Review

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Ryzumvi: pioneering advances in countering drug-induced mydriasis

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Abstract

This article discusses the prevalence and impact of pharmacologically-induced mydriasis, a condition where the pupil becomes excessively dilated due to certain drugs. It highlights the challenges faced by medical professionals in dealing with this condition and the limitations of current treatments, like pilocarpine and dapiprazole, which come with systemic side effects and specific contra-indications, limiting their regular use. The article introduces Ryzumvi, a novel ophthalmic solution approved by the US FDA, which effectively reverses mydriasis caused by adrenergic agonists and antimuscarinic drugs. The article provides insights into its mechanism of action, clinical efficacy, pharmacokinetics, safety, and tolerance based on extensive clinical trials. It emphasizes its rapid onset of action and effectiveness in restoring pupils to their initial size. It also underlines the potential for expanded applications, including in pediatric patients, solidifying its importance in the field of ophthalmology. Furthermore, Ryzumvi represents a promising advancement in managing pharmacologically-induced mydriasis, offering swift and effective relief while highlighting the importance of adhering to safety precautions and the continuous research and development efforts in ophthalmology to comprehensively address vision-related disorders and enhance patient outcomes.

Keywords: FDA, mydriasis, ophthalmology, phentolamine, Ryzumvi

Introduction

Pharmacologic drugs that affect the central nervous system or the peripheral autonomic nervous system can modify the physiologic response of the iris, resulting in a change in pupil size[1]. When a parasympatholytic drug is accidentally or purposefully applied, the result is nearly invariably a very dilated pupil that completely obliterates the iris and is unresponsive to light or close stimuli[2]. In 2017, it was determined that there were 7.98 million cases of mydriasis prevalent in seven major market nations overall[3]. Based on estimations, the country with the highest prevalence of mydriasis is the United States[3]. France and Germany have the highest prevalence of mydriasis among the European Union, with Italy following closely behind[3]. In contrast, Spain had the fewest cases overall, with only 0.35 million cases in 2017[3].

Medical professionals, such as nurses, physicians, and pharmacists, are particularly vulnerable to inadvertent mydriatic agent instillation[2]. Over 100 million eye dilations are performed annually in the United States, for purposes such as regular examinations, disease surveillance, or retinal surgery[4]. Pharmacologically induced mydriasis can include side effects such as photophobia, sensitivity to light, and impaired vision that can last up to 24 h[5]. Being more sensitive to light can cause discomfort, which makes it difficult to do tasks like driving or spending time in highly lit areas. Disturbances in

HIGHLIGHTS

- Mydriasis is excessive dilation of the pupils, which often results in poor or blurry vision, photophobia, eye pain, and fatigue.
- Pharmacologically-induced mydriasis is caused by certain drugs such as belladonna, scopolamine or as a result of ophthalmic examinations.
- Current treatment options for pharmacologically-induced mydriasis include cholinergic agents such as pilocarpine or alpha blockers such as dapiprazole. However, both come with systemic side effects and contraindications, limiting their use.
- In September, 2023, the US FDA approved Ryzumvi (phentolamine opthalmic solution) for the treatment of pharmacologically-induced mydriasis.
- Ryzumvi has demonstrated considerable efficacy in clinical trials but further research is needed into its contraindications and limitations.

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accommodation, vision and impaired depth perception might impact activities that demand accurate near vision, such as reading or operating machinery, which could result in mishaps. The emotional impact of these changes in eyesight can also affect general health and day-to-day functioning. It is critical to differentiate this condition clinically from other serious diseases that seem identical, most notably compressive lesions of cranial nerve III.

Pharmacologically-induced mydriasis can be distinguished from other causes of a large, unreactive pupil by administering 1% pilocarpine[2]. Bilateral mydriasis can be caused by centrally acting drugs like atropine, lysergic acid diethylamide, scopolamine, marijuana, amphetamine, and glutethimide; however, this usually happens only after additional signs of involvement of the central nervous system, like depression, agitation, or an altered state of consciousness[6]. The cause of the unilaterally dilated pupil is often topical or local exposure to a variety of dilating substances, such as mydriatic drops[7]. The blockade of parasympathetic muscarinic acetylcholine receptors on the iris sphincter muscle causes anticholinergic mydriasis, while overstimulation of the α1-receptors of the iris dilator muscle causes adrenergic mydriasis[7]. The most common cause of dilated pupils in outpatients is finger-to-eye contact with belladonna or scopolamine; inpatients, on the other hand, may have dilated pupils from direct exposure to nebulized anticholinergic drugs, especially ipatropium[1]. This can be made worse by an improperly fitted mask and is particularly likely in individuals getting nebulized bronchodilators regularly[8]. Local botulinum toxin overexposure or systemic poisoning causes mydriasis through presynaptic inhibition of acetylcholine release from the short ciliary nerves innervating the iris sphincter muscles[7].

