

# Systemic Effects of Topical $\beta$ -Blocker Therapy: The Family Physician's Role

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The relationship of advancing age with an increased prevalence of eye disease is well established.<sup>1-3</sup> Glaucoma, second only to macular degeneration as a cause of blindness, is an excellent example of this relationship, with prevalence increasing in each decade after the age of 40 years.<sup>3-6</sup> Approximately 3% of people aged over 65 years have glaucoma,<sup>7</sup> increasing to between 4% and 5% of people aged over 75 years.<sup>8</sup> The number of cases of glaucoma will undoubtedly increase and perhaps double in the next few decades as a result of an increasing life expectancy. As more glaucoma cases are diagnosed, family physicians may play an increasing role in routine glaucoma care.

## Case Report

The cardiovascular and possible neurogenic effects of  $\beta$ -blockers are well illustrated in the case of a 73-year-old hypertensive woman admitted to a medical intensive care unit with junctional bradycardia. The patient complained of nausea, dizziness, diaphoresis, weakness, and mild chest pain followed by diarrhea. She said these symptoms had begun approximately 5 or 6 days earlier and had become gradually more intense. Her admission heart rate was 36 beats per minute, and blood pressure was 90/60 mm Hg. Her current pertinent medication history included treatment for hypertension with metoprolol for 11 years, and the addition of timolol for the treatment of her glaucoma approximately 10 days before her admission. The patient's medications were discontinued after

admission, and her heart resumed a normal sinus rhythm, with a heart rate of 50 to 60 beats per minute and a blood pressure of 120/70 mm Hg. Her other symptoms also subsided shortly after  $\beta$ -blocker therapy was discontinued. A complete hospital record and cover letter were sent to both her family physician and ophthalmologist to ensure coordination of her future hypertension and glaucoma treatment.

## Discussion

The cul-de-sac of the eye is a highly effective site for systemic introduction of a drug. Drainage into the lacrimal duct initiates absorption through the vascular nasal mucosa with subsequent direct drainage into the ophthalmic and facial veins.<sup>9</sup> Avoiding the first-pass hepatic metabolism is especially relevant in the case the  $\beta$ -blockers, which may be 90% metabolized on a first hepatic pass when administered orally. Older patients often have difficulties administering precise doses with squeeze bottles; thus systemic absorption and resultant blood levels vary greatly. Systemic absorption can be reduced significantly by occluding the lacrimal puncta with gentle fingertip pressure for 5 minutes after instilling eye drops.<sup>10</sup> In younger patients excess medication will often run out of the eyes. In older patients, baggy lids, decreased periorbital fat, decreased eye sensation, increased physical difficulty with dropper bottle dosing, and the greater likelihood of the dose being administered while at rest can all contribute to excessive as well as inadequate dosing in older patients.<sup>11,12</sup> These factors are compounded by an increased incidence of preexisting disease and a higher susceptibility to side effects of  $\beta$ -blockers in the elderly population. Decreased cardiac response to adrenergic agents is a physiologic aging change that can lead to increased suppression of  $\beta$ -blockers.

Agents used in the treatment of glaucoma have

*Submitted, revised, July 17, 1990.*

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included a variety of drugs. Pilocarpine, in use for over 100 years, is an effective drug for lowering intraocular pressure, but its short duration of action, coupled with such side effects as headaches, pupil constriction, and iatrogenic nearsightedness, have contributed to its reduced use. Carbonic anhydrase inhibitors are also effective in lowering intraocular pressure by reducing aqueous humor production, but they have systemic side effects such as paresthesia, nausea, vomiting, and anorexia. These side effects limit the long-term usefulness of these drugs in glaucoma treatment.

The three topical  $\beta$ -blockers licensed for ophthalmic use in the United States (timolol, levobunolol, and betaxolol) have rapidly replaced most other drugs in the treatment of glaucoma in recent years.<sup>13-18</sup> Timolol was the first introduced in the United States for ophthalmic use and is the most widely prescribed. All of the  $\beta$ -blockers decrease intraocular pressure by reducing aqueous humor production,<sup>19-21</sup> but the precise mechanism of this action is unknown. Ophthalmologists generally agree that all three are similar in efficacy.<sup>15-20</sup> As a non-selective  $\beta$ -blocker, timolol has a well-documented history of adverse pulmonary effects, ranging from fatal status asthmaticus to mild respiratory distress.<sup>22-25</sup> Levobunolol, another nonselective  $\beta$ -blocker, may be suspect for similar pulmonary effects. Betaxolol, a  $\beta_1$  selective  $\beta$ -blocker, has also been associated with nonfatal respiratory distress in elderly patients.<sup>26,27</sup> Because of its beta selectivity, the risk of these side effects appears to be less. It is important to recognize that all three  $\beta$ -blockers have the potential to cause respiratory distress in some patients.

All three agents can affect the cardiovascular system as well. Most commonly,  $\beta$ -blockers are associated with a reduction in heart rate, although more serious cardiac complications have been reported.<sup>24,28,29</sup>

Oral  $\beta$ -blockers have also been linked with the development of central nervous system symptoms.<sup>30-32</sup> Several case reports have also demonstrated the same link associated with the use of the ophthalmic solutions timolol and betaxolol.<sup>33,34</sup>

## Conclusions

As the older population increases, so will the number of patients with glaucoma. Family physicians should be cognizant of the possible systemic effects prompted by glaucoma medications. Predisposing factors for overdosing topical glaucoma medications in older patients and the likelihood that older patients will fail to report "eye drops" in a current medication history may serve to help

initiate side-effect problems. Patients often do not appreciate that ophthalmic drops can have systemic effects and that the outcome of overdosing these medications can be profound in susceptible individuals. Ophthalmologists who prescribe these medications must be aware of medications prescribed for other conditions.

All physicians must periodically inventory individual patient medications. This inventory is best done in the elderly by asking the patient or caregiver to bring to the physician *all* medications (including over-the-counter medications) taken on a regular basis. This effort will help the physician maintain an accurate medication list, essential in the care of the elderly.

This report underscores the need for a thorough current drug history and increased communication among all parties. Family physicians should maintain a high index of suspicion concerning systemic effects of glaucoma medications, particularly when dealing with elderly patients.

## Acknowledgments

This report is supported in part by an unrestricted grant to the Department of Ophthalmology at the University of Utah School of Medicine, Salt Lake City, from Research to Prevent Blindness.

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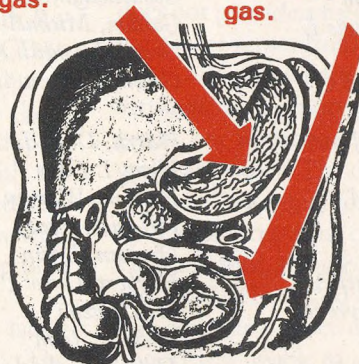
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