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Putative Side Effects of Prostaglandin Analogs

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Abstract. Anecdotal case reports describe the occurrence of cystoid macular edema, iritis, herpes simplex keratitis, periocular skin darkening, and headaches in patients treated with prostaglandin analogs for glaucoma. The purpose of this article is to critically analyze these anecdotal case reports in light of a few well-controlled, randomized clinical studies to determine whether conclusions can be made about a causal relationship between the use of prostaglandin analogs and the occurrence of these side effects. None of these putative side effects has been proven to be causally related to latanoprost therapy using valid scientific methodology. These possible side effects occur rarely. Cystoid macular edema, iritis, and herpes simplex keratitis occur in eyes with risk factors. To scientifically establish a causal relationship between drug therapy and rare side effects, repeated rechallenging with masked controls is required. With rare exception, such methodology has not been used with any of these putative side effects. Nevertheless, even without firm establishment of a causal relationship, caution is advised with the use of prostaglandin analogs in eyes with risk factors for cystoid macular edema, iritis, and herpes simplex keratitis until properly designed, large, controlled studies provide more definitive information. (**Surv Ophthalmol 47 (Suppl 1)**:S219–S230, 2002.

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Several side effects have been noted with the use of prostaglandin (PG) analogs in glaucoma therapy.[14] The side effects discussed in other articles in this supplement include iris color darkening,[27,74] eyelash changes,[38] and cystoid macular edema (CME).[53] Compared with timolol, PG analogs have been proven to cause three side effects: mild conjunctival hyperemia, iris color darkening, and eyelash changes.[14]

The purpose of this article is to discuss putative, but unproven, side effects which have been reported with the use of PG analogs, including CME, iritis, activation of herpes simplex keratitis (HSK), periorbital skin darkening, and headaches. Unfortunately, the appropriate randomized, double-masked, controlled, clinical trials have not been performed to establish whether definite causal relationships exist with the use of PG analogs and the occurrence of these rare side effects. Because many more anecdotal reports exist on CME than on the other potential side effects, this article will concentrate on this particular putative side effect.

Cystoid Macular Edema

Another article in this supplement reviews recent randomized, double-masked, controlled trials evaluating the effect of treatment with latanoprost (LP), timolol, and vehicles with and without preservatives on leakage determined by fluorescein angiography at 5 weeks after cataract surgery.[53–55] No clinical CME was detected in these studies in any of the treatment or control groups.[12] The leakage detected by fluores-

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cein angiography occurred as frequently in the timolol and preserved vehicle groups as in the LP groups. The authors' conclusion was that the preservative in glaucoma medications, including LP or timolol, may account for the fluorescein angiography leakage, which was not accompanied by a reduction in visual acuity.[53–55] The purpose of this section is to review cumulative data on the occurrence of CME in patients treated with LP to assess whether conclusions can be made about a causal relationship.

Several clinical case reports[5,6,10,23,30,58,61,64,67,77,85,86,90] have shown that CME has occurred in some eyes treated with LP. Most of these publications describe 1 or 2 eyes, although a single report describes as many as 7 eyes.[58] It is not possible to draw conclusions about a potentially causal relationship based on single case reports or small case series.[11,66,67]

Clinical information was extracted from all known reports of the co-occurrence of CME and LP use arising from three general sources: clinical trials, the compassionate use program, and post-market release spontaneous reports, including published reports of cases not independently reported to the manufacturer. The clinical trials included relatively short-term phase I and II trials, and long-term phase III and IV studies performed in the United States, the United Kingdom, Scandinavia, Japan, and worldwide from 1992 until 1999.[3,15–17,52,88,89] In the compassionate use protocol, carried out from May 1995 through September 1996, approximately 3,500 patients were enrolled. Nomination for inclusion was at the discretion of designated physician-participants. Patients on maximally tolerated medical therapy and in need of additional IOP reduction were included. No exclusions were made on the basis of concurrent ocular diagnoses or history. Almost all patients had glaucomatous visual field defects. Patients were treated once daily with 0.005% LP in addition to their other ocular medications, if any.

The final, largest source of cases derives from all patients worldwide who have been treated with LP following market introduction in their country. Spontaneous reports to the manufacturer of occurrences of CME are included in the present analysis. Because clinical information about these patients derives chiefly from spontaneous reports, great variation in the quality and comprehensiveness of available clinical information was encountered, despite efforts made to obtain detailed information whenever possible.

Twenty-nine cases of CME in association with LP use have been reported in the literature.[5,6,10,23,30,58,61,64,67,77,85,86,90] Approximately 10 of these 29 cases may have been reported to the manufacturer. We gathered information from the published descriptions of the other 19 cases for inclusion in the present analysis.

For each occurrence of CME, all available clinical information was reviewed, and an attempt was made to identify all risk factors for the development of CME. Candidate risk factors were compiled from major, accepted causes of CME.[62] Each risk factor was counted once for each occurrence in an individual eye to give a crude estimation of the relative risk for CME.

