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SHORT COMMUNICATION

The Placebo Effect in Early-Phase Glaucoma Clinical Trials

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ABSTRACT

Purpose: To analyze the extent and prevalence of the placebo effect in prior early-phase glaucoma clinical studies.

Methods: Articles were evaluated on phase I and II trials of glaucoma medicines that became commercially available after 1977 with a placebo arm that involved glaucoma patients.

Results: We included 23 studies with 23 treatment arms with a total of 1703 patients in articles evaluating 10 different glaucoma medications. This study showed that at 8 AM ($n = 18$), the average decrease in placebo from untreated baseline was 2.3 ± 1.6 mm Hg (9%), while for the diurnal curve ($n = 17$), the mean decrease was 1.4 ± 1.1 mm Hg (6%). At 8 AM, 8/18 treatment arms had greater than 2 mm Hg intraocular pressure (IOP) decrease, and all had at least some reduction in IOP. For the diurnal curve, 4 of 17 studies had reduced IOP greater than 2 mm Hg. One treatment arm had no placebo effect.

Conclusions: This study suggests that a placebo effect is common in glaucoma clinical trials and potentially could limit the ability to evaluate the efficacy of a new medicine.

Keywords: Clinical studies, phase, placebo effect, glaucoma

INTRODUCTION

A placebo effect occurs in glaucoma when a reduction from untreated baseline is noted when administering a non-active control. Placebos are used most commonly in early-phase clinical trials. A placebo effect is important because it may cause confusion when interpreting results since the decrease in intraocular pressure (IOP) for an active medicine will appear less compared to placebo than to the active's own baseline. Unfortunately, little information exists regarding the placebo effect in glaucoma. The purpose of this evaluation was to analyze the extent and prevalence of the placebo effect in prior early-phase glaucoma clinical studies.

METHODS

Study Criteria

Articles evaluated in this analysis were clinical trials on glaucoma medicines found on PubMed (www.pubmed.gov) and published between January 1977 and August 2011 or the FDA's drug approval website (www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). We included in this study, the phase I and II trials for glaucoma medicines that became commercially available after 1977 that had a placebo arm and involved glaucoma patients. Articles were included if they were: prospective, parallel, placebo-controlled, monotherapy studies with $\geq$10

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ocular hypertension or open-angle patients who were treated for at least 24 h.

The following search terms were used: primary open angle glaucoma, ocular hypertension, IOP, diurnal, monotherapy, baseline, reduction, β blockers (timolol, timolol gel forming solution, betaxolol, carteolol and levobunolol), carbonic anhydrase inhibitors (dorzolamide and brinzolamide), α agonists (brimonidine, brimonidine preserved with polyquaternium 1, brimonidine preserved with chlorine dioxide and apraclonidine), prostaglandins (latanoprost, travoprost and bimatoprost) and combination treatment (brinzolamide/timolol, dorzolamide/timolol, latanoprost/timolol, travoprost/timolol, brimonidine/timolol and bimatoprost/timolol). Brand names of single and fixed combination agents were also used as search terms.

Articles were excluded if they were crossover or open label studies. We excluded early studies that did not have a placebo comparison or did not evaluate at least a three-point diurnal curve or morning trough. Studies with the concentration difference greater than ±25% of the one which would become commercially available were excluded. We also excluded medicines for which we could find no published phase I and II articles or if they were shorter than 24 h. Studies that did not state at which time the IOP measurements were taken were also excluded. If a study provided both diurnal and trough measurements on the last active treatment day but did not provide the appropriate baseline of one of those measurements, then we only included the one with the proper baseline.

Data from articles meeting the study criteria data were entered into an Excel spreadsheet by medicine group: citation, medicine name, medicine class, trough IOP, diurnal IOP, trough percent reduction and diurnal percent reduction. Quality assurance was performed on 10% of the entries, in which a separate Excel spreadsheet was created and compared to the original to assure there were no mistakes. Results of the quality assurance analysis showed no data entry errors.

From the collected data, we were able to determine the average diurnal IOP reduction and standard deviation and average trough IOP reduction and standard deviation as well as the average percent diurnal IOP reduction and average percent trough IOP reduction. The analysis was descriptive in nature, and no statistical tests were performed.

