PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Twenty-four-hour effects of bimatoprost 0.01% monotherapy on intraocular pressure and ocular perfusion pressure
AUTHORS	Liu, John ; Tung, Jonathan; Tafreshi, Ali; Weinreb, Robert; Slight, J; Medeiros, Felipe

VERSION 1 - REVIEW

REVIEWER	Rossetti, Lucca
REVIEW RETURNED	25-Apr-2012

GENERAL COMMENTS	The paper “Twenty-four-hour effects of bimatoprost 0.01%monotherapy on intraocular pressure and ocular perfusion pressure” is about the effect of bimatoprost on 24-hour IOP and OPP. The study methodology is sound and findings seems to be interesting. I have a few comments about this paper and are following - Patients: how was the sample of 16 subjects considered? Was it based on any calculation on bimatoprost “potential effect” on 24-hour IOP? - Patients: a Table reporting patients’ main characteristics should be presented. In particular, as many of the subjects had ocular hypertension, how was CCT? - Patients: some of the subjects were newly diagnosed, while others were treated and underwent a drug wash-out before inclusion. Numbers should be presented. - Patients: for those who were on therapy, type of drugs should be reported. Were there any patients treated with 0.03% bimatoprost? - Patients: the vast majority of the cases had ocular hypertension and only 3 had glaucoma. This could have a potential effect on the results’ generalizability to the glaucoma population. This needs to be discussed. - Stats: baseline and data after treatment were compared with paired-t test, which is a parametric test. Was normality of data distribution checked? Wilcoxon (non-parametric) test is usually applied when sample size is limited. - Results: Figure 1 is missing from the paper pdf file.

REVIEWER	E. Randy Craven, MD Associate Clinical Professor, Rocky Vista University Speaker and Consultant for Allergan Speaker for Merck Speaker for Alcon
REVIEW RETURNED	24-Apr-2012

GENERAL COMMENTS	Not clear why this would be Cardiovascular, dermatology and anesthesia as searchable words. They don't fit at all

REVIEWER	Andreas Katsanos Ophthalmology Department University of Ioannina, Ioannina, Greece
REVIEW RETURNED	21-May-2012

THE STUDY	Figure 1 does not appear in the PDF version of the manuscript, but does appear in the html version.
GENERAL COMMENTS	The authors have examined the ocular hypotensive effect and the effect on the calculated ocular perfusion pressure of the recently introduced bimatoprost 0.01% solution. Following are a number of issues that need to be addressed. Introduction, 2nd paragraph, 1st line. The authors should support their statement that “peak IOP is related to glaucoma progression” with relevant literature. Materials & methods, 1st paragraph. I would recommend mentioning the clinicaltrials.gov identifier. Materials & methods, page 8, 1st line. Did the authors use any formal way of determining measurement variability? How exactly were “…the variations of IOP measurements confirmed as insignificant”? Results, page 11, last lines. Can the authors offer an explanation regarding the nocturnal reduction of heart rate at the supine position after bimatoprost treatment? The authors have published several interesting papers in the past (eg Liu, Kripke et al IOVS 1998; Liu, Zhang et al IOVS 2003; Liu, Bouligny et al IOVS 2003) showing that nocturnal IOP readings are higher than diurnal readings, at least in healthy participants. In the current study, baseline supine readings at night are lower than daytime readings. This finding fits well with the more traditional understanding that in general, IOP tends to be higher in the morning. In addition, figure 2 of the currently submitted manuscript seems quite similar with figure 1 of the Liu, Zhang et al paper (IOVS 2003;44:1586), in which glaucoma patients have a morning, rather than a night-time peak. The authors are encouraged to comment on the potentially different IOP peaks that healthy individuals and POAG patients may have. It could be worth mentioning in the discussion that nocturnal & diurnal efficacy is related, at least in part, to the time of drug instillation and the peak/trough efficacy of the medication.

VERSION 1 – AUTHOR RESPONSE

Reviewer: E. Randy Craven, MD
Associate Clinical Professor, Rocky Vista University

Speaker and Consultant for Allergan
Speaker for Merck
Speaker for Alcon

Not clear why this would be Cardiovascular, dermatology and anesthesia as searchable words. They don't fit at all
Appropriate headings and keywords were added.

Reviewer: Luca Rossetti, MD
Director Eye Clinic, University of Milan at San Paolo Hospital, Milan, Italy

Consultant for Alcon, Allergan, MSD, Baush and Lomb, Pfizer

The paper “Twenty-four-hour effects of bimatoprost 0.01%monotherapy on intraocular pressure and ocular perfusion pressure” is about the effect of bimatoprost on 24-hour IOP and OPP. The study methodology is sound and findings seem to be interesting. I have a few comments about this paper and are following
- Patients: how was the sample of 16 subjects considered? Was it based on any calculation on bimatoprost “potential effect” on 24-hour IOP?
A pre-study calculation of sample size was performed when we applied the research funding. An anticipated standard deviation of the nocturnal IOP difference (2 mmHg) between the two experimental conditions and a desirable nocturnal IOP-lowering effect (1.6 mmHg) were used based upon our previous experience with IOP-lowering drugs including prostaglandin analogs. When accepting the statistical power of 0.80 and 0.05 Type I error, the calculated sample size was 15. We enrolled 16 subjects with caution that one subject may not complete both 24-hour laboratory recordings. Please note that this pre-study sample calculation was not presented since the real data variation (not the assumption as shown before) was presented in the manuscript and the results were positive.