In cases in which complicated cataract surgery was performed, multiple risk factors were tabulated separately. Thus, an eye that had undergone phacoemulsification with inadvertently broken posterior capsule and placement of an anterior chamber intraocular lens (AC IOL) implant would have 3 risk factors (one each for cataract surgery, AC IOL, and open posterior capsule), because we assumed that each of these risk factors may contribute to the likelihood of development of CME. In a case in which an eye had had three separate retinal detachment procedures including vitrectomy and cryotherapy,[85] we tabulated 3 risk factors (retinal surgery) because we assumed that each additional retinal procedure may increase the likelihood of CME developing.

Putative cases of CME arising in 113 eyes of 103 patients were collected. The sources of these cases were the following: 3 eyes in 2 patients in clinical trials, 1 eye in 1 patient in the compassionate program (which was subsequently published[67]), 90 eyes in 84 patients in spontaneous reports (including 9 eyes of 9 patients that subsequently appeared in published literature), and 19 eyes in 16 patients in published cases not known to be already included in the spontaneous reports.

CME did not occur in phase I and phase II clinical trials, involving more than 800 eyes, some treated for as long as 3 months. Cases arising during clinical trials all derived from approximately 2,400 patients treated with LP in phase III clinical trials of at least 6 months duration. Of these, about 1,800 patients were treated for 1 year, 600 patients for 2 years, and more than 400 for 3 years. CME did not occur in other phase III or IV trials of duration less than 6 months, involving about 1,000 patients. In the compassionate program, approximately 3,500 patients were approved for treatment with LP. Some were treated for up to 18 months. Following market approval of LP, and up to the database closure date of 20 July 1998, an estimated more than 1 million patients with glaucoma or ocular hypertension had been treated with LP.

Of the 113 eyes, 79% were reported to have had decreased visual acuity at the time of the diagnosis of CME, although presumably 100% actually had decreased visual acuity. Fluorescein angiography or funduscopic examination reportedly confirmed the diagnosis in 56% or 48% of eyes, respectively, and 70% of

TABLE 1

Known Risk Factors for Cystoid Macular Edema During Latanoprost Treatment, by Eye[a]

Eye#	Patient#	Source	Duration of Latanoprost Treatment until Onset of Symptoms (in months)	Recovery Status[b]	Duration Following Cessation of Latanoprost Until Recovery (in months)	Known Risk Factors[c]	# of Known Risk Factors
1	1	CT	4.0	2	not stopped	1,	1
2	2	CT	1.3	2	1.0	1,2,5,11,11,11	6
3	2	CT	1.3	2	1.0	1,2,5	3
4	3	Comp and Schumer et al[67]	0.5	2	0.0	1,4,5,6,7,11	6
5	4	SR	0.3	2	4.0	1,4,7,13	4
6	5	SR	0.5	?	?	1,5	2
7	6	SR	1.4	2	4.0	9	1
8	7	SR	0.3	1	1.0	12,14	2
9	8	SR	0.5	2	2.0	1,2,4,15	4
10	9	SR	2.0	1	?	1,3	2
11	10	SR	2.0	2	0.5	1,5,8,11	4
12	11	SR and Gaddie & Bennett[23]	3.0	2	1.0	1,5	2
13	12	SR	0.6	2	3.0	1,5,11	3
14	13	SR	0.6	?	?	1,4,22	3
15	14	SR	0.0	1	1.0	1	1
16	15	SR	0.5	2	0.9	1,3	2
17	16	SR	4.0	?	?	1,2,4,5,6,6,15	7
18	17	SR	6.0	2	1.3	1,9	2
19	18	SR	0.5	2	3.0	1,4	2
20	19	SR	1.1	2	1.0	1,4,5,624	
21	20	SR and Wardrop & Wishart[85]	1.8	2	0.5	1,7,7,7	4
22	21	SR	0.7	2	2.0	1,4,5	3
23	22	SR	0.7	?	?	1,2,4,5	4
24	22	SR	0.7	?	?	1,2,4,5	4
25	23	SR	0.5	?	?	1,3	2
26	23	SR	0.5	?	?	1,3	2
27	24	SR	1.0	1	3.5	1,9,14	3
28	25	SR	0.4	2	?	1,3	2
29	26	SR	2.0	0	?	1,5,7,10,14	5
30	26	SR	6.0	1	1.0	1,5,14	3
31	27	SR	6.0	1	2.3	1,5,6	3
32	28	SR	0.8	?	?	1,11	2
33	29	SR	11.0	2	0.5	1,9	2
34	30	SR	9.0	2	0.3	1,9	2
35	31	SR	1.0	2	1.5	1,7,9	3
36	32	SR	1.0	1	4.0	1,11	2
37	33	SR	0.4	2	1.0	1,5,6,9,20	5
38	34	SR	?	1	?	1	1
39	35	SR	1.0	2	7.0	1,2,4,5,6	5
40	36	SR	10.0	1	?	1,9	2
41	37	SR	1.0	2	9.0	1,2,3,5	4
42	38	SR	4.0	2	3.0	1,5	2
43	39	SR	1.0	2	1.5	1,5	2
44	39	SR	1.0	2	1.5	1,5	2
45	40	SR	0.1	2	1.0	1	1
46	41	SR	1.1	2	0.3	1,11	2
47	42	SR	1.6	2	11.0	1,5,10	3
48	43	SR	9.0	0	?	1,5,10	3
49	44	SR	0.9	2	?	1,2	2
50	45	SR	0.7	?	?	10	1
51	45	SR	0.7	?	?	?	0
52	46	SR	0.9	1	?	1	1
53	46	SR	3.0	1	?	1,9	2
54	47	SR	7.0	2	2.5	1,10	2
55	48	SR and Rowe et al[64]	1.0	2	1.3	1,11	2

