Medical Therapy of Pediatric Glaucoma and Glaucoma in Pregnancy

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Medical therapy is usually allocated to a supportive role in the management of pediatric glaucoma patients. In children, medical therapy is used to reduce intraocular pressure temporarily or to clear the cornea so that surgical therapy, the definitive treatment for primary congenital glaucoma, can be undertaken. Those patients who do require long-term medical therapy usually have intractable disease that has not responded adequately to surgical therapy. Our purpose is to review medical therapy of pediatric patients. We also review medical treatment of glaucoma in pregnant women, considering the risks and benefits of treatment of the patient and potential adverse effects on the fetus.

Medical therapy of pediatric glaucoma

Some children with congenital glaucoma and elevated intraocular pressure respond well to medical therapy. In 161 eyes with congenital glaucoma, medical therapy by itself reduced the intraocular pressure to less than 21 mm Hg in 12% of eyes in the short term and 10% of eyes in the long term [1]. When considering medical therapy in pediatric patients, clinicians should evaluate the risks and benefits of specific medications, use the minimum dosages required for therapeutic efficacy, and follow the patient closely for ocular and systemic side effects [2,3]. Although regulatory agencies worldwide do not typically include children in antiglaucoma drug approval studies, clinicians have found several medications to be useful in treating children with elevated intraocular pressure (Box 1). Evidence has appeared in the literature regarding the efficacy and safety of different classes of glaucoma medications.

Carbonic anhydrase inhibitors

In adult patients, the side effects of systemic carbonic anhydrase inhibitors are well known to clinicians. In children, growth suppression has been associated with oral acetazolamide therapy, and infants may experience severe metabolic acidosis [4,5]. Side effects from the use of systemic carbonic anhydrase inhibitors in infants and young children are not commonly reported, although these patients may not verbalize the occurrence of side effects to their parents or health care providers. Oral administration of acetazolamide suspension at a dosage of 10 (range: 5–15) mg/kg/d in divided doses (three times daily) is usually tolerated by children, reduces intraocular pressure, and diminishes corneal edema before surgery [6,7].

Topical versus oral carbonic anhydrase inhibitor therapy has been evaluated for pediatric glaucoma in a crossover design study [8]. The mean intraocular pressure was reduced by 36% and 27% compared with baseline after treatment with oral acetazolamide...
and topical dorzolamide, respectively (Fig. 1). Although not as effective as acetazolamide in this group of patients, topical dorzolamide caused a significant reduction in intraocular pressure [8]. Furthermore, treatment with topical dorzolamide caused few side effects. One patient noted a burning sensation after installation during the first month of use, but none experienced corneal toxicity or allergic symptoms.

Presently, topical carbonic anhydrase inhibitors are more widely prescribed compared with systemic carbonic anhydrase inhibitors. Many clinicians prefer twice-daily dosing to minimize the discomfort and inconvenience to the parent and the child associated with three times daily dosing. Taking the fixed combination of dorzolamide with timolol twice a day can simplify the medical regimen by reducing the number of drops instilled per day and may be more appropriate for older children.

**Beta-blockers**

Adjunctive treatment with timolol has been studied in patients with a variety of pediatric glaucomas. In 34 patients with childhood glaucoma, timolol was combined with other medical therapy, causing a definite improvement in 29%, a modest or equivocal improvement in 32%, and no improvement in 39% [9]. In 38 eyes being treated with timolol as adjunctive therapy, 37% of eyes were controlled at 22 mm Hg or lower [10]. In 89% of eyes with various types of pediatric glaucoma, lowering of intraocular pressure was significantly reduced from baseline (on a topical beta-blocker alone) after addition of acetazolamide (mean ± standard deviation decrease of 35.7% ± 15.6%) or dorzolamide (27.4% ± 17.1%). Y error bars indicate standard error of mean. Asterisk indicates P < .01 compared with baseline. (B) Correlation between efficacy of oral and topical carbonic anhydrase inhibitor therapy. The percentage reduction of IOP in eight eyes on topical beta-blocker therapy was similar after the addition of acetazolamide (oral) or dorzolamide (topical) treatment (r = 0.94). (Adapted from Portellos M, Buckley EG, Freedman SF. Topical versus oral carbonic anhydrase inhibitor therapy for pediatric glaucoma. J AAPOS 1998;2:43–7; with permission.)