- Patients: a Table reporting patients’ main characteristics should be presented. In particular, as many of the subjects had ocular hypertension, how was CCT?
A new Table with patients’ demographic information was added. Also, we deleted the redundant information from the text.

- Patients: some of the subjects were newly diagnosed, while others were treated and underwent a drug wash-out before inclusion. Numbers should be presented.
14 patients were newly diagnosed and 2 existing patients underwent washout. This information was added to the first paragraph of Results.

- Patients: for those who were on therapy, type of drugs should be reported. Were there any patients treated with 0.03% bimatoprost?
Information was added to the first paragraph in Results. No patient was treated with bimatoprost before the study.

- Patients: the vast majority of the cases had ocular hypertension and only 3 had glaucoma. This could have a potential effect on the results generalizability to the glaucoma population. This needs to be discussed.
Discussion of this issue was added to the 2nd paragraph of Discussion (last four sentences).

- Stats: baseline and data after treatment were compared with paired-t test, which is a parametric test. Was normality of data distribution checked? Wilcoxon (non-parametric) test is usually applied when sample size is limited.

Thank you for this reminder. Normal distribution of test data was confirmed using the Kolmogorov-Smirnov test. This information was added at the end of Materials and Methods.

- Results: Figure 1 is missing from the paper pdf file.
This problem will be checked for the revision.

Reviewer: Andreas Katsanos
Ophthalmology Department
University of Ioannina, Ioannina, Greece

The authors have examined the ocular hypotensive effect and the effect on the calculated ocular perfusion pressure of the recently introduced bimatoprost 0.01% solution.
Following are a number of issues that need to be addressed.

Introduction, 2nd paragraph, 1st line. The authors should support their statement that “peak IOP is related to glaucoma progression” with relevant literature.
A new reference (a review/consensus article) was added as Reference 3.

Materials & methods, 1st paragraph. I would recommend mentioning the clinicaltrials.gov identifier.
Number of identifier (NCT01271686) was added.

Materials & methods, page 8, 1st line. Did the authors use any formal way of determining measurement variability? How exactly were “…the variations of IOP measurements confirmed as insignificant”?
We used ±2 mmHg as the guideline to test the variability. It was added to the text. This number is used in the manufacturer manual to verify the accuracy of the instrument.

Results, page 11, last lines. Can the authors offer an explanation regarding the nocturnal reduction of heart rate at the supine position after bimatoprost treatment?
The real reason is unknown. We suspect that the study order of baseline-treatment may be a factor. However, we prefer not adding the speculation to the text.

The authors have published several interesting papers in the past (eg Liu, Kripke et al IOVS 1998; Liu, Zhang et al IOVS 2003; Liu, Bouligny et al IOVS 2003) showing that nocturnal IOP readings are higher than diurnal readings, at least in healthy participants. In the current study, baseline supine readings at night are lower than daytime readings. This finding fits well with the more traditional understanding that in general, IOP tends to be higher in the morning. In addition, figure 2 of the currently submitted manuscript seems quite similar with figure 1 of the Liu, Zhang et al paper (IOVS 2003;44:1586), in which glaucoma patients have a morning, rather than a night-time peak. The authors are encouraged to comment on the potentially different IOP peaks that healthy individuals and POAG patients may have.
In the present study, there were 13 patients with ocular hypertension and only 3 with primary open-angle glaucoma (POAG). The 2003 article by Liu et al specifically showed the 24-hour IOP pattern in patients with early glaucomatous changes. The potentially different IOP peaks in the healthy individuals and POAG has been discussed in that article. To the best of our knowledge, there is no published paper that shows the 24-hour IOP pattern in patients with ocular hypertension. We agree with the reviewer that this is an important area for research and look forward to seeing relevant publications.

It could be worth mentioning in the discussion that nocturnal & diurnal efficacy is related, at least in part, to the time of drug instillation and the peak/trough efficacy of the medication.
We added the following sentence “It is possible that the difference in diurnal and nocturnal efficacies

is related to the pharmacokinetics of prostaglandin analogs given once a day in the evening" to the first paragraph of Discussion.

VERSION 2 – REVIEW

REVIEWER	Luca Rossetti, MD Director Eye Clinic, University of Milan at San Paolo Hospital, Milan, Italy Consultant for Alcon, Allergan, MSD, Baush and Lomb, Pfizer
REVIEW RETURNED	25-Jun-2012

- The reviewer completed the checklist but made no further comments.

REVIEWER	Andreas Katsanos, Ophthalmology Department, University of Ioannina, Ioannina, Greece.
REVIEW RETURNED	19-Jun-2012

- The reviewer completed the checklist but made no further comments.