(Continued)

TABLE 1

Continued

Eye#	Patient#	Source	Duration of Latanoprost Treatment until Onset of Symptoms (in months)	Recovery Status[b]	Duration Following Cessation of Latanoprost Until Recovery (in months)	Known Risk Factors[c]	# of Known Risk Factors
56	49	SR	?	?	?	7	1
57	50	SR	?	?	?	7	1
58	51	SR	?	?	?	7	1
59	52	SR	?	?	?	1,3	2
60	53	SR	2.0	?	?	11	1
61	54	SR	?	1	?	1,9	2
62	55	SR	?	2	?	1,13	2
63	56	SR	0.6	?	?	1,5,6	3
64	57	SR	7.0	1	?	1,9	2
65	58	SR	?	?	?	15	1
66	59	SR	8.0	?	?	1,4	2
67	60	SR	?	2	?	1,11	2
68	61	SR	0.5	1	?	1,5,6,11	4
69	62	SR	1.0	?	?	1,3	2
70	63	SR and Reis et al[61]	0.3	2	0.3	1	1
71	64	SR	0.6	?	?	1,8,9,14	4
72	65	SR	1.9	2	1.9	1,5,7	3
73	66	SR	0.5	2	?	1,4,5	3
74	67	SR	?	?	?	1,3	2
75	68	SR	2.0	0	?	1,2,3,5	4
76	69	SR	1.0	2	?	1,5,14,16	4
77	70	Heier et al[30]	0.8	2	1.8	1,4,5,6,8,20	6
78	71	Warwar et al[86]	2.0	2	1.5	1,4,5,11	4
79	72	Warwar et al[86]	8.0	1	4.0	1,8	2
80	73	Avakian et al[5]	0.8	2	0.3	1,4,5,6	4
81	74	Avakian et al[5]	2.0	2	2.0	1,15	2
82	75	Thorne et al[77]	1.0	1	4.0	1,4,5	3
83	75	Thorne et al[77]	1.0	1	4.0	1,4,5	3
84	76	Callanan et al[10]	4.0	1	4.0	1,5	2
85	77	Callanan et al[10]	1.8	2	3.0	1,5,6	3
86	78	Gaddie & Bennett[23]	0.5	2	3.0	1,4,5,8,16,22	6
87	79	Ayyala et al[6]	0.3	2	0.5	1,5	2
88	79	Ayyala et al[6]	0.3	2	0.5	1,5	2
89	80	Ayyala et al[6]	1.0	2	1.5	1,2,3,5	4
90	80	Ayyala et al[6]	1.0	2	1.5	1,2,3,5	4
91	81	Ayyala et al[6]	0.2	1	1.5	1,5	2
92	82	Ayyala et al[6]	0.5	2	2.0	1,8,9,11	4
93	83	Moroi et al[58]	1.0	2	?	10,11,13,16	4
94	84	Moroi et al[58]	2.0	2	?	1,8,10	3
95	85	SR and Moroi et al[58]	7.0	2	?	5,6,8	3
96	86	Moroi et al[58]	11.0	1	?	1,5,7,10	4
97	87	Moroi et al[58]	1.0	2	?	1,5,11,13	4
98	88	Moroi et al[58]	2.0	2	?	1,5,10	3
99	89	Moroi et al[58]	1.5	2	0.8	1,5,7,8	4
100	90	Weisz et al[90]	?	?	?	1,5,22	3
		n[d]	89		54		100
		Means:	2.2		2.2		2.8
		S.E.M.:	0.28		0.28		0.13

? = no information available; CT = Clinical trials; Comp = Compassionate Program; SR = spontaneous reports.

[a]Includes only the 100 eyes (of the total 113) for which some clinical information is available.

[b]1 = partial; 2 = full; ? = none.

[c]Numbers refer to category of risk factor as specified in Table 2.

[d]Total number of eyes for which the specified information is available.

eyes had fluorescein angiography and/or funduscopy. Funduscopy without fluorescein angiography confirmation reportedly occurred in 14% of eyes. Neither fluorescein angiography, nor funduscopy, nor decreased visual acuity was documented in 19% of eyes.

In 13 eyes, essentially no clinical detail other than the apparent occurrence of CME was available. The initial lack of submitted information persisted despite repeated inquiries from the investigators because the submitting physicians did not remember or did not have access to medical records. Insofar as no pertinent clinical information was available, and analysis of the circumstances surrounding the diagnosis of CME was impossible, these eyes were removed from further consideration. Analysis of the other 100 eyes appears in Table 1. The average age of these patients was 72 years (range: 45–90); 59% were male.

