CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number __21-496__

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 21-496
Drug Name: Duocaine™ ' ⎯⎯⎯ Inj.)
Applicant: Amphastar Pharmaceuticals
Rancho Cucamonga, CA 91730
Indication: Anesthesia for Ophthalmic Surgery
Documents Reviewed: Vol. 1.10 (Papers #37 and #38), and 1.12 (Paper #97), Dated March 7, 2002
Medical Officer: William Boyd, M.D.
Biostatistician: M. Atiar Rahman, Ph.D.
Project manager: Mr. Raphael Rodriguez

1. Introduction

This NDA submission includes a compilation of 136 publications. The medical officer, Dr. Boyd, requested this reviewer to review and provide comments on the statistical analyses and conclusions on three of these papers, namely Papers #37, #38 and #97. The following sections contain the titles, abstracts, main results and this reviewer's comments on these three papers.

2. Paper #37

Title: Regional Anaesthesia for 12,000 Cataract Extraction and Intraocular Lens Implantation Procedures. (Ref: Can. J. Aneaesth 1988/35:6/pp 615-23)

Authors: Robert C. Hamilton MB FRCPC, Howard V. Gimbel MD FRCSC, and Leo Strunin MD FFARCS FRCPC

Abstract: Twelve thousand regional anaesthetics for cataract extraction and intraocular lens implantation surgery were administered by one anesthetist over a period of 52 months in a free-standing outpatient surgical facility. The ophthalmologist, who did all the operations, assessed the quality of the blocks using an objective scoring system which is described. The first 3,595 patients (Group A) had retrobulbar and seventh nerve blocks. The following 1,640 patients (Group B) had higher volume retrobulbar blocking alone. The next 3,478 patients (Group C) had peribulbar blocks, followed by 2,226 patients (Group D) who had a modified form of peribulbar blocking. A final group of 1,061 patients (Group E) had a combination of peribulbar and periorbital blocks with added retrobulbar injection if indicated. As the method of blocking evolved, the more closely was the goal of safe, painless and effective regional anaesthesia approached. The requirements for effective anaesthesia of this type are presented, the complications described and the importance of familiarity with the anatomy of the orbit and its contents stressed.

Results: The following table shows the Block score and supplementation rate

Table 1: Block score and supplementation rate
(Author's Table II, Page 3051)

	Group				
	A	B	C	D	E
Number of patients	3595	1640	3478	2226	1061
Block score:					
Excellent	90.0%	90.8%	83.3%	84.0%	89.8%
Good	6.5%	6.2%	11.2%	11.5%	7.1%
Fair	3.5%	3.0%	5.5%	4.5%	3.1%
Block supplement required	19.8%	9.0%	24.0%	24.0%	1.6%*

* $p < 0.05$

Conclusions: 1) Chi-square analysis of the results shown in Table 1 revealed no significant difference in the Block Scores in Group A to E. However, Group E was statistically better than the others in the Block Supplement required category. 2) A "cook-book" approach (Groups C and D) was less effective in producing an early onset of akinesia than a customized technique (Group E). 3) Regional anaesthesia for cataract extraction and intraocular lens implantation can be accomplished virtually painlessly and therefore without the use of sedative or narcotic drugs. 4) Topical conjunctival anaesthesia with the judicious combination of peribulbar, periorbital and retrobulbar injections approached most ideally the goal of a safe, painless and effective technique.

Reviewer's comments:

1) Regarding conclusion #1, this reviewer reanalyzed the Block score data (in Table 1) using the Fisher Exact test. Reviewer's conclusion on the comparison of Group A and Group E agrees with that of the sponsor, i.e. there is no statistically significant difference in the Block scores between Group A and E.

2) Regarding conclusion #2, the authors did not report any time to onset data in this publication. The conclusion might have been drawn from some other database.

3) Regarding conclusion #3 and 4, this reviewer is not sure, based on which end point the author drew such conclusions.

