

Three Miotics You Should Know About (1 hour)

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Summary/Abstract

Miotics have historically been prescribed for glaucoma, but recently have been approved for the management of presbyopia. This course will discuss three common miotics – pilocarpine, carbachol, and aceclidine. The similarities and differences in the mechanisms of action for all three miotics will be examined. The most recent evidence from studies will be discussed to examine the efficacy and safety profiles in detail.

Learning Objectives

1. Understand the current state of miotics (for both approved and under investigation) the management of presbyopia
2. Explain the optimal pupil size necessarily for miotics to achieve to improve presbyopic symptoms
3. Explain the mechanism of action for each of the three miotics: pilocarpine, aceclidine, and carbachol
4. Discuss the safety profile for each of the three miotics.

Outline

- I. Background review
 1. Presbyopia
 - i. Prevalence
 - ii. Pathophysiology
 - iii. Accommodative mechanism
 2. Current management options for presbyopia
 - i. Glasses
 - a. SV/BF/TF/PALs
 - ii. Contacts
 - a. SV + readers/Monovision/MFs
 - iii. Refractive Surgery
 - a. Cornea: CK/LASIK/PRK/ICL
 - b. Lens: IOLs (Monofocal/MF/Accommodating)
- II. New Ways to Manage Presbyopia
 1. Lens softeners

- i. Oxysterols
 - ii. Lipoic acid choline esters
 - a. Not developed past FDA phase 2
- 2. Improving DOF
 - i. Three ways
 - a. Change the focus distance
 - b. Change the focal length
 - c. Change the aperture
 - a. Smaller aperture extends the depth of field
 - b. Decreases spherical aberration as well as other higher order aberrations

III. Pupil size

- 1. Ideal pupil size 2-3 mm
- 2. Minimizes diffraction (resulting from too small of a pupil)
- 3. Minimizes aberrations (resulting from too larger of a pupil)
- 4. But, this pupil size is best for distance, not near.
 - i. Optical modeling shows between 1-2 mm is better for improved near VA
 - ii. Corneal inlays and IOLs with artificial pupil agree use apertures in this range.

IV. Pilocarpine

- 1. Vuity, 1st in class, 1.25% pilocarpine
 - i. Preserved with BAK
 - a. All new drops under investigation are preservative-free
 - ii. Studies
 - a. GEMINI 1
 - a. 31% vs. 8% efficacy
 - b. GEMINI 2
 - a. 26% vs. 11% efficacy
 - c. VIRGO
 - a. 35% vs. 8% efficacy
- 2. MicroLine/MAP, 1%/2% pilocarpine
 - i. QD/PRN dosing
 - ii. VISION-1
 - a. Subjects age range: 40-60
 - iii. VISION-2
 - a. Subjects age range: 40-55
 - iv. NDA pending
 - a. Efficacy data currently not available
- 3. CSF-1, 0.4% pilocarpine
 - i. NEAR-1
 - ii. NEAR-2
 - a. Subjects age range: 45-64
 - iii. BID dosing
 - a. 40-50% reach endpoint at D8

- b. However, likely high % of controls reach endpoint based on D15 data
 - a. Control data not currently available
4. Nyxol, 0.4% pilocarpine (+ 0.75% phentolamine)
 - i. Phase 2 done 2Q21
 - a. 61% vs. 28% efficacy at 1 hour
 - b. 47% vs. 21% efficacy at 3 hours
 - ii. Phase 3 ongoing (VEGA-2)
- V. Aceclidine
- 1. Phase 2 done (INSIGHT)
 - i. Subjects age range: 46-73
 - ii. QD dosing
 - iii. 100: 1hr: 715 vs. 6% efficacy; 10 hrs: 37% vs. 4%
 - iv. 101 (+ brmonidine): 1 hr 56% vs. 4%; 10 hrs: 48% vs. 4%
 - 2. Phase 3 ongoing
- VI. Carbachol
- 1. Phase 2 completed 11/21 (VIVID)
 - 2. Phase 3 data pending (BRIO-1/BRIO-2)
 - 3. Subjects age range in studies: 45-80
 - i. Widest age range of any study
 - 4. QD dosing
- VII. Comparing pupil effects of the three miotics
- 1. Pilocarpine in studies achieves 2mm pupil or greater
 - i. Pupil size did not reach a new minimum with BID dosing
 - 2. Aceclidine in studies shows achieving pupil sizes between 1-2 mm
 - 3. Carbachol in studies achieve pupil sizes between 1-2 mm
 - i. Using a higher 3% dose
 - ii. Lower 2.25% does did not achieve pupil size below 2mm
- VIII. Comparing muscle stimulation ratio of the three miotics
- 1. Comparison of stimulation of ciliary muscle vs. iris sphincter muscle
 - 2. Use a ratio with higher ratios indicating increased stimulation of ciliary muscle vs. iris sphincter muscle
 - i. Higher ratios likely associated with more side effects
 - a. Pilocarpine = 25
 - b. Aceclidine = 1.7
 - c. Carbachol = 5.3
- IX. Comparing side effects and safety profile of the three miotics
- 1. General side effect categories
 - i. Comfort/discomfort with instillation
 - a. Irritation/Eye pain
 - ii. Comfort/discomfort after instillation
 - a. Browache/headache
 - a. GEMINI 1 > GEMINI 2 > VIRGO
 - i. Authors indicate due to way question was asked
 - b. Conjunctival hyperemia
 - iii. Retinal complications

- a. PVD
- b. Retinal tear
- c. Retinal detachment
 - a. More likely in higher myopia
 - b. More likely in eyes with prior retinal pathology
- iv. Sensory perception changes
 - a. Blurred vision/Visual impairment
 - a. Distance vision due to miosis or ciliary muscle contraction
 - b. Dimming of vision
 - a. Monocular use mention in bromochol study did not report stereovision issues with differential brightness
 - b. Worse issue with smaller pupil in theory
 - c. Adaptation effects
 - i. Improvement in symptoms over time

X. Conclusion

1. Current status of approved miotics/indications
 - i. QD or BID dosing
 - ii. Careful patient selection needed given potential side effects
 - iii. Preserved with BAK
 - iv. Tighter age range in P3 trials even though indication is 18+
2. Pending status of miotics under investigation
 - i. QD dosing
 - ii. Less expected side effects
 - iii. Non-preserved
 - iv. Wider age range enrolled in P3 studies