Table 2 lists the risk factors that were encountered among the 100 eyes, and shows the number of occurrences of each risk factor. The number of risk factors may be underestimated because complete clinical information may have been lacking. Eighty-nine of 100 eyes (89%) were known to have undergone cataract surgery. Eighty-three of these 89 eyes (93%) were known to have other risk factors as well. AC IOLs were present in 19%, and 12% were aphakic.

Of the 11 eyes that were not known to have had cataract surgery, the following risk factors were identified: three eyes had repair of retinal detachment; two eyes had pre-macular fibrosis; one eye had prior CME; one eye had undergone recent unspecified eye surgery (possibly cataract extraction); one eye had diabetic retinopathy, may have had diabetic maculopathy rather than, or in addition to CME, and had a major IOP reduction with LP (pre-treatment 24 mm Hg, post-treatment 9 mm Hg); one eye had HLA B27-associated uveitis, a dislocated lens secondary to Marfan's syndrome, an anterior vitrectomy, and no posterior capsule; one eye had argon laser trabeculoplasty (ALT) 2 weeks prior to the onset of CME; and one eye had no known risk factors for CME. The 11 eyes that were not known to have had cataract surgery had an average of 1.5 risk factors per eye (range: 0–4).

Forty-eight of 100 eyes (48%) were known to have disrupted posterior capsules, due either to inadvertent rupture during surgery, neodymium (Nd):YAG laser posterior capsulotomy, or some other cause (e.g., trauma). Prior episodes of CME had occurred in 15%. One eye had 3 prior episodes of CME. Only 1 eye had no known risk factors. In this case, the diagnosis was based on decreased visual acuity and fundus examination, but was not confirmed by fluorescein angiography. The reporting doctor stated that the change in acuity could also have been related to age-related macular degeneration. There was no follow-up information available regarding the outcome.

Fig. 1 shows the percentage of eyes having various numbers of known risk factors. Eyes that developed CME had an average of 2.8 known risk factors. Fig. 2 shows the percentage of eyes having the specified number of known risk factors, or more. Of the 94 eyes, 99% had 1 or more known risk factors, 86% had 2 or more, 49% had 3 or more, and 29% had 4 to 7 known risk factors.

For 78 of 100 eyes (78%), information was available regarding whether, besides LP, other topical anti-glaucoma medications were being used. Sixty-two of these 78 eyes (79%) were being concurrently co-medicated with topical anti-glaucoma drugs. Eyes for which such data were available received an average of 1.2 topical anti-glaucoma medications in addition to LP (range: 0–4). Three eyes (2 of them previously published)[23,58] were being treated with either dipivefrin or epinephrine. Fifty-one eyes (65%) were being treated with beta-adrenergic blockers, and 3 eyes with echothiophate iodide.

The duration of treatment with LP until onset of CME was known for 89 of the 100 eyes (Table 1). Mean duration of treatment was 2.2 months (range: 1 day to 11 months). In 10 eyes, intraocular surgery was performed after therapy with LP was begun; thus, the date of surgery was closer to the onset of CME than was the beginning of therapy with LP. The length of time between surgery and onset of CME averaged 1.4 months (range: 0.5–5 months). The duration of treatment with LP until symptoms of CME appeared was known for 9 of the 10 eyes, averaging 5.9 months (range: 1.4–11 months). In one eye, LP was begun 1 day after cataract surgery, followed by symptoms of CME 4 months later.

Information regarding recovery following the diagnosis of CME was available in 78 of the 100 eyes (78%). LP was discontinued following diagnosis of CME in all but 3 eyes. CME improved in all 3 eyes in which LP was continued, although it recurred upon discontinuation of topical corticosteroid and nonsteroidal anti-inflammatory drug (NSAID) therapy in 2 of the 3 eyes.[6,14] The third eye had full recovery without use of anti-inflammatory medications. Fifty-five of the 78 eyes (71%) experienced full recovery by the time of latest follow-up, and 96% had at least partial recovery. Of 54 eyes for which information was available, visual acuity recovered an average of 2.2 months after discontinuation of LP (range: 1 day to 11 months).

Three eyes (3%) had not experienced any recovery at the time of latest follow-up. One of these 3 eyes had not improved after 4 months, possibly because of a macular hole. This eye had had prior cata-

TABLE 2

Frequency of Occurrence of Risk Factors for Cystoid Macular Edema (CME) during Latanoprost Therapy

Risk Factor	Number of Occurrences	% of Eyes Having Risk Factor[b]
Cataract surgery (1)	89	89
Open posterior capsule (secondary to surgery or to Nd: YAG laser capsulotomy) (5)	48	48
Anterior chamber intraocular lens implant (4)	19	19
History of prior CME[c] (11)	17	15
Anterior vitrectomy[d] (6)	13	12
Retinal or vitreoretinal surgery[e] (7)	13	11
Concurrent uveitis (9)	13	13
Intracapsular cataract surgery (2)	12	12
Aphakia (3)	12	12
Premacular fibrosis (10)	9	9
History of uveitis (8)	9	9
Treated intraocular pressure <10 mm Hg (14)	6	6
Retinal vein occlusion (13)	4	4
Filtering or other intraocular surgery (other than cataract surgery) within one year before CME (15)	4	4
Concurrent treatment with epinephrine compounds (16)	3	3
Retinal inflammatory disease (e.g., pars planitis, birdshot, toxoplasmosis, others) (18)	3	3
Penetrating keratoplasty (17)	2	2
Diabetic retinopathy (12)	1	1
Total # of occurrences of risk factors:	277	

[a]Numbers in the parentheses ( ) following the specific risk factor correspond to the number in the "Known Risk Factors" column of table 1.

