Latanoprost in pediatric glaucoma—pediatric exposure over a decade

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BACKGROUND Although numerous studies of latanoprost in adult glaucoma have shown it to be an effective hypotensive agent with a low incidence of side effects, these issues have not been well studied in pediatric glaucomas. The purpose of the current study is to evaluate the safety and intraocular pressure (IOP) lowering effect of latanoprost in various pediatric glaucomas over a long period.

SUBJECTS AND METHODS This retrospective study included all children treated with latanoprost at our institution from 1996 to 2007. Demographic, glaucoma-related, and side-effect information was recorded for each subject. Duration of latanoprost exposure was calculated in child-months (1 child exposed for 1 month). If interpretable IOP data were available, the presence or absence of a treatment response (IOP reduction ≥15% from baseline) was determined for each subject.

RESULTS A total of 115 subjects with latanoprost exposure were identified, with a collective exposure of 2,325 child-months. Exposure for ≥1 year occurred in 52 subjects. Side effects were mild and infrequently reported. Of the 115 subjects, 63 had interpretable IOP data, and 22 (35%) were treatment responders. Predictors of a response included a diagnosis of juvenile open-angle glaucoma, monotherapy, and older age.

CONCLUSIONS This large study of latanoprost-treated children confirms the excellent safety profile of the drug in the treatment of pediatric glaucoma. The study also confirms latanoprost's IOP-lowering ability in older children with juvenile open-angle glaucoma and in some children with aphakic glaucoma. Prospective studies are needed to better define the optimal role of latanoprost in the treatment of pediatric glaucoma, especially congenital glaucoma. (J AAPOS 2009;13:558-562)

Introduction

Latanoprost (Xalatan, Pfizer, New York, New York), a prostaglandin analog that reduces intraocular pressure (IOP) by increasing uveoscleral outflow, has not been well studied in children. Although numerous studies of latanoprost in adult glaucoma have shown it to be an effective hypotensive agent[1-8] with a low incidence of both serious ocular and systemic side effects, the issues of relative safety and IOP-lowering ability in pediatric glaucomas have not been well studied.[9-12] Reported ocular side effects include conjunctival hyperemia, hypertrichosis, increased iris pigmentation, and periocular skin pigmentation. Iris cysts, cystoid macular edema, anterior uveitis, and reactivation of herpes simplex keratitis have also been reported.[13-20] One small prospective study of latanoprost in children with glaucoma[12] suggested that this drug may work better in those with juvenile open-angle glaucoma (JOAG) than with congenital or aphakic glaucoma, but the study was limited by its small numbers and short duration. The purpose of this study was to evaluate the safety and IOP-lowering effect of latanoprost in various pediatric glaucomas over a long period of time.

Subjects and Methods

This study was a consecutive chart review of all children (<18 years old) treated with latanoprost 0.005% in 1 tertiary referral center under a single provider from 1996 to 2007. The study was approved by the Institutional Review Board of Duke University Medical Center and conformed to the requirements of the United States Health Insurance Portability and Accountability Act. All children with latanoprost exposure were included in the study. This chart review included 48 children exposed to latanoprost as part of a previously published prospective study of the drug.[12] Demographic information, systemic medical problems, glaucoma and other ocular diagnoses, number of prior glaucoma surgeries, number of prior glaucoma medications, duration of latanoprost exposure, and all reported side effects were recorded for

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each child. Also recorded was whether or not each child remained on latanoprost therapy as of the last documented examination. Both incisional and nonincisional surgeries were included in the number of prior surgeries. The dorzolamide/timolol combination (Cosopt; Merck & Co, Inc, Whitehouse Station, New Jersey) was counted as 2 medications. Latanoprost exposure was calculated as child-months of exposure to the drug. A child-month was defined as exposure to latanoprost (one or both eyes) for 1 month. It was the clinician's practice to examine for notable changes in eyelashes, iris color, and periocular skin pigmentation and to ask the parents whether the child had experienced any new systemic or ocular symptoms since starting latanoprost. Eyelash trimming was not performed by the investigators nor was it reported by parents of subjects with hypertrichosis. Because this was a retrospective study, any side effect recorded in the chart was included in this study (whether or not it was deemed drug related), as was the need to discontinue the drug based on the given side effect.

An attempt was made to evaluate the IOP response to latanoprost treatment in all children; however, many subjects lacked valid pre-latanoprost baseline IOP data for a variety of reasons, including exposure to latanoprost before the first examination at our institution, change in another medication at the time of latanoprost addition, and lack of an IOP measurement in the 6 months preceding drug addition. Lack of adequate IOP measurements after starting latanoprost also prevented evaluation of IOP response to the drug. All latanoprost-exposed subjects were included for evaluation of side effects (ie, safety of the drug). Only those with interpretable IOP data were included for analysis of IOP response to latanoprost (IOP group).