**Box 1. Glaucoma medications commonly used in childhood glaucoma**

- **Beta-blockers**
  - Betaxolol 0.25% (every day, twice daily)
  - Levobunolol 0.25% (every day, twice daily)
  - Timolol solution 0.25% (every day, twice daily)
  - Timolol gel-forming solution 0.25% (every day)
- **Carbonic anhydrase inhibitors**
  - Acetazolamide elixir, 5 to 15 mg/kg/d in divided doses (twice daily, three times daily)
  - Brinzolamide 1% (twice daily, three times daily)
  - Dorzolamide 2% (twice daily, three times daily)
- **Cholinergic drugs**
  - Pilocarpine 1%, 2% (three times daily, four times daily)
- **Prostaglandin-related drugs**
  - Bimatoprost 0.03% (every day)
  - Latanoprost 0.005% (every day)
  - Travoprost 0.004% (every day)
pressure was achieved only in 20% of eyes [11]. Similarly, in 100 eyes with childhood glaucoma treated with timolol, 31% experienced a reduction of intraocular pressure (Fig. 2) [12]. After the initial response, however, increased intraocular pressure may occur over time [10].

Plasma timolol levels in children after treatment with 0.25% timolol greatly exceed those in adults after instillation of 0.5% timolol, particularly in infants [13]. Increased plasma timolol levels in children are explained by the volume of distribution of the drug, which is much smaller in children compared with adults. The ocular volume of the neonate is approximately half that of the adult, reaching full size by approximately 2 years, whereas the blood volume of the neonate as a function of body weight is only a small fraction of that of the adult. Thus, administering the usual adult ocular dosage may be needed for the eye; however, when it is systemically absorbed, the dosage is diluted by a much smaller volume of blood.

In addition, the infant’s immature metabolic enzyme systems may prolong the half-life of drugs in the neonate from two to six times beyond that of the typical adult [14]. Higher plasma levels of drug in infants and children would be expected to increase the risk of systemic side effects as compared with adults.

In children older than 5 years of age, a reduction in resting pulse rates has been associated with timolol use and is comparable to that of adults [9]. Side effects have occurred in 4% to 13% of children [10,11], and timolol therapy has been discontinued in 3% to 7% of patients [9,10]. Alarming side effects of timolol therapy, such as Cheyne-Stokes breathing and apneic spells, have been reported, especially in infants and younger children [15–17]. Provocation of asthma has been associated with timolol treatment. Betaxolol, a selective β1 antagonist, reduces the risk of pulmonary side effects in adults as compared with timolol, but its effect on children is not known. Likewise, the effects of long-term use of any of the topical beta-blockers in children have not been reported.

Timolol in 0.25% and 0.5% solutions should be used cautiously in young glaucoma patients. Because of the possibility of apnea, the drug should be used with extreme caution in neonates. A detailed pediatric history and examination to elicit the presence of systemic abnormalities, such as bronchial asthma and cardiac disease, should precede the use of timolol. In such cases, therapy with a beta-blocker is contraindicated. The use of 0.25% timolol instead of 0.5% timolol is strongly recommended to reduce the risk of side effects. Additionally, a significant reduction in the systemic absorption of timolol has been observed when performing punctal occlusion and simple eyelid closure after drop administration [13]. Although the practice of punctal occlusion with the eyelids closed for at least 1 minute may be considerably more difficult to execute in children than in adults, simply blotting off excess drops from the child’s lids may help to minimize unwanted systemic absorption [13]. Once-daily dosing with timolol 0.25% in a gel-forming solution may similarly help to simplify the medical regimen.