Current treatment options for pharmacologically-induced mydriasis

Multiple drug regimens have been used for pharmacologically-induced mydriasis, all of which have their respective merits and limitations. These treatments primarily revolve around reversing the mydriatic effects of certain drugs to restore normal pupillary function[9]. Some of the most commonly used pharmacologic agents are described below.

Pilocarpine

The most widely employed approach involves using cholinergic agents, such as pilocarpine, to induce pupillary constriction[10]. Pilocarpine operates by stimulating the parasympathetic nervous system and mimicking the action of acetylcholine, facilitating swift and effective reversal of mydriasis[11]. This made it valuable in clinical situations where rapid restoration of pupil size was essential, such as during eye examinations or when managing patients experiencing adverse reactions to mydriatic medications[11]. However, using cholinergic agents for treating pharmacological-induced mydriasis came with notable limitations. One primary challenge was the risk of systemic side effects. When applied topically, these agents could lead to systemic absorption, resulting in side effects like bradycardia, bronchoconstriction, and gastrointestinal disturbances. Moreover, an increased risk of retinal detachment has been reported with its use that presents as flashes, floaters, and visual field loss[12]. These effects restricted their use in patients with specific medical conditions, including chronic obstructive pulmonary disease, peptic ulcer disease, hyperthyroidism, and severe cases of miosis, making them less ideal for regular use[13].

Dapiprazole

Dapiprazole blocks alpha-adrenergic receptors in smooth muscle. It was considered an alternative to cholinergic agents, demonstrating its effectiveness and safety in reducing mydriasis induced by drugs like tropicamide and phenylephrine[14]. However, its limitations included side effects such as conjunctival injection, ptosis, erythema, lid edema, redness and itching, punctate keratitis, photophobia, and severe headache[15]. These limitations paved the way for a more effective, convenient, and well-tolerated treatment option for pharmacologically-induced mydriasis[16].

Advent of ryzumvi

Over 100 million thorough eye examinations involving pharmacologically induced pupil mydriasis are performed in the United States each year. It enables comprehensive posterior segment evaluation during Ophthalmic examination and the effects can last up to 24 h. However, individuals reported blurred vision and light sensitivity as side effects[16,17]. Additionally, many mydriases inducing eye drops cause cycloplegia, this necessitates the administration of a novel agent to counteract the side effects and discomfort it causes[18].

On September 27, the US Food and Drug Administration approved the use of Ryzumvi (phentolamine ophthalmic solution) 0.75% to reverse the pharmacologically-induced mydriasis that is mediated by adrenergic agonists (e.g. phenylephrine) or antimuscarinic drugs (e.g. tropicamide)[16,19]. Approval was granted based on MIRA clinical trial programs that conducted experiments on various subject populations involving children and older adults and consistently showed a favorable safety and tolerability profile across all trials[20,21].

Mechanism of action

Pupil size is regulated by two opposing sets of muscles: the iris sphincter muscles controlled by the cholinergic agonists and the iris dilator muscles controlled by the adrenergic agonists[18]. Ryzumvi or phentolamine ophthalmic solution 0.75% is classified as a nonselective, reversible alpha-1 and alpha-2 adrenergic antagonist[22]. Dilation of the pupil is primarily controlled by the radial iris dilator muscles that surround the pupil; these muscles are stimulated by the alpha-1 adrenergic receptors. Ryzumvi exerts its mechanism of action by reversibly binding to alpha-1 adrenergic receptors, thereby designed effectively to reduce pupil diameter without affecting the ciliary muscle[16,22]. Phentolamine directly inhibits the mydriatic effect of an alpha-1 adrenergic agonist and poses an indirect action to reverse the mydriasis associated with antimuscarinic agents on the iris sphincter muscle[16,22].