[b]Number of eyes in denominator: 100.

[c]1 eye had CME three times.

[d]1 eye had anterior vitrectomy twice.

[e]1 eye had retinal detachment three times.

ract surgery, trabeculectomy, retinal surgery, and pre-macular fibrosis. Because fluorescein angiography was not performed as part of the diagnosis, vision loss could have been due to the pre-macular fibrosis/macular hole instead of to CME. Another eye was aphakic following intracapsular cataract extraction, and had not improved after only one month of follow-up. The third eye had undergone extracapsular cataract extraction (ECCE) with posterior chamber (PC) IOL implantation, Nd:YAG laser posterior capsulotomy, placement of a glaucoma tube-shunt device, and had pre-macular fibrosis, and corneal edema. Duration of follow-up for this eye is unknown. The first 2 eyes had 4 risk factors and the third had 3 risk factors.

Five eyes (3 of them previously published)[5,10,77] were rechallenged with LP after resolution of the initial episode. All 5 had shown a reduction of visual acuity and four had fluorescein angiography confirmation of the initial episode of CME. LP was discontinued in all 5 eyes and topical treatment with a corticosteroid and a NSAID was known to have been instituted in 2 of the 5 eyes. One of the 5 eyes was known not to have been treated. Visual acuity returned to within one line of Snellen visual acuity from the baseline of 20/20 to 20/25 in 4 eyes. The recovery status was unknown in the fifth eye. Duration from recovery until rechallenge was unknown for 1 eye, and was 3 days to 3 months for the other 4 eyes. In 2 eyes that had a fluorescein angiography repeated just prior to rechallenge, persisting angiographic CME was demonstrated in one,[5] and no CME was seen in the other.[77] Upon rechallenge with LP, 2 eyes failed to show a recurrence of CME after an unknown duration of therapy. One patient, with bilateral AC IOLs, had developed bilateral CME after being treated with LP in both eyes. He was unilaterally rechallenged with LP an unknown number of weeks after bilateral resolution of the CME. CME subsequently recurred in the non-treated fellow eye, but not in the rechallenged eye. In another rechallenged eye, there was no evidence of recurrence of CME after 3 separate 1 month–long rechallenges.[77] The 3 other rechallenged eyes had decreased visual acuity of from 3 to 8 lines occurring, respectively, 2 weeks, 2 months, and an unknown duration after restarting LP. Fluorescein angiography confirmed

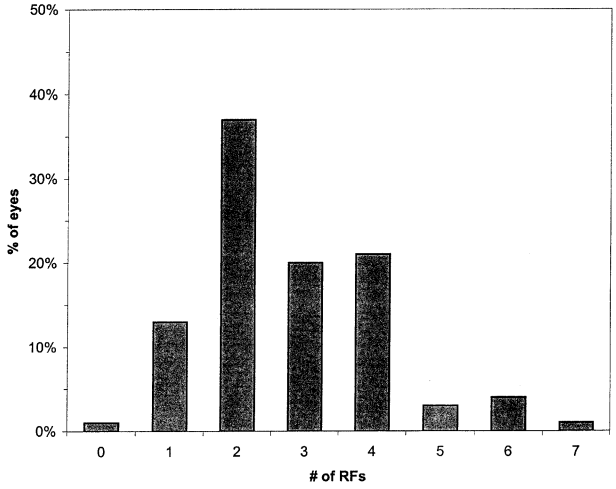

Fig. 1. Percentages of eyes having specified number of risk factors (RFs) for cystoid macular edema. Percentages expressed in relation to number of eyes (n = 100) for which clinical information was available.

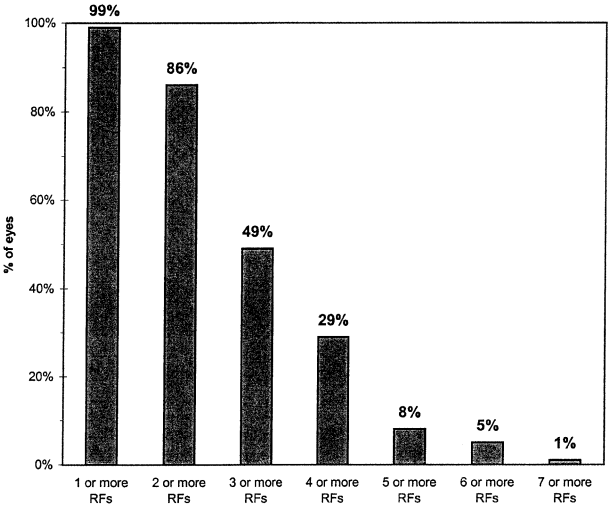

Fig. 2. Percentages of eyes having the specified number of risk factors (RFs) for cystoid macular edema, or more. Percentages expressed in relation to number of eyes (n = 100) for which clinical information was available.

