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A double-masked comparison of betaxolol and levobunolol for the treatment of primary open-angle glaucoma.

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RESUMO

Este artigo mostra os resultados de um estudo duplo-cego entre betaxolol solução oftálmica a 0,5% e levobunolol solução oftálmica a 0,5% em 40 pacientes glaucomatosos.

Vinte (20) pacientes, ao acaso, receberam betaxolol e outros vinte (20) pacientes foram, aleatoriamente, selecionados para o tratamento com levobunolol.

O trabalho desenvolveu-se durante 12 semanas, nas quais os efeitos das drogas mencionadas foram obervados, especialmente sobre a pressão intra-ocular, bem como seus possíveis efeitos sistêmicos.

INTRODUCTION

The introduction of topical beta-adrenergic blocking agents has improved the treatment of Glaucoma, showing its effectiveness in reducing the intra-ocular pressure. However, non selective adrenergic beta-blockers may often cause adverse reactions, specially in the respiratory[3,6,12], cardiovascular[16] and central nervous systems[17].

Evaluation of agents that would provide ocular hypotensive activity and reduced systemic side effects. An ophthalmic selective beta-adrenergic blocker hás emerged as a strong candidate with demonstrated efficacy and safety[1,2,7,11,13].

PATIENTS AND METHODS

This study was a twelve-week double-masked, randomized, parallel-group comparison of Betaxolol 0,5% Ophthalmic Solution versus Lebobunolol 0,5% Ophthalmic Solution with forty (40) primary open-angle glaucoma patients participating in the clinical trial.

Before enrollment, patients[32] currently receiving ocular hypotensive medication underwent a wash-out period (four weeks for beta-blockers; three weeks with epinephrine products; 48 hours for pilocarpine. After wash-out, baseline intra-ocular pressure measurements were taken before 11:00 a.m. on two separate days, not less than three days apart. Enrollment was permitted if each of these two measurements was greater than 23 mmHg at least one eye.

Addtional exclusion criteria for participation in the study included: recent history of ocular trauma, infection or inflamatory diseases, any abnormality preventing reliable applanation tonometry, history of retinal detachment, diabetic retinopathy, or any retinal disease that could be expected to be progressive, intraocular surgery in the last six months, current contact lens wear, any unstable cardiovascular or pulmonary disease, current use of systemic beta-blocker hypersensitivity to betaxolol or to any formulation component, pregnant or nursing women and of

child-bearing potencial not using adequate contraceptive methods. Further, patients could be declared ineligible for any sound medical reason. Signed informed consent was obtained from patients meeting the enrollment criteria. Following enrollment, patients were randomly assigned in equal numbers to either the Betaxolol or Levobunolol treatment groups.

A pretherapy examination was administered and the following data were recorded: demographic information, medical history, visual acuity, pupillary diameter, perimetry, intraocular pressure, ocular signs and symptoms (slit-lamp biomicroscopy), cup/disc ratios, resting pulse rate and blood pressure. Baseline parameters were repeated at weeks 1, 2, 4, 8 and 12 except for perimetry and fundus examinations which were conducted only at the 12 week examination.

The test medications were then dispensed to the patients, who were instructed to administer the eye drops in the affected eyes every 12 hours. No adjunctive glaucoma therapy was allowed during the study. However, the investigator could remove any patient from the study if intraocular pressure was not considered to be well controlled by the study medication.

Analyses of variance were used to compare 0.25% Betaxolol Suspension versus 0.5% Betaxolol Solution at 8 hours and at 12 hours after dosing with respect to changes from baseline in intraocular pressure pulse rate, and mean arterial pressure. Patient comments referring to burning, stinging and perceived changes in the discomfort scale upon instillation of the eye drops were combined and considered as "ocular discomfort". Included in this category were reports of discomfort considered related, possibly related, and not related to the study medication. Chi-square was used to test for differences between the two treatments in the incidence of ocular discomfort and blurred vision.

Data were submitted to statystical analysis. Tables and figures show average and standard errors; F Test (Fisher) was used for simple correlation of nonpaired data; two-way analysis of variance was used for multiple correlation.

When indicated by the F Test, correlation between averages was established through the LSD (Least Significant Differences) method.

DATA AND RESULTS (BETAXOLOL)

Perimetry: 15 out of the 20 patients presented normal visual field, 3 with visual field loss in both eyes, and 2 patients presented visual field loss in one of the eyes.