$\alpha_2$ Agonists

Several noncomparative case series describing the use of brimonidine in pediatric glaucoma patients exist in the ophthalmic literature, whereas the pediatric use of apraclonidine has not been described. In 30 patients with a mean age of 10 years, brimonidine treatment achieved a mean 7% reduction in intraocular pressure from baseline [18]. Two young
children (aged 2 and 4 years) were transiently un-
arousable after administration of brimonidine, and
five other children experienced severe fatigue [18].
In a study of 23 patients with a mean age of 8 years,
18% experienced serious systemic adverse effects
necessitating cessation of the drug [19]. Four pe-
diatric patients have been reported to develop som-
nolence after treatment with brimonidine [20].
Additionally, a 1-month-old infant experienced re-
peated episodes of “coma,” characterized by unre-
sponsiveness, hypotension, hypotonia, hypothermia
and bradycardia after treatment with brimonidine [21].

The \( \alpha_2 \) agonists are less often used in pediatric
patients compared with adult patients. The possibility
of central nervous system–mediated side effects is
greater with lipophilic drugs (eg, brimonidine)
than for more hydrophilic drugs (eg, apraclonidine),
which are less likely to cross the blood-brain barrier.
Lipidation may help to minimize intraoperative hy-
phema precipitated by goniotomy [22]. Brimonidine
should be used cautiously in pediatric patients, and its
use should be restricted to older children.

Other adrenergic agonists

Although uncommonly prescribed at present as an
ocular hypotensive agent in the adult population,
epinephrine (1%) has been used in children [23].
Lack of efficacy as well as the potential for systemic
toxicity, including cardiac tachyarrhythmia and
hypertension, limit the use of this drug. When used,
a reactive conjunctival hyperemia may occur after the
initial \( \alpha_1 \)-mediated vasoconstriction. After prolonged
use of topical epinephrine (1%), melanin-like ade-
rochromine deposits consisting of oxidation products
of the compound may be noted in the conjunctiva and
occasionally in the cornea. Dipivefrin hydrochloride
0.1%, a prodrug of epinephrine, may also be used
in pediatric patients. Given its produrg composition,
side effects may be attenuated compared with epi-
 nephrine. Still, local allergic reactions occur fre-
quently. These drops are administered every 12 to
24 hours. Epinephrine (1%) and dipivefrin hydro-
chloride 0.1% should be avoided in aphakic or pseu-
dophakic pediatric patients because of the risk of
cystoid macular edema.

Cholinergic drugs

Although miotic drugs enhance aqueous outflow
through the trabecular meshwork in normal patients
as well as in glaucoma patients, thereby lowering
intraocular pressure, these drugs are likely not as
effective in developmental glaucoma. This reduced
efficacy in developmental glaucoma is believed to be
attributable to the abnormal insertion of the ciliary
muscle into the trabecular meshwork. In pediatric
patients, the use of pilocarpine (2% applied every
6–8 hours) has been limited [6]. These drugs may
benefit aphakic and pseudophakic children with ele-
vated intraocular pressure, however. In addition,
cholinergic drugs serve a useful purpose in the sur-
gical management of pediatric glaucoma by causing
pupillary miosis before and after goniotomy [22].

The induced myopia produced by miotic therapy
can cause disabling visual difficulties. A slow-release
pilocarpine membrane delivery system, Ocusert (Alza
Pharmaceuticals, Palo Alto, California), currently not
available from the manufacturer, was helpful in some
young patients [24], and the sudden release of pilo-
carpine (burst effect) seldom induced myopic spasms.

The long-acting anticholinesterase drugs are not
readily available, are associated with serious adverse
effects, and offer no advantages over pilocarpine for
use in pediatric glaucoma. Echothiopate iodide
(phospholine iodide), usually administered topically
every 12 to 24 hours, is a potent and relatively ir-
reversible inhibitor of the enzyme cholinesterase.
Ciliary spasm and angle-closure glaucoma have been
precipitated by the use of echothiopate iodide to
 treat esotropia in a child [25]. Also, the systemic ab-
sorption of anticholinesterase agents can significantly
reduce the serum cholinesterase and pseudocholinest-
erase levels. Affected patients, particularly children,
may show signs of excessive parasympathetic ner-
vous system activation. These signs can include
generalized weakness, diarrhea, nausea, vomiting,
excessive salivation, and decreased heart rate.