Clinical efficacy of ryzumvi

RYZUMVI's ophthalmic solution underwent a rigorous assessment within the extensive MIRA clinical trial program, encompassing more than 600 participants in various phases, including MIRA-1 Phase 2b, MIRA-2, MIRA-3 Phase 3 pivotal trials, and MIRA-4 Phase 3 pediatric trials. Notably, the solution delivered remarkable results in the MIRA-2 and MIRA-3 trials by meeting primary and vital secondary goals. It confirmed its statistical

superiority over a placebo in swiftly restoring dilated pupils to their initial size within 60 and 90 min. Equally important, the ophthalmic solution consistently demonstrated safety and tolerability in all trial phases. Additionally, the favorable outcomes from the MIRA-4 pediatric trial suggest the potential for an expanded application of the solution, including for individuals aged three and above, in managing Reversal Mydriasis[23].

Diving into MIRA-2 and MIRA-3: a closer look at the clinical trials

MIRA-2 and MIRA-3 were multicenter, randomized, placebo-controlled, double-masked clinical trials involving 553 healthy subjects aged 12 to 80. These individuals had mydriasis induced by phenylephrine, tropicamide, or a combination of hydroxy amphetamine hydrobromide and tropicamide (Paremyd). Subjects were randomly assigned, with consideration for iris color, to receive different mydriatic agents, and then they were further divided into groups receiving either Ryzumvi (POS) or a placebo. Across both trials, 338 subjects received POS, with an average age of 33 years and a 60% female representation, while 215 subjects received a placebo, with similar age and gender proportions. The primary result of the trials revealed that the administration of Ryzumvi, in the form of two drops in the study eye or one drop in the fellow eye, 1 h after mydriatic agent instillation, significantly and consistently reduced pupil dilation (pupil size returning to ≤ 0.2 mm from baseline) at various time intervals from 60 min up to 24 h compared to the placebo (vehicle) group in both MIRA-2 and MIRA-3, with statistical significance ($P < 0.01$)[24,25].

MIRA-4 (NCT#05223478) is a double-masked, placebo-controlled, parallel-arm trial involving around 20 pediatric participants. This study assesses the safety and effectiveness of Ryzumvi (0.75% Phentolamine Ophthalmic Solution) for reversing drug-induced pupil dilation caused by three dilating substances (such as phenylephrine, tropicamide, and Paremyd) in children. The trial aims to evaluate its use in treating Pharmacologically Induced Mydriasis in healthy pediatric subjects. The study will include two age groups for participant recruitment: 10 subjects aged 3–5 years and another 10 subjects aged 6–11 years. Furthermore, the positive results from the MIRA-4 pediatric study indicate the possibility of broader use of the solution, benefiting individuals aged three and older by managing Reversal Mydriasis[23,26].

Pharmacokinetics

In a Phase 3 trial (MIRA-3)[21], systemic exposure to phentolamine ophthalmic solution 0.75% was assessed following topical ocular application of three drops, each of 0.03 ml, with two drops applied to the eye under study, and one drop to the fellow eye, approximately post 1 h of pharmacologically induced mydriasis. The onset of action occurs in 30 min, whereas the maximal effects were achieved between 60 and 90 min, with a longer duration of action lasting 24 h. Additionally, peak plasma concentrations occurred 15–60 mins after dosage, with a median value of 0.45 ng/ml[21,22].

Safety and tolerance

During clinical trials involving 642 subjects from diverse populations, Ryzumvi's safety and tolerability profile were comprehensively assessed. The most frequent ocular adverse reactions that were reported in $>5\%$ of the patients in clinical studies were instillation site discomfort including pain, burning, and stinging (16%) and conjunctival hyperemia (12%) The only nonocular adverse reaction reported in $>5\%$ of subjects was dysgeusia (6%).

However, due to heterogeneity associated with the studies due to varying conditions, the rates may not reflect the actual encounters observed in practice[22]. Throughout all studies, Ryzumvi consistently displayed a positive safety and tolerability profile. Additionally, the safety and efficacy of Ryzumvi have been established in pediatric patients as well, supported by the (MIRA 4) clinical trial that involved subjects aged 3 and older[20]. It is worth highlighting that there have been no reported fatalities resulting from acute poisoning with phentolamine, further underscoring the medication's safety profile[19,24].

However, certain patients with underlying immunologic disorders conditions should avoid use.

1. Uveitis: Ryzumvi is contraindicated in patients with active ocular inflammation (e.g. iritis), as it can lead to adhesions between the iris and lens.
2. Risk for eye injury or contamination: to prevent any threat of eye damage or contamination, touching the vial tip to the eye or any other surface should be avoided.
3. Use with contact lenses: contact lens wearers should remove their lenses before application and wait 10 min after the dosage before reinserting their contact lenses[15,21].