Visual field was examined at pre-therapy phase and at the end treatment on the 12th week.

No changes were observed in 19 patients; one patient however, patient number 7 of this study, who had non-diagnosed glaucoma with a very high pressure in both eyes, showed a marked improvement in his visual field after 10 wering IOP due to medication.

Intraocular Pressure: IOP average in mmHg in 39 eyes, verified in the pretherapy phase and in the following examinations are shown below.

Pre-therapy	25,2 ± 0.4
1st week	16.8 ± 0.5
2nd week	17.2 ± 0.4 xxx
4th week	16.8 ± 0.5 xxx
8th week	18.8 ± 0.4 xxx
12th week	17.20 ± 0.4 xxx

Least Significant Differences (LSD)

x = P < 0.05
xx = P < 0.01
xxx = P < 0.001

Comparing with the average of obtained pressures in the pre-therapy phase with the ones obtained in the examinations during the whole study, we have:

Pre-therapy	following examinations
25.2	16.9 = 8.3 mmHg (33.0%)

Pulse: We obtained the following figures with the 20 patients studied:

Pre-therapy	77.7 ± 2.0
1st week	75.4 ± 1.8
2nd week	76.4 ± 2.7
4th week	76.0 ± 2.1
8th week	74.7 ± 1.8
12th week	74.4 ± 2.5

Pre-therapy	Following examinations
25.2	16.9 = 8.3 mmHg (33.0%)

Arterial Tension: The average of arterial tension in pre-therapy phase compared with the average of the ones observed during treatment has shown the following figures:

Pre-Therapy	Average during treatment
Maximum = 128 mmHg	124 mmHg = 4 mmHg
Minimum = 80 mmHg	78 mmHg = 2 mmHg

Visual Acuity: Visual acuity was unaltered in 18 (90%) patients, having improved in 2 (10%) patients (4 eyes) – the nrs. 7 and 8 of the study.

Patient nr. 7

Pre-therapy		12th week
R.E. = 20/60	improved to	20/40
L.E. = 20/400	improved to	20/100

This is the same patient who also showed improvement in visual fields.

Patient nr. 8

Pre-therapy	12th week
R.E. = 20/40 improved to	20/30
L.E. = 20/40 improved to	20/30

We can verify an improvement in circulation conditions at optical nerve level.

Pupillary Diameter: Measured on pre-therapy phase and on the following examinations it has not shown any alterations in its size.

Fundus Examinations: Retina and optical nerve have not shown alterations along the treatment.

Local Symptoms: It was searched for in all patients by using the following scale:

0 = absent
1 = weak
2 = moderate
3 = intense

The 20 patients presented ocular buring. In 12 of them the symptoms were weak (1) with improvement during the treatment. 8 patients presented moderate burning symptoms (2) while 3 patients improved to weak (1) and 5 of them remained unaltered.

Ocular Signs

No visible ocular modifications were observed during the treatment.

Systemic Alterations

There were no alterations on a general level. We would like to point out that 4 of the patients included in this group showed steady bronchial asthma and were using Timolol Maleate 0.5%, 2 times/day to control Glaucoma.

They were presenting chest squeaking sometimes and low intense dyspneia. With the switch to Betaxolol drops they did not present the above described symptoms anymore.

DATA AND RESULTS (LEVOBUNOLOL)

Perimetry: Out of the 20 patients, 15 presented campimetric defects on both eyes and 1 patient had loss of visual field in one of the eyes. These figures remained unaltered during the observed period.

Intraocular Pressure: IOP average in mmHg on the 38 eyes, measured on pretherapy phase and on the following examinations are shown below:

Pre-therapy	26.2 ± 0.7
1st week	16.0 ± 0.3
2nd week	15.8 ± 0.3
4th week	xxx 15.7 ± 0.3
8th week	xxx 15.8 ± 0.3
12th week	xxx 16.0 ± 0.4

Least significant differences (LSD)

x = $P < 0.05$
xx = $P < 0.01$
xxx = $P < 0.001$

Comparing IOP average measured on pre-therapy phase with the average of the pressure measures along the treatment during the 12 weeks of the study, we have the following figures:

Pre-Therapy	Following Examinations
26.2	15.9 = 10.3 (39.3%)

Pulse: The following figures were obtained from 20 patients during the study.

