Generic Glaucoma Medications

Is it safe to switch?

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Primary open-angle glaucoma is a multifactorial optic neuropathy with characteristic changes to the optic disc and visual field loss. Although mechanisms other than elevated IOP may contribute to the underlying pathophysiology of glaucoma, reducing IOP remains the cornerstone of therapy. Recent clinical studies have shown that decreasing IOP can delay, or in some cases prevent, glaucomatous progression.[1,2]

After the diagnosis of glaucoma, the clinician must tailor an appropriate therapeutic regimen to the individual patient's needs. Intervention typically begins with topical medical therapy supplemented, if necessary, by laser or incisional surgery to achieve an adequate reduction in IOP. Currently, there are five classes of medications used to lower IOP: beta-adrenergic antagonists; alpha-2 adrenergic agonists; carbonic anhydrase inhibitors (CAIs); prostaglandin analogs; and cholinergic agonists. Each class comprises a number of different products offered by various pharmaceutical companies.

Patients' adherence to therapy is an important concern, and increasing drug costs can be a factor.[3] In all fields of medicine, generic medications have become more widely used because they cost patients less,[4] and recent years have brought the development of several generic ocular hypotensive agents for the treatment of glaucoma (Table 1). Although generics are only available in certain classes (beta-adrenergic antagonists, alpha-2 adrenergic agonists, cholinergic agonists, and systemic CAIs), additional agents should become available in the future as the patents of branded drugs expire. The question for clinicians, then, is how equivalent are generics to their brand-name counterparts.

FDA APPROVAL PROCESS

Prior to the FDA's legislative hallmark, the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), generic medications composed a small portion of the drug industry. The Hatch-Waxman Act benefited the generic industry by allowing generic drugs to forego expensive and time-consuming clinical trials. The FDA has attempted to increase these agents' availability further by implementing initiatives to streamline the application process for generics. In June 2003, the FDA launched the initiative, "Improving Access to Generic Drugs," to expedite the time necessary to market these agents.[5]

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When the patent for a brand-name drug expires, competing pharmaceutical companies may issue an Abbreviated New Drug Application to the FDA for approval of their generic agent. The innovating company of the brand-name drug typically holds the patent for 20 years following its issuance. When a generic drug is submitted for approval, the applicant must provide evidence of the bioequivalence of the product. For systemic medications, this proof is typically obtained by measuring plasma levels of the drug following administration. The concentrations of the drug must be within a certain range (85% to 125%) of that measured for the branded drug during clinical trials. In addition to bioequivalence, generics must have the same active ingredients, dosage, route of administration, labeled strength, and labeling as the brand-name drug. The company applying to the FDA must also provide evidence of its compliance with the federal regulation of good manufacturing practices and demonstrate that finished materials meet the specifications of the US Pharmacopoeia.

Once approved, generic medications receive a rating based on their equivalence to the branded drug as determined by the FDA. There are four different rating categories: (1) A-rated (considered equivalent and can be substituted by a pharmacist when filling a prescription); (2) B-rated (has not demonstrated evidence of bioequivalence and should not be substituted for a branded product); (3) AB-rated (has undergone some in vitro and in vivo testing and may have probable or actual bioequivalence to the branded product); and (4) AT-rated (topical product that has probable bioequivalence to the branded product). Ophthalmic preparations typically receive an AT rating.

CONCERNS WITH GENERIC OCULAR HYPOTENSIVE MEDICATIONS

A concern among clinicians is whether generic ocular hypotensive agents are as effective at reducing IOP as their brand-name predecessors. One presumes that generic medications have the same level of bioequivalence, because they are required to contain the same active ingredient as the brand-name drug. Their inactive ingredients may differ, however. Inactive ingredients include preservatives and adjusters of pH and tonicity. They can affect the bioavailability of the drug by interfering with its solubility and ocular penetration, and inactive ingredients may ultimately affect the drug's effectiveness.

Preservatives alone can influence a drug's ability to penetrate the eye. Animal studies performed by both Dong et al[6] and Acheampong et al[7] provided evidence that brimonidine tartrate preserved with chlorine dioxide (Purite; Allergan, Inc., Irvine, CA) had superior ocular penetration and aqueous levels compared with brimonidine tartrate preserved with benzalkonium chloride. Moreover, the addition of sorbic acid has been shown to improve the ocular bioavailability of timolol maleate.[8]