Future applications and limitations

Ryzumvi marks a significant breakthrough in overcoming challenges related to pupil dilation, leading to expanded access to eye examinations and better outcomes for eye health. As an alpha-adrenergic blocker, Ryzumvi introduces a novel and highly effective approach to reversing pharmacologically induced mydriasis. Ryzumvi's remarkable attributes include its swift onset of action, with peak effectiveness manifesting within a mere 60–90 min postadministration. This quick response ensures convenience and efficacy, enabling timely diagnosis and treatment while maintaining its effect for a sustained 24 h period[19]. Our unwavering dedication to advancing eye care extends to a robust pipeline addressing a broad spectrum of vision-related disorders. This commitment underscores our commitment to ongoing research and development within the field of ophthalmology, paving the way for continual progress in eye care and the potential for innovative solutions tailored to a diverse range of conditions.

However, it is crucial to acknowledge that Ryzumvi is not without its limitations and safety considerations. Given the potential seriousness of its side effects, including a boxed warning serves as a necessary caution for healthcare practitioners. This warning highlights the risks associated with uveitis and the risk of eye injury or contamination. Additionally, for the safety and informed use of this medication, contact lens users should remove their lenses before administering Ryzumvi and wait 10 min before reinsertion[24]. These precautions underscore our commitment to prioritizing patient safety and well-being.

Conclusion

Ryzumvi represents a valuable addition to the management of pharmacologically-induced mydriasis, with its fast onset of action and proven clinical efficacy. It offers new hope for patients and healthcare practitioners dealing with this condition, though safety precautions must be carefully observed in its use. Its limitations, such as contraindication in people with underlying immunologic disorders and those using contact lenses must be investigated further. However, the advent of Ryzumvi for pharmacologically-induced mydriasis highlights the importance of ongoing research and development in the field of ophthalmology to address vision-related disorders comprehensively.