CME in 2 of the 3 eyes following rechallenge, but also confirmed persistent CME prior to the rechallenge in one of these 2 eyes.[5]

Although lens status was known for most of the eyes described here, it is not known how many eyes that have been treated with LP since market introduction are pseudophakic or aphakic. However, the lens status was known in 1,116 of the approximately 3,500 patients in the compassionate program, which included 138 (12%) aphakic eyes, 39 eyes (3%) with AC IOLs and 344 eyes (31%) with PC IOLs. Although cataract surgery, aphakia, and AC IOLs are all major recognized risk factors for CME, only 1 of these several thousand patients was reported to develop CME.

Limitations to the interpretability of the present database apply even more to isolated case reports.[5,6,10,23,30,58,61,64,67,77,85,86,90] Published case reports describing CME following institution of therapy with LP, though compelling and perhaps clinically significant, unfortunately are impossible to interpret because of the absence of proper statistical context. Although the observation of an isolated occurrence of CME following use of LP may seem persuasive to the clinician who observes the case, informal inductive reasoning has been shown to be insensitive to the a priori probabilities of outcomes.[80] Applied, in the present case, to the drawing of general inferences from case reports, this means that one may easily overlook the fact that for each episode of CME in a LP-treated eye, there may be many thousands of eyes that have been treated with LP which did not manifest CME. Furthermore, by definition, some eyes which are at risk for CME will develop CME spontaneously whether or not treated with LP.

Experience with isolated cases of at-risk eyes, and even analysis of our more extensive database, is incapable of leading to firm conclusions regarding a causal relationship between LP and CME. A causal relationship would have been suggested if there had been reports of CME in LP-treated eyes that were not otherwise at risk for development of CME. This, however, was not the case. Recurrence of CME upon rechallenge with LP would make a strong case for a causal relationship if performed with adequate controls. Of the 5 eyes that were rechallenged, a control was used in only 2 patients. In one of these patients who had bilateral CME while using LP bilaterally, and who was rechallenged unilaterally, CME only recurred in the contralateral control eye that was not rechallenged. In a similar patient with bilateral CME, CME did not recur after multiple rechallenges in one eye only.[77] These 2 case reports emphasize the importance of proper controls. In 1 of the other 5 eyes, the rechallenge was performed before the prior episode of CME had resolved, as clearly demonstrated by a fluorescein angiogram demonstrating moderate CME when performed just before the rechallenge.[5]

In addition to the randomized, masked, controlled clinical trials evaluating the effect of LP, timolol, preserved vehicle, or non-preserved vehicle given before and after cataract surgery on foveal leakage detectable by fluorescein angiography,[53–55] another randomized, double-masked clinical trial was carried out in pseudophakic eyes.[36] In this study, 24 patients with posterior chamber lenses and with intact posterior capsules were treated with LP unilaterally for 4 weeks.[36] Randomization was assigned on a 2:1 basis

so that 16 received LP 0.006% twice daily (twice the clinical dose) and 8 received placebo. They were examined with macular biomicroscopy and fluorescein angiography before and after treatment. There was no indication of macular edema nor was there a reduction in visual acuity in the LP-treated eyes. One of the placebo-treated eyes demonstrated mild perifoveal leakage on fluorescein angiography. This study demonstrates the importance of having proper controls before making conclusions. Despite randomization resulting in twice as many patients in the LP group compared with the placebo group in this small study, the single occurrence of leakage on fluorescein angiography occurred by chance in the placebo group.

Besides these few randomized, masked studies, 3 retrospective or prospective studies have evaluated the occurrence of CME in eyes with multiple risk factors.[46,76,82] In 40 eyes with previous cataract surgery, all with open posterior capsules, none developed CME when treated with LP for 6 months to 2 years.[76] In a retrospective review of LP treatment in 225 pseudophakic or aphakic eyes, 44% of which had open posterior capsules, 3 had at least a 2-line decrease in Snellen visual acuity thought to be due to CME when treated with LP.[46] All 3 of these eyes had undergone complicated cataract surgery with anterior vitrectomies, and one had a previous history of CME prior to LP therapy. In another study, 40 consecutive patients with pseudophakic or aphakic eyes, all with open posterior capsules and 72% with at least one additional risk factor, were evaluated.[82] They were treated with LP and carefully observed for visual acuity changes and the development of CME with follow-up visits every 1 to 3 months. Two (5%) of these eyes developed CME with a reduction of visual acuity of 2 lines. These 3 studies confirm the rare occurrence of CME even in high risk eyes treated with LP, and they fail to establish a causal relationship.[46,76,82] In a study using optical coherence tomography as a sensitive indicator of macular edema, none of 68 eyes without risk factors for CME developed any evidence of increased retinal thickness in the fovea as determined by multiple measurements during 6 months of treatment with LP.[22] Moreover, pharmacokinetic considerations indicate that the concentration of latanoprost expected in the posterior segment of the eye is too low to have a pharmacological effect, and latanoprost is not known to exhibit vasoactive or inflammatory properties.[50,67,69–72]

