION, THIS PREPARATION IS AVAILABLE FROM O'BRIEN PHARMACY, MISSION, KANSAS.)

Using rapid onset beta blockers, such as a topical to eyes, sublingual, or nasal spray delivery, was also favorably reviewed by several national headache experts.

Why Do Oral Beta Blockers Work for Chronic Migraines But Not Acute Migraines?

Daily oral beta blockers are U.S. Food and Drug Administration (FDA)-approved for chronic migraine prophylaxis. Oral beta blockers taken intermittently at the first onset of acute migraine have been shown *not* to be effective for aborting acute migraines. The author JH[4-6] and others[7-10] have discussed at length the reasons for this seeming paradox. Daily oral beta blockers maintain anti-migraine therapeutic blood levels. When taken sporadically for migraine, oral beta blockers take too long to achieve therapeutic blood levels and let the acute migraine inflammatory-pain cascade spiral out of control. Beta-blocker eye drops applied properly to a normal eye/eyelids/lacrimal duct/nasal mucosa or taken sublingually are rapidly absorbed and achieve 80% or > beta blockade within 15 minutes.[7-10]

Beta blocker eye drops were first reported helpful for migraines in 1980.[11] In 2014, the authors JH and Migliazzo reported the largest case report series using topical and sublingual timolol 0.5% eye drops to successfully treat acute migraine.[4] Since then JH has collected over 40 anecdotal successes from other physicians and patient self-reports.[12] A small, prospective placebo-controlled study of topical timolol 0.5% eye drops was performed in 2018.[11] While too small for statistical study, the results were encouraging, and those researchers determined "*A future crossover study will require 86 patients to power a study with* $\alpha \leq 0.05$ *and* $\beta \leq 0.2$*.*"[10] They further commented, "*We believe that, together, our work advances the notion that timolol drops are a safe effective, and already widely available abortive treatment in select migraineurs.*"[10] Using rapid onset beta blockers, such as a topical to eyes, sublingual, or nasal spray delivery, was also favorably reviewed by several national headache experts.[7-9]

Why is Nasal Delivery the Preferred Method for Treatment?

Many people have trouble properly instilling eye drops. In the patients JH has treated, which includes nurses, ophthalmic technician, and physicians, the preferred route of administration is sublingual. The absorption of beta blockers topical to the eye, sublingual, and nasal has been studied. Nasal is the fastest (100%) being equal to intravenous administration in a study of 80 healthy volunteers.[13] From JH's first report, he has felt that nasal application would be the easiest, fastest, and most effective way to deliver the beta blocker.[4,5] Unfortunately, there has been no commercial beta-blocker nasal spray available.

The author JH has spent the past six years trying unsuccessfully to get Big Pharma to develop and test a timolol nasal spray for acute migraine. His encounters with Big Pharma can be paraphrased "This is a great idea that pharmacologically makes perfect sense. However, we don't see enough profit, and it might compete with our other expensive-high profit migraine products."

To determine if nasal beta blockers had ever been tested, an Internet search was conducted. A careful review of Questcor Pharmaceutical Company Form 10-K annual reports from 1998 to 2005 disclosed Questcor did a Phase-1 study of nasal propranolol spray for acute migraine. Questcor, apparently encouraged by the results, began a much larger Phase-2 study. Optimistically they copyrighted the name "Migrastat" for the new product, which was favorably touted in these annual reports. On October 13, 2005, Questcor ran out of cash, closed all their clinical studies and sold their company to Mallinckrodt. Those Phase-1 results were never published. It is unlikely Questcor, having a cash flow problem, would have invested precious monies in Phase-2 studies if the Phase-1 results were not highly favorable. Mallinckrodt (Personal Communication, E-mail JH 2018) indicated the results of the Questcor Phase-1 and Phase-2 studies cannot be located.

The author JH had worked with O'Brien Pharmacy to develop a widely used compounded hyaluronidase for eye surgery during a national shortage.[14] In late 2019, a presentation of the literature and clinical experience with timolol eye drops for acute migraine was made to the pharmaceutical staff of O'Brien Pharmacy. Authors EE and TC agreed to prepare a 0.125% timolol nasal spray with Mucolox and 0.9% saline, delivering a 0.125-mg/0.1-mL spray (available from O'Brien Pharmacy with a proper prescription).

Rx

TIMOLOL 0.125%/MUCOLOX 15%/0.9% NORMAL SALINE NASAL SPRAY

For 100 mL

Timolol 0.5% Opthalmic	25 mL
Mucolex Gel	15 mL
Sodium Chloride Bacteriostatic 0.9%	100 mL

Note: The finished preparation will be a semi-transparent solution, free of particulates.