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Author contribution

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References

[1] Moeller JJ, Maxner CE. The dilated pupil: an update. Curr Neurol Neurosci Rep 2007;7:417–22.
[2] Spector RH. The Pupils. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Boston: Butterworths; 1990.
[3] Business Wire. Global Mydriasis Epidemiology Forecast 2017-2020 & 2030 – ResearchAndMarkets.com. Global Mydriasis Epidemiology Forecast 2017-2020 & 2030 - ResearchAndMarketsCom | Business Wire 2020. [Internet]. Accessed 28 October 2023. https://www.businesswire.com/news/home/20201009005459/en/Global-Mydriasis-Epidemiology-Forecast-2017-2020-2030---ResearchAndMarkets.com
[4] Wilson FA, Stimpson JP, Wang Y. Inconsistencies exist in national estimates of eye care services utilization in the United States. J Ophthalmol 2015;2015:1–4.
[5] Ophthalmology Times. US FDA approves RYZUMVI (Phentolamine Ophthalmic Solution) for the treatment of pharmacologically-induced mydriasis. Accessed 22 October 2023. https://europe.ophthalmologytimes.com/view/us-fda-approves-ryzumvi-phentolamine-ophthalmic-solution-for-the-treatment-of-pharmacologically-induced-mydriasis
[6] Selhorst JB. The pupil and its disorders. Neurol Clin 1983;1:859–81.
[7] Pharmacologic Dilation of Pupil - EyeWiki. Pharmacologic Dilation of Pupil - EyeWiki n.d. [cited 2023 Oct 22]; Pharmacologic Dilation of Pupil - EyeWiki. Pharmacologic Dilation of Pupil - EyeWiki.
[8] Iosson N. Images in clinical medicine. Nebulizer-associated anisocoria. N Engl J Med 2006;354:e8.
[9] Miller PE. Ocular Emergencies, Slatter's Fundamentals of Veterinary Ophthalmology (Fourth Edition). Ocular Emergencies Slatter's Fundamentals of Veterinary Ophthalmology 2008;19:419–26.
[10] Pilocarpine - StatPearls - NCBI Bookshelf [Internet]. Accessed 25 October 2023. https://www.ncbi.nlm.nih.gov/books/NBK556128/
[11] Pronin AN, Wang Q, Slepak VZ. Teaching an old drug new tricks: agonism, antagonism, and biased signaling of pilocarpine through M3 Muscarinic Acetylcholine Receptor. Mol Pharmacol 2017;92:601–12.
[12] Al-Khersan H, Flynn HW, Townsend JH. Retinal detachments associated with topical pilocarpine use for presbyopia. Am J Ophthalmol 2022;242:52–5.
[13] Cholinergic Medications - PubMed. Accessed 25 October 2023. https://pubmed.ncbi.nlm.nih.gov/30844190/
[14] Nyman N, Keates EU. Effects of dapiprazole on the reversal of pharmacologically induced mydriasis. Optom Vis Sci 1990;67:705–9.
[15] Drugs.com. Dapiprazole Ophthalmic Solution: Package Insert - Drugs.com [Internet]. Accessed 25 October 2023. https://www.drugs.com/pro/dapiprazole-ophthalmic-solution.html
[16] Ocuphire. Ocuphire Pharma and Viatris Announce FDA Approval of RYZUMVI™ (Phentolamine Ophthalmic Solution) 0.75% Eye Drops for the Treatment of Pharmacologically-Induced Mydriasis Produced by Adrenergic Agonists (e.g., Phenylephrine) or Parasympatholytic (e.g., Tropicamide) Agents : Ocuphire Pharma, Inc. (OCUP). Accessed 25 October 2023. https://www.ocuphire.com/news-media/press-releases/detail/415/ocuphire-pharma-and-viatris-announce-fda-approval-of
[17] Pumphrey SA, Moon Y, Francis JM, *et al*. Duration of mydriasis produced by 0.5% and 1% tropicamide in sprague–Dawley Rats. J Am Assoc Lab Anim Sci 2021;60:576.
[18] Karpecki PM, Foster SA, Montaquila SM, *et al*. Phentolamine eye drops reverse pharmacologically induced mydriasis in a randomized phase 2b trial. Optom Vis Sci [Internet] 2021;98:234–42.
[19] FDA. fda, cder. Highlights of prescribing information full prescribing information: contents* 1 indications and usage 2 dosage and administration 3 dosage forms and strengths 4 contraindications 5 warnings and precautions 5.1 uveitis 5.2 potential for eye. Accessed 25 October 2023. www.fda.gov/medwatch
[20] ClinicalTrials.gov. Nyxol (0.75% Phentolamine Ophthalmic Solution) to Reverse Pharmacologically-Induced Mydriasis in Pediatric Subjects - Full Text View - ClinicalTrials.gov [Internet]. Accessed 23 October 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05223478
[21] ClinicalTrials.gov. Safety and Efficacy of Nyxol (0.75% Phentolamine Ophthalmic Solution) to Reverse Pharmacologically-Induced Mydriasis (MIRA-3) - Full Text View - ClinicalTrials.gov [Internet]. Accessed 23 October 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05134974
[22] FDA. Highlights of Prescribing Information. Accessed 23 October 2023. Available from: www.fda.gov/medwatch
[23] OphthalmologyTimes. FDA approves RYZUMVI (Phentolamine Ophthalmic Solution) for the treatment of pharmacologically-induced mydriasis [Internet]. Accessed 22 October 2023. https://www.ophthal

mologytimes.com/view/fda-approves-ryzumvi-phentolamine-ophthalmic-solution-for-the-treatment-of-pharmacologically-induced-mydriasis

[24] PR Newswire. Viatris and Ocuphire Pharma Announce FDA Approval of RYZUMVI™ (Phentolamine Ophthalmic Solution) 0.75% Eye Drops for the Treatment of Pharmacologically-Induced Mydriasis Produced by Adrenergic Agonists (e.g., Phenylephrine) or Parasympatholytic (e.g., Tropicamide) Agents [Internet]. Accessed 22 October 2023. https://www.prnewswire.com/news-releases/viatris-and-ocuphire-pharma-announce-fda-approval-of-ryzumvi-phentolamine-ophthalmic-solution-0-75-eye-drops-for-the-treatment-of-pharmacologically-induced-mydriasis-produced-by-adrenergic-agonists-eg-phenylephrine-or-par-301940275.html

[25] Sooch M, Pepose JS, Haddad L, *et al*. Phentolamine ophthalmic solution rapidly reverses pharmacologically induced mydriasis in two pivotal phase 3 mira trial. Invest Ophthalmol Vis Sci 2023;64:30993099.

[26] ClinicalTrials.gov. Nyxol (0.75% Phentolamine Ophthalmic Solution) to Reverse Pharmacologically-Induced Mydriasis in Pediatric Subjects (MIRA-4) [Internet]. Accessed 18 March 2023. https://clinicaltrials.gov/study/NCT05223478