Iritis

Multicenter, randomized, double-masked, clinical trials performed in over 1,000 patients have failed to demonstrate a difference in the occurrence of aqueous flare or an anterior chamber cellular response in eyes treated with LP or timolol.[3,16,52,88] Very sensitive techniques used to assess small changes in the blood–aqueous barrier, including fluorophotometry and laser-flare meters, failed to detect an effect of LP in several controlled studies in normotensive volunteers and in glaucoma patients treated for as long as 1 year.[18,35,48,79,92]

However, anecdotal reports have described iritis occurring in eyes treated with LP.[21,65,73,81,86] Many of these eyes exhibited a very mild cellular response with minimal evidence for a cause and effect relationship.[11] With few exceptions, eyes were not rechallenged, and none were rechallenged repeatedly with proper controls. Nevertheless, four select patients with predisposing risk factors exhibited a rather compelling history for a causal relationship.[21] In a controlled clinical trial, LP applied four times daily for 2 weeks produced transient photophobia, mild flare, and/or a few cells in 15 of 28 volunteers.[47] In general, these symptoms and signs resolved in the first few days of treatment despite continued excessive dosing at four times the daily recommended dose. This study demonstrates that LP applied in excessive doses produces statistically significant, low grade, transient inflammation in some eyes.

A hallmark of inflammation is chemotaxis, or the infiltration of white blood cells (inflammatory cells). No PG has been demonstrated to have chemotactic properties. The precursor of PGs is arachidonic acid. Products of arachidonic acid other than PGs have been demonstrated to produce chemotaxis. Leukotriene B_4, one of the most potent chemotactic agents produced during inflammation, is a product of the lipoxygenase pathway of metabolism of arachidonic acid. This pathway is distinctly different from the cyclooxygenase pathway, which is responsible for the production of PGs. In contrast to their purported, but unproven, pro-inflammatory effects, PGs have been shown to have anti-inflammatory activity in several tissues and organs[25,41] including the eye.[7,37,57]

Other medications used in glaucoma therapy have been demonstrated to cause inflammation with evidence more convincing than that for LP. Pilocarpine produces adverse effects on the blood–aqueous barrier, constricts the pupil to increase the possibility of posterior synechia, and is contraindicated in inflammatory glaucomas. Likewise, epinephrine has an adverse effect on the blood–aqueous barrier, and is not used in inflamed eyes. Several reports document the occurrence of a granulomatous uveitis occurring in some eyes treated with metipranolol.[2,51,60,87] Uveitis or iridocyclitis is reported in the Food and Drug Administration–approved package insert as a possible adverse event occurring in some

eyes treated with timolol or dorzolamide. Brimonidine has been reported to cause a moderate to severe granulomatous uveitis with keratic precipates in four patients.[9] Unilateral rechallenges in each of these patients provided strong evidence for a causal relationship with brimonidine. As opposed to the reports of uveitis with LP,[21,65,86] these patients treated with brimonidine had no predisposing risk factors for uveitis, and all underwent a thorough medical work-up which failed to yield other possible causes for the intraocular inflammation.[9] Notably, even topically applied corticosteroids, the treatment for iritis, have been demonstrated to cause iritis in select eyes.[43,49]

Herpes Simplex Keratitis Reactivation

Two anecdotal publications describe four patients who purportedly developed reactivation of herpes simplex keratitis (HSK) when treated with LP.[19,83] In general, these patients had a history of previous episodes of HSK, viral cultures were not obtained to confirm the diagnoses, and the eyes were not rechallanged. Pseudodendrites, which may be mistaken for HSK, have been reported with the use of LP,[75] beta-blockers, anti-virals, contact lens solutions, and other topically applied medications. Other medications used in glaucoma therapy, including beta-blockers[29,34] and epinephrine,[33,44,63,68] have been reported to reactivate HSK. Herpetic dermatitis of the periocular skin purportedly developed in two patients treated with LP.[56] The patients were not rechallenged to establish a causal relationship.