TABLE 1. COMMONLY USED GLAUCOMA MEDICATIONS WITH GENERIC EQUIVALENTS

CLASS	TRADE NAME	ACTIVE INGREDIENT	COMPANY	GENERIC EQUIVALENT*	COMPANY
Alpha-2 adrenergic agonists	Alphagan	Brimonidine 0.2%	Allergan, Inc.	Brimonidine 0.2%	Bausch & Lomb and Falcon Pharmaceuticals, Ltd.
Beta-adrenergic antagonists	Timoptic	Timolol maleate solution 0.25% and 0.5%	Merck & Co., Inc.	Timolol maleate 0.25% and 0.5%	Bausch & Lomb and Falcon Pharmaceuticals, Ltd.
	Istalol	Timolol maleate solution 0.5%	ISTA Pharmaceuticals, Inc.	Timolol maleate 0.5%	Bausch & Lomb and Falcon Pharmaceuticals, Ltd.
	Timoptic XE	Timolol maleate gel 0.25% and 0.5%	Merck & Co., Inc.	Timolol GFS 0.25% and 0.5%	Falcon Pharmaceuticals, Ltd.
	Betoptic S	Betaxolol HCl 0.25% and 0.5%	Alcon Laboratories, Inc.	Betaxolol HCl 0.25% and 0.5%	Bausch & Lomb
	Betagan	Levobunolol HCl 0.25% and 0.5%	Allergan, Inc.	Levobunolol HCl 0.25% and 0.5%	Bausch & Lomb
Cholinergic agonists	Isopto Carpine	Pilocarpine HCl 1%, 2%, and 4%	Alcon Laboratories, Inc.	Pilocarpine HCl 1%, 2%, 4%, and 6%	Bausch & Lomb
	Pilopine-HS gel	Pilocarpine HCl 4% gel	Alcon Laboratories, Inc.	Pilocarpine HCl 4%	Bausch & Lomb
Sympathomimetics	Propine	Dipivefrin hydrochloride 0.1%	Allergan, Inc.	Dipivefrin hydrochloride 0.1%	Bausch & Lomb
Systemic CAIs	Diamox SR	Acetazolamide 500 mg	Duramed Pharmaceuticals Inc.	Acetazolamide 250 mg	TARO Pharmaceuticals U.S.A., Inc.
	Neptazane	Methazolamide 25 mg and 50 mg	Wyeth Pharmaceuticals	Methazolamide 25 mg and 50 mg	TEVA Pharmaceuticals USA

Data adapted from Physicians' Desk Reference for Ophthalmic Medicines. *34th ed. Montvale, NJ: Thomson PDR; 2006.*

**There are several manufacturers of generic pilocarpine hydrochloride and acetazolamide. Due to limited space, only one company was listed in the table.*

Without published head-to-head clinical trials comparing the safety, side-effect profile, and efficacy of topical generic ophthalmic drugs to brand-name agents, it is difficult to ascertain whether generic ocular agents are truly equivalent. There have already been reports of the differences of generic ophthalmic medications previously on the market. For instance, the generic topical nonsteroidal anti-inflammatory 1% diclofenac sodium ophthalmic solution manufactured by Falcon Pharmaceuticals, Ltd. (Fort Worth, TX), was associated with a high incidence of corneal toxicity, including several cases of corneal melt that ultimately led to the agent's voluntary recall from the market.[9] Cases of differences for generic prednisolone acetate have also been reported in the literature.[10]

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AVAILABLE GENERIC GLAUCOMA MEDICATIONS

There are few published reports comparing the safety and efficacy of generic agents with the brand-name drugs of the same class. Clinical trials, however, are sometimes conducted when a medication is altered by changing the drug's delivery vehicle or preservative in the solution. These studies not only help provide evidence of the agent's equality, but they may also aid the marketing efforts of the pharmaceutical companies. Currently, the selective alpha-2 adrenergic agonists, cholinergic agonists, selective and nonselective beta-adrenoreceptor antagonists, and oral CAIs have generic equivalents available on the market (Table 1). The prostaglandin analogs and topical CAIs are still under patent.

Alpha-2 Adrenergic Agonists

Allergan, Inc., developed the first selective alpha-2 adrenergic agonist, brimonidine tartrate 0.2%, preserved with benzalkonium chloride (Alphagan). This agent was introduced to the US market in 1996. It has since been reformulated by reducing the concentration of the active ingredient, brimonidine tartrate, to 0.15%, and by replacing the preservative with Purite (Alphagan-P; Allergan, Inc.). The two drugs reduce IOP comparably.[11,12]

The patent on the original Alphagan solution has expired, and two generic equivalents are available in the US from Falcon Pharmaceuticals, Ltd., and Bausch and Lomb (Rochester, NY). To our knowledge, there are no published peer-reviewed studies comparing the efficacy and safety of these two generic agents to Alphagan.

Beta-Adrenergic Antagonists

Timolol maleate is a nonselective topical beta-blocker for treating ocular hypertension and glaucoma, and the agent is typically administered b.i.d. when in solution. Timoptic XE 0.5% ophthalmic solution (Merck & Co., Inc, West Point, PA) is a gel formulation of timolol maleate that was developed to enhance the drug's delivery into the eye and to lower systemic absorption by providing a longer ocular contact time. The efficacy and safety of Timoptic XE 0.5% administered q.d. is similar to timolol maleate 0.5% solution used b.i.d.[13]

Two additional formulations of timolol maleate are available in the US. Timolol GFS 0.5% (Falcon Pharmaceuticals, Ltd.) is a generic version of Timoptic XE 0.5%. Clinical studies have shown this agent to be equally effective at reducing IOP as its brand-name predecessor.[14] A newly developed timolol maleate solution recently came to market that is preserved with potassium sorbate (Istalol; ISTA Pharmaceuticals, Inc., Irvine, CA). The agent has been shown to be as effective and safe as timolol maleate ophthalmic solution.[15]

Systemic Acetazolamide

Diamox (Duramed Pharmaceuticals Inc., Cincinnati, OH) is an oral CAI that is very effective at reducing IOP. The systemic administration of a CAI is usually reserved for patients with uncontrolled IOP who are on maximal tolerated topical medical therapy. A study comparing oral Diamox to generic acetazolamide found the two drugs to be similar in safety and efficacy.[16] In a cost comparison, the generic acetazolamide was 37% less expensive.[17]

DISCUSSION

Because they can reduce costs to patients,[17] generic medications are becoming more widely used in the treatment of glaucoma. As the overall price of healthcare rises, these agents' popularity should continue to grow. The use of some, but not all, generic medications is supported by published head-to-head clinical trials in the literature. Until more peer-reviewed, published studies are available, however, clinicians must closely monitor patients after they switch from a brand-name drug to a generic equivalent in order to ensure the safety and efficacy of that agent. ❑

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