In those subjects with interpretable IOP data, a baseline IOP was calculated using the average IOP measurements at 2 to 3 visits prior to commencement of latanoprost. In selected cases where IOP was stable but addition of prior non-latanoprost medications had occurred, a single baseline IOP measurement was accepted. Multiple IOP readings from 1 visit were averaged to calculate a single measurement for any given date. IOP was then recorded for each visit after starting latanoprost until the drug was discontinued or until another ocular hypotensive drug was added to the subject's medication regimen. Collection of IOP data also stopped after glaucoma surgery. IOP measurements for all post-latanoprost visits were averaged for each child, and the presence or absence of a "treatment response" was determined. A clinically significant treatment response was defined as an average IOP reduction of $\geq$15% from baseline. It should be noted that the decision to continue latanoprost treatment for all subjects was based on the clinician's judgment, and the drug was often continued despite the lack of a treatment response as defined in this study.

Only the first treated eye of a given child was included for IOP calculations. If latanoprost was started in both eyes simultaneously, the clinically worse eye was included in the IOP group. If both eyes were deemed equal with respect to disease severity, the right eye was included for IOP calculations. IOP was measured with a Tono-Pen (Mentor/Reichert, Inc, Depew, New York), by Goldmann applanation tonometry, or by pneumatonometry (Mentor/Reichert, Inc). The same method was used consistently for a given child, and the IOP measurement deemed most reliable by the measuring clinician was used for data analysis. If IOP was measured during examination under anesthesia, measurements were taken as soon as possible after induction of anesthesia.

Statistical comparisons were performed with the use of *t*-test (paired or unpaired, as appropriate), Fisher exact test, Wilcoxon rank sum test, and odds ratios/adjusted odds ratios with their 95% confidence intervals. Survival analysis was performed using Kaplan-Meier curves, and curves were compared using the Mantel-Cox log-rank test. *P*-values <0.05 were considered significant. SAS Version 8.2 software (Cary, North Carolina) was used for the data analysis.

Results

The charts of 340 children were reviewed for the study; of these, 115 children had documented latanoprost exposure and were included in the study. Demographic data for the study subjects are shown in Table 1, which compares all latanoprost-exposed subjects (safety group) to those in the IOP group and to those with no interpretable IOP data (safety-only group). The most common glaucoma diagnoses among latanoprost-exposed children were congenital (26%), aphakic (23%), and juvenile open-angle (JOAG, 22%) glaucoma. Other diagnoses included anterior segment dysgenesis-associated, Sturge-Weber–associated, aniridic, traumatic, steroid response, uveitic, and neovascular glaucoma. The distribution of glaucoma diagnoses between the IOP group and the safety-only group was not statistically significant overall. When considered alone, however, the diagnosis of JOAG was more common in the IOP group than in the safety-only group ($p = 0.02$).

Total latanoprost exposure among the 115 subjects was 2,325 child-months (mean, 24.2 $\pm$ 24.6 mo/child; median, 9.9 mo/child). Long-term latanoprost exposure (1 or both eyes exposed for $\geq$1 year) occurred in 52 children, and 22 subjects were exposed to the drug for 3 years or longer. The medication was discontinued in 71 subjects. The most common reason for medication discontinuation was inadequate IOP control or need for glaucoma surgery (n = 54, 76%). Latanoprost was discontinued in 5 subjects because IOP control was felt to be adequate without the medication. Reported and/or observed side effects are given in Table 2. The most common side effect of latanoprost exposure was lash growth, which occurred in 100% of subjects exposed to the drug for $\geq$6 months. All other reported side effects combined occurred in 10% of exposed children. Iris cysts, cystoid macular edema, anterior uveitis, and reactivation of herpes simplex keratitis were not reported. Side effects required discontinuation of the medication in a total of 3 children—1 with irritation from hypertrichosis and 2 with conjunctival hyperemia and/or nonspecific ocular irritation.

Of the 115 subjects, 63 had interpretable IOP data (IOP group) and were considered for the following IOP analysis. The mean IOP at baseline vs post-latanoprost exposure for the IOP group was 24.0 $\pm$ 5.5 mmHg vs 22.5 $\pm$ 6.9 mmHg, a statistically significant reduction ($p = 0.04$). Of the 63 subjects, 22 (35%) had a clinically significant treatment