Significantly reduced systemic levels of cholinest-
erase and pseudocholinesterase can be particularly
dangerous when surgery is contemplated, because succ-
cinylcholine is commonly used as a muscle relaxant
during general anesthesia. Succinylcholine is nor-
mally quickly hydrolyzed by systemic cholinesterase
at nerve endings. When serum cholinesterase levels
are low, however, prolonged apnea can result because
of this excess of unhydrolyzed succinylcholine.

Prostaglandin-related drugs

Prostaglandin-related drugs, specifically latano-
prost, have been evaluated in studies of a variety of
glaucoma diagnoses, including glaucoma associated
with Sturge-Weber syndrome [26–30]. In 31 eyes
with a variety of glaucoma diagnoses, 6 (19%) of the
treated eyes responded with a mean reduction in
intraocular pressure of 8.5 mm Hg, which represented
a 34% decrease from baseline. Most eyes were
nonresponders, however (Fig. 3). Subjects who responded favorably were more likely to have juvenile-onset open-angle glaucoma and to be older than nonresponders [26]. The drug was well tolerated in this short-term study.

In glaucoma associated with Sturge-Weber syndrome, 17% to 28% of eyes treated with latanoprost responded with a reduction in intraocular pressure [27,28]. Increased episcleral venous engorgement was noted, and one patient (6%) discontinued latanoprost therapy because of intolerable hyperemia of the conjunctiva [28]. Although a decline in success over time was noted, half of the patients were controlled at 1 year of follow-up after a trial of latanoprost as adjunctive therapy [29].

Although most children do not respond well to latanoprost therapy, some children may experience an appreciable hypotensive effect with treatment [30]. Likewise, the once-daily dosing schedule for latanoprost is convenient. Although local side effects are infrequent and mild, parents and patients should be warned about them, including iris pigmentation changes, eyelash growth, and hyperemia. When short-term medical therapy is planned, such as before surgery, these local side effects are usually not a problem. The prevalence and types of side effects associated with long-term latanoprost use are not known, however.

**Osmotic drugs**

Glycerol is administered orally at a dose of 0.75 to 1.5 g/kg of body weight in a 50% solution [31]. The excessively sweet taste may be partially masked by chilling the solution over ice or by using fruit juice (commonly lemon or orange) or flavored water as a diluent. This drug is not commonly used in the treatment of developmental glaucoma. Mannitol (20% solution) is dosed intravenously at 0.5 to 1.5 g/kg of body weight at approximately 60 drops per minute. A rapid fall in intraocular pressure occurs in 20 to 30 minutes after drug administration and can last for 4 to 10 hours. Mannitol may also be used to reduce markedly elevated intraocular pressure before surgery in patients with developmental glaucomas refractory to standard medical therapy.

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**Fig. 3. Latanoprost in pediatric glaucomas.** (A) In a series of 31 eyes, most children (n = 25) were nonresponders (defined as <15% decrease in intraocular pressure [IOP]). Medical therapy using any particular drug is usually effective in a few pediatric glaucoma patients. (B) In 31 eyes, latanoprost was effective in six responders (defined as ≥15% decrease in IOP). The average IOP reduction in latanoprost responders was 8.5 ± 3.6 mm Hg (34.0% ± 10.9%; asterisk denotes P = .002). Y error bars indicate standard deviation. (Adapted from Enyedi LB, Freeman SF, Buckley EG. The effectiveness of latanoprost for the treatment of pediatric glaucoma. J AAPOS 1999;3:33–9; with permission.)
Glaucoma in pregnancy

Although glaucoma in adults is primarily a disease of the older population, it can affect women of childbearing age. In managing the pregnant glaucoma patient with medical therapy, one must consider not only the systemic side effects on the mother but any potentially harmful effects on the developing fetus. Based on the limited available literature on the subject, the risk associated with prescribing ophthalmic drops to pregnant women is low [32]. Clinicians should consult experts in the field when in doubt about any deleterious effects of ophthalmic medications, however.