In a rabbit model, LP was reported to increase the severity and the recurrence rate of HSK.[39] This publication has been criticized for several reasons.[13] Only one of the two strains of herpes simplex which were evaluated demonstrated an adverse effect with LP. The minimally elevated severity of the keratitis compared with controls lasted for only 5 days, despite continued treatment with LP for 10 days. LP was given at twice the daily dose used clinically. No viral cultures were obtained to determine whether this apparent mild adverse effect was due to persistence of the virus or to a nonspecific effect on the corneal epithelium, perhaps related to the preservative, which was not utilized as a control. A subsequent study purportedly demonstrated an adverse effect of LP compared with unoprostone in this rabbit model.[40] Whereas the clinically used dosage of unoprostone was used, twice the dosage of LP was utilized. Equi-effective dosages of the drugs were not utilized to determine whether differences occurred in this HSK model relative to ocular hypotensive efficacy of the medications, which would have represented a more meaningful finding. It should be emphasized that rabbits represent a poor model for predicting the effect of PGs in humans.[8,13] Another controlled, randomized study failed to demonstrate an adverse effect of LP in 123 rabbits.[26] The primary difference in the latter study[26] compared with the previous ones[39,40] is that cultures were obtained to truly evaluate induced reactivation and viral shedding,[26] which must be distinguished from nonspecific corneal epithelial toxicity. Of interest is that some PGs have been demonstrated to have antiviral activity against herpes simplex virus in human corneal stromal cells in tissue culture.[59]

Periocular Skin Darkening

Whereas iris color darkening is a scientifically established side effect of PG analog therapy for glaucoma,[27,74] the evidence for periocular skin darkening is anecdotal.[42,84] Nevertheless, several publications suggest that endogenous PGs may be involved in skin darkening resulting from light exposure (tanning)[28] or from other conditions.[1,31,32,78]

Despite an estimated 2 to 3 million patient years of clinical experience with LP, only 2 reports have described periorbital skin darkening, each describing a single patient.[42,84] Color photographs were shown in only one[84] of these 2 publications. The photographs of this single patient failed to convincingly demonstrate skin darkening because of varying photographic techniques, which can result in pronounced differences in appearance. The published photograph taken after discontinuation of LP demonstrated lightening of skin color of the nose and cheeks (and fewer wrinkles), suggesting inappropriate matching of the photographic technique or film developing. Further experience is required to determine whether a causal relationship exists. Nevertheless, the occurrence must be very rare. Interestingly, periocular skin pigmentation changes also has been reported anecdotally with the use of betaxolol.[4]

Headaches

PGF_2 alpha tromethamine salt, the first PG used in clinical studies, was found to produce headaches in 30–50% of subjects treated with high doses.[20,24,45] Headaches occurring at a rate statistically significant as compared with controls has not occurred with other PG analogs which have been carefully evaluated in clinical trials. In large, multicenter, randomized, double-masked, controlled clinical trials involving over 1,000 patients, the occurrence of headaches was not different in the LP group than with timolol group.[3,16,52,88] No systemic side effect has been proven to occur with LP therapy, and one is not expected because of the pharmacokinetics of LP, including its exceedingly low systemic levels and short half-life in plasma.[69–72]

Despite the lack of statistical significance, a single publication exists which reports the occurrence of

migraine headache in three patients treated with LP.[91] One of these patients reported headaches after the first 3 doses of LP without a subsequent recurrence despite continued treatment with LP. A second patient in this series was not rechallenged with LP in an attempt to establish a causal relationship. Considerable additional work is required before establishing a causal relationship between headaches and the use of LP in some patients. Certainly, this possible relationship appears to be very rare.

Summary

Clinicians treating patients with glaucoma should know of potential side effects of prescribed medications. Despite case reports suggesting a causal relationship, coincidences occur by chance when dealing with large numbers of treated patients. Definitive conclusions about causal relationships cannot be made without the proper randomized, controlled trial demonstrating a statistically significant relationship. Occasionally, a rare side effect will not be demonstrated even in randomized clinical trials involving hundreds of patients. They may be reported only after hundreds of thousands or millions of patients are treated. In the case of these rare events, a causal relationship may be established by repeated rechallenges using a placebo control in the few affected patients. With rare possible exceptions in a few very unusual patients, a causal relationship between the use of PG analogs and the occurrence of CME, iritis, HSK, or periorbital skin darkening or headaches has not been established by the scientific method. Occasionally, clinical decisions must be made based on anecdotal associations in the absence of scientific proof of causal relationships. In view of these cases, and despite the lack of definitive proof of a causal relationship, caution might be advised when using PG analogs in eyes with multiple risk factors for the development of CME, iritis, or HSK. It would be prudent to consider alternatives in medical therapy for glaucoma prior to using PG analogs in these high risk eyes.

Method of Literature Search

References on the ocular effects of PGs and their analogs have been compiled by the authors for over two decades, including references dating back to the mid 1950s. Additional searches were made in Medline from 1975 to 2001 using the following search words: *prostaglandin, latanoprost, Xalatan, unoprostone, Rescula, docosanoid, travoprost, Travatan, fluprostenol, Lumigan, bimatoprost, prostamide, ocular hypotensive lipids, cystoid macular edema, inflammation, iritis, uveitis, herpes simplex keratitis, and/or headaches.* In general, articles written in English relevant to the topic were included regardless of their scientific merit. When possible, the cases of CME included reports from MedWatch (http://www.fda.gov/medwatch/index.html) and from the National Registry of Drug-Induced Ocular Side Effects (F.T. Fraunfelder, MD, Director, Casey Eye Institute, Oregon Health Sciences/University, 3375 SW Terwilliger Blvd, Portland, OR 97201-4197 USA).

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