RESULTS

We included 23 studies with 23 treatment arms with a total of 1703 patients in articles evaluating 10 different glaucoma medications.[1–23] Results from a total of 427 patients in the placebo arms were analyzed (Table 1). This study showed that at 8 AM ($n = 18$), the average IOP decrease in the placebo group from untreated baseline was 2.3 ± 1.6 mm Hg (9%), while for the diurnal curve ($n = 17$), the mean IOP decrease was 1.4 ± 1.1 mm Hg (6%). At 8 AM, 8 of 18 treatment arms had greater than 2 mm Hg IOP decrease, and all had at least some reduction in IOP. For the diurnal curve, 4 of 17 studies had reduced IOP greater than 2 mm Hg. One treatment arm had no placebo effect.

DISCUSSION

The results of this study show that a placebo effect commonly does occur in early-phase glaucoma trials for both the 8 AM and diurnal curve IOPs. Although the causes of the placebo effect are not known in the systemic literature, the placebo effect for objectively measured data has been related most commonly to a regression of the mean phenomenon. This effect occurs when a value is measured at one clinic visit at the upper end of the patient's usual range and then returns to the middle point of their usual range by the next visit. If a new treatment was started at the former visit, then it may appear that the new treatment had an effect when there was simply a regression to the mean.[24]

Several other causes have also been discussed in the systemic literature such as spontaneous improvement of the disease, which is unlikely to happen with glaucoma, and treatment taken by the patient unknown to the physician.[25] In addition, some evidence indicates the effect might be real from endorphins, which have been found in the anterior chamber of rabbits with elevated IOP and a conditional effect by receiving treatment.[26]

Causes specific to glaucoma might be related to measurement of the IOP itself as well as lifestyle habits that might reduce the IOP, which are unknown to the physician (i.e. exercise or alcohol use).[27]

The placebo effect may be important in glaucoma because it may raise interpretation issues for the IOP. A medicine that has been shown to reduce the effect from baseline 25% if there is a 2 mm Hg placebo effect, might only be demonstrating a 16% reduction from the placebo group. Consequently, what might appear to be a commercially successful medication when compared to baseline may have a marginal effect when compared to placebo. This might be important for a startup company trying to obtain funding for their product depending on which criteria for efficacy are used. This study suggests that a placebo effect is common in glaucoma clinical trials and potentially could limit the ability to evaluate the efficacy of a new medicine.

More research is needed to evaluate the causes and prevent the placebo effect in glaucoma. More information is also needed to determine which early-phase parameter best predicts long-term efficacy reduction

TABLE 1 Summary of articles included in this study.

					AM trough IOP		Diurnal IOP	
Reference	Treatment	Phase	Patients enrolled	Patients in placebo group	Baseline	Active	Baseline	Active
1	Betaxolol	2	10	5			29.2	25.5
2	Betaxolol	2	19	10			29.9	29.4
3	Bimatoprost	2	60	12	27.8	27.5	24.7	24.4
4	Bimatoprost	2	100	20	24.5	23.7	23.5	23.2
5	Bimatoprost	2	32	16	24.9	19.2	22.6	19.2
6	Bimatoprost	2	106	21	25.8	23.9	23.4	22.5
7	Brimonidine	1	21	21			21.3	20.0
8	Brimonidine	2	194	45	25.3	23.7	25.3	23.9
9	Brinzolamide	2	157	31	27.5	26.4	26.0	24.6
10	Dorzolamide	2	82	10	26.2	24.9	28.2	26.9
11	Dorzolamide	2	73	19	26.6	25.8	28.3	25.1
12	Dorzolamide	2	48	17	25.5	25.5	27.1	26.4
13	Latanoprost	1	15	6	25.2	22.1	26.5	21.0
14	Latanoprost	1	22	22			21.3	19.5
15	Latanoprost	1	40	20			20.1	20.0
16	Latanoprost	2	60	15	23.4	23.0		
17	Latanoprost	2	50	10	25.3	23.6	26.1	24.0
18	Latanoprost	2	40	8	24.9	22.9		
19	Levobunolol	2	48	8	25.6	22.5		
20	Levobunolol	2	42	16	27.3	24.0		
21	Timolol	2	20	4	22.0	20.0		
22	Travoprost	2	227	45	27.0	24.4	25.0	22.9
23	Unoprostone	2	237	46	25.5	22.2		
			1703	427				

IOP = intraocular pressure.

from baseline or placebo. Mitigating the placebo effect by repeat IOP measures pre-baseline when selecting patients for studies might be one way of reducing the regression to the mean effect.

DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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