Glaucoma is rarely first discovered during pregnancy because intraocular pressure is usually noted to decrease during pregnancy and stays decreased for several months postpartum [33,34]. This reduction in intraocular pressure has been proposed to be caused by several factors: an increase in uveoscleral outflow based on changes in the mother’s endogenous hormone levels, a decrease in episcleral venous pressure reflecting an overall reduction of venous pressure in the upper extremities, and a slight metabolic acidosis induced by the mother’s pregnant state [35]. This hypotensive effect is believed to increase slightly during the course of the pregnancy. In one study of a group of pregnant women, the mean intraocular pressure in the third trimester was demonstrated to be 1.5 mm Hg lower than in the first trimester [36].

Little is known regarding the teratogenic effects of the commonly prescribed glaucoma medications, and few human studies have specifically examined the potential for harm rendered by the topically applied glaucoma medications. The information that does exist on the subject has been extrapolated from studies of adverse effects attributable to systemic treatment with various agents. For example, a large collaborative study examining the use of systemic cholinergic drugs (eg, pilocarpine) found no association between their use during the first 4 months of gestation and congenital abnormalities [37]. Systemic adrenergic compounds (analogues of topical epinephrine 1% and dipivefrin) have been shown to inhibit the spontaneous and oxytocin-induced contractions of the human uterus, however, and may delay the second stage of labor or cause a prolonged period of uterine atony with hemorrhage [37].

The US Food and Drug Administration (FDA) and other groups specify safety in pregnancy according to categories or classes based on human and animal studies. Class A indicates that safety is established using human studies. Class B indicates presumed safety based on animal studies. Class C indicates uncertain safety, with no human studies and animal studies showing an adverse effect. Class D indicates unsafe, with evidence of risk that may be justifiable in certain clinical circumstances. Class X indicates highly unsafe, with the risk of use outweighing any possible benefit. No topical ophthalmic drugs are placed in category A or X.

Most topical glaucoma medications belong to the pregnancy category C (Fig. 4), deemed as having uncertain safety because of adverse fetal effects in animals. Brimonidine and dipivefrin have been ascribed class B status, which presumes safety based on animal studies only. What specifically may confer the additional safety of these two compounds, although similar agents, such as apraclonidine, remain class C, is not apparent when reviewing the literature, however. The fixed-combination timolol 0.5%/dorzolamide 2% has been designated category D.

Prostaglandin-related drugs are in pregnancy category C because of adverse fetal effects in animals. Use of the prostaglandin-F₂α analogues during pregnancy arouses concern because of their presumed abortifacient actions [38]. Manufacturer reports indicate that 25% of pregnant rabbits exposed to 80 times the human dose of latanoprost delivered no viable fetus at term (FDA latanoprost prescribing information [NDA 20-597/S-023]; available at: http://www.fda.gov/cder/approval/x.htm). One observational study of 11 pregnant women revealed no systemic side effects threatening abortion or preterm delivery as a consequence of topical exposure, however [39]. Although this series was too small to achieve statistical significance, the study found no evidence of adverse effects of topical once-daily latanoprost therapy on pregnancy or neonatal outcomes.

If the new mother plans on nursing her infant, it is important to consider the excretion of any maternally administered glaucoma medications in her breast milk and their effect on the infant. Clinical evidence
does exist for the excretion of timolol 0.5% and betaxolol in a nursing mother’s breast milk [37]. In the case of timolol 0.5%, the concentration of timolol in the mother’s milk was determined to be a factor of one eightieth of the cardiac-effective dose [40]. This level of timolol should probably not cause concern unless the infant’s hepatic or renal function is impaired. Nevertheless, if timolol treatment in a nursing mother is deemed absolutely necessary, the infant should be closely observed for signs of beta-blockade or should be weaned altogether.

Summary

The primary goals of medical therapy in pediatric glaucoma are to decrease intraocular pressure temporarily, to clear an edematous cornea, and to facilitate surgical intervention. Most pediatric patients who require long-term medical therapy have severe disease that has not responded sufficiently to surgical therapy, and these patients may experience additional intraocular pressure reduction with a medical regimen. Before commencing medical glaucoma therapy in a child, clinicians need to consider the potential for side effects carefully. During treatment, children need to be closely monitored because they may be at increased risk of systemic side effects compared with adults as a result of their reduced body mass and blood volume for drug distribution. Similar caution should be exercised when treating the pregnant glaucoma patient or the nursing mother.

References