3. Paper #38

Title: Hyaluronidase as an Adjuvant in Bupivacaine-Lidocaine Mixture for
Retrobulbar/Peribulbar Block. (Ref: Anesth Analg 2000;91:934-7)

Authors: Helena Kallio, MD, Markku Paloheimo, MD, PhD, and Eeva-Liisa Maunuksela, MD, PhD

Abstract: Hyaluronidase 7.5 IU/mL added to the local anesthetic improves peribulbar block, but smaller concentrations have not been shown to be effective. In this prospective, double-blinded study, 714 consecutive ocular surgery patients were randomized into three groups: no hyaluronidase (n=241), hyaluronidase 3.75 IU/mL (n=244), and hyaluronidase 7.5 IU/mL (n=229). Retrobulbar/peribulbar block was performed with two injections of a 1:1 mixture of bupivacaine 0.75% and lidocaine 2%, 6-8 mL. Patient data were collected on demographics, initial volume of local anesthetic, need for supplementary block, and akinesia of the anesthetized eye. When hyaluronidase was used (3.75 or 7.5 IU/mL), the initial block was sufficient and the anesthetized eye was akinetic significantly more often than in the group without hyaluronidase. The hyaluronidase groups (3.75 and 7.5 IU/mL) did not differ

significantly in any respect. We conclude that the addition of hyaluronidase 3.75 or 7.5 IU/mL improved the success of the initial retrobulbar/peribulbar block and akinesia and reduced the need for supplementary block.

Results: The following table shows the Retrobulbar/peribulbar Block score

Table 2: Retrobulbar/peribulbar Block
(Author's Table 1 and 2, Page 3059)

	Group		
	G0	G3.75	G7.5
Number of patients	241	244	229
Initial volume (mL)	7■1 (3-8)	7■1 (5-9)	7■1 (5-8)
Adequate initial block, n (%)	181 (75%)	219 (90%)	196 (86%)
Supplementary blocks:			
Retrobulbar/peribulbar n (%)	50 (21%)	18 (7%)	27 (12%)
Topical (n)	9	6	4
Sub-Tenon (n)	1	1	2

Conclusions: The initial block was adequate significantly more often in the groups with hyaluronidase. G3.75 and G7.5 did not differ in this respect (Table 2). With ■=0.01, the initial block in G3.75 was successful more often than in G0 with a power of 0.999.

Reviewer's comment: This reviewer reanalyzed the initial block data (in Table 2) using the Fisher Exact test. This reviewer's conclusion on the comparison of three groups for initial block agrees with that of the sponsor.

4. Paper #97

Title: Prospective Study of a Single-Injection Peribulbar Technique (Ref: J Cataract Refract Surg-Vol. 18, March 1992)

Author: Paul N. Arnold, M.D.

Abstract: The single-injection peribulbar technique is an effective method of obtaining anesthesia and akinesia prior to anterior segment eye surgery. I (author) conducted a prospective study of 2,684 consecutive cases of a particular peribulbar block that I performed for more than three years. The incidence of sight-threatening complications was 0.6%. None of the cases was canceled because of peribulbar hemorrhage. Only 1.2% of the cases required a supplemental injection of anesthesia.

Results: In 2,684 cases, only 31 patients, 1.2%, required a supplemental block. Only two cases required an additional seventh nerve block because of insufficient orbicularis akinesia.

Reviewer's comments: Since this was a one-arm study, no statistical comparison of efficacy was involved. This reviewer's calculation showed that the percentage of cases who required a supplemental injection of anesthesia is 1.155% with 95% confidence interval of (0.751% to 1.56%). Also the percentage of cases who required an additional seventh nerve block is 0.075% with 95% confidence interval of (0% to 0.179%).

M. Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Stan Lin, Ph.D.
Team Leader, Biometrics III

cc:

Archival NDA 21-496
HFD-550/Division File
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**APPEARS THIS WAY
ON ORIGINAL**

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