METHOD OF PREPARATION

1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Verify that the compounding area, equipment, and materials are appropriate and meet the standard operating procedures for this preparation.
3. Weigh and/or measure each ingredient accurately.
4. Add the liquids directly to a nasal spray bottle.
5. Assemble nasal spray attachment and bottle.
5. Shake well and label container.

PACKAGING

Package in a 3-mL white nasal spray bottle with a nasal spray adapter.

LABELING

Shake well. Store at room temperature.

STABILITY

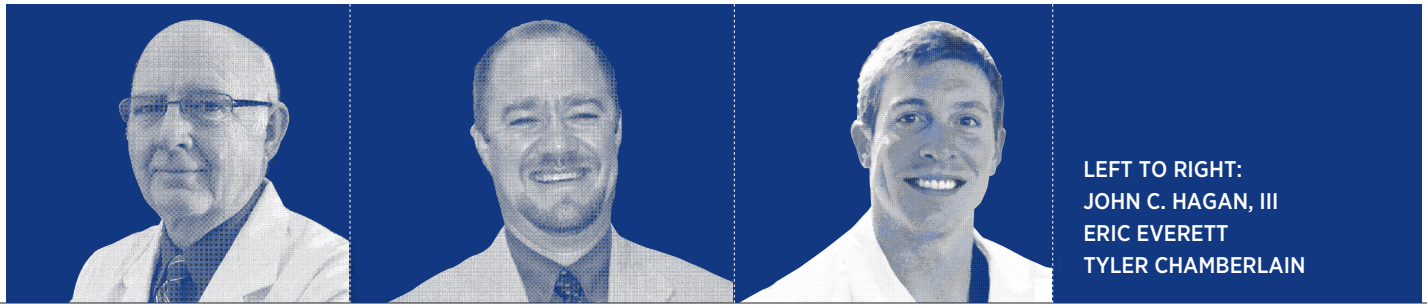
Per United States Pharmacopeia <795>, this preparation has a beyond-use date of 30 days when stored at room temperature.

USE

This preparation is used for acute migraines.

DOSAGE

Shake well. Instill 1 spray in each nostril at onset of headache. May repeat once in 15 minutes if the headache persists.



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Beta blockers, taken in a form that quickly produces therapeutic blood levels, offer excellent promise of being a useful treatment for acute migraine. Of all the methods that meet this criterion, nasal mucosa delivery is the most promising and is equivalent to intravenous dosing.

Suggestions for Use of Beta-blocker Nasal Spray for Acute Migraine

It is extremely important to inquire about any beta-blocker contraindication. We will not review all of them, but the most important are reactive airway disease, marked bradycardia, hypotension, or a previous history of problems with beta blockers. Patients already on beta blockers (e.g., cardiovascular disease) *should not* be treated, as they are already in chronic beta blockade. Patients satisfied with their acute migraine treatment do not need additional medication. Beta blockers in solution form are much more effective when taken quickly at the first onset of acute migraine symptoms. Patients are instructed to shake the bottle and swiftly apply one spray per nostril. They may take their other acute migraine abortive drugs such as analgesics, triptans, or ergot alkaloid. If their acute migraine is still symptomatic after 10 minutes to 15 minutes, one additional spray may be placed in each nostril. The maximum allowed sprays are four in twenty-four hours. Beta blockers have been shown to be compatible with a wide variety of medications. One study of beta-blocker eye drops found they had a beneficial effect on migraines when added to a calcium channel blocker (flunarizine).[15]

Other acute migraine beneficial properties of rapid therapeutic levels of beta blockers include lowering the blood pressure, slowing the pulse, and anti-anxiety effects. Beta blockers have been widely studied and used; physicians are familiar with beta blockers. They are relatively inexpensive.

Conclusion

Beta blockers, taken in a form that quickly produces therapeutic blood levels, offer excellent promise of being a useful treatment for acute migraine. Of all the methods that meet this criterion, nasal mucosa delivery is the most promising and is equivalent to intravenous dosing. There has not been a commercially available beta-blocker nasal spray anywhere in the world. O'Brien Pharmacy prepared their first compounded timolol 0.125% with Mucolox in 2019. Although the U.S. pharmaceutical market for migraine medications is estimated at $22 billion,[16] Big Pharma has not shown any interest in developing a commercial nasal-delivered beta-blocker migraine product, in spite of the relatively low cost and rapid FDA approval potential compared to a new molecule investment now estimated at $314 million to $2.8 billion.[17] It is hoped that if widespread success is obtained with the compounded nasal beta-blocker spray that the National Institutes of Health or other funding agencies might finance a large, prospective, placebo-controlled study of the new product.[18]

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