Pre-therapy	71.6 ± 2.2
1st week	69.0 ± 2.3
2nd week	69.7 ± 2.3
4th week	66.4 ± 1.9
8th week	67.2 ± 2.1
12th week	66.8 ± 2.1

Pre-Therapy	Following examinations
71.6	67.8 = 3.8

Arterial Tension: The figures below were obtained from the average of pretherapy arterial tension compared with the average of the arterial tensions along the treatment.

Pre-therapy	Average during treatment
Maximum = 135 mmHg	126 mmHg = 9 mmHg
Minimum = 83 mmHg	78 mmHg = 5 mmHg

Visual Acuity: Unchanged during the treatment.

Pupillary Diameter: There was no change on pupillary size with the use of the drug.

Fundus Examination: The were no alterations as to retina and optical nerve level along the oberved period.

Local signs: We have not observed any different ocular signs.

Systemic alterations: We have observed significant differences in Pulse and Arterial Tension (LSD Test).

Local Symptoms: Out of 20 patients, 5 did not present complaints (0), 15 presented weak burning which have disappeared in 6 of them up to the end of the treatment.

RESULTS AND COMMENTS

The demographic characteristics of the patients in the two treatment groups are compared in Table 1. No significant differences were detected in between treatment groups.

Intraocular Pressure: Both treatments were clinically effective as illustrated in Figure 1, which shows a significant reduction ($p < 0.001$) in intraocular pressure for both treatment groups at each examination over the 12 week period. Analysis of variance revealed no significant difference ($p > 0.05$) in the mean intraocular pressure values between the treatment groups at each examination period.

Perimetry: On patient showed a marked improvement in visual fields from baseline to the twelve week of treatment in the Betaxolol group, there were no measurable changes in the visual fields of the other 19 patients in this group or in the 20 patients in the Levobunolol group.

Visual Acuity: Two of twenty patients improved from baseline to the 12 week evaluation in the Betaxolol group (Table 2). There were no changes detected in the Levobunolol group.

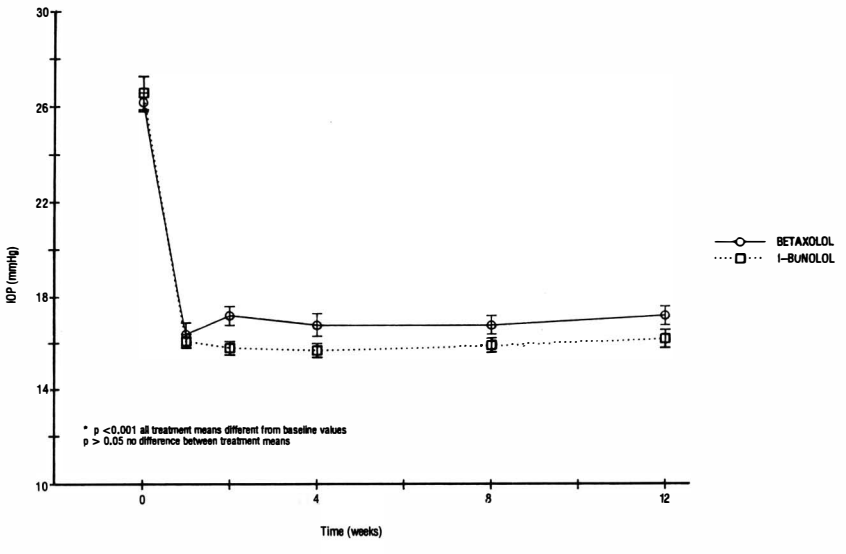
Pupillary Diameter, Fundus Evaluation: There were no changes observed from baseline values in pupillary diameter or fundus examination in either treatment group.

Ocular Signs and Symptoms: No changes were observed in ocular signs in either treatment group during the study. A transient stinging upon instalation of the eye drop was reported by all patients in the Betaxolol group which improved during the course of the study in 75% of the patients. Fifteen patients reported stinging in the Levobunolol group with improvement noted in 40% of the patients. There were no clinical significant differences observed btween the treatment groups in the other symptoms evaluated.

TABLE 1
Demographic Characteristics

	Betaxolol	Levobunolol
No. of patients entering study	20	20
Age (years)		
Mean +S.D.	61.2	63.6
Range	28-83	40-82
Sex		
Male (%)	7(35%)	4(20%)
Female (%)	13(65%)	16(80%)
Iris color (%)		
Brown/Black	11(55%)	16(80%)
Blue	6(30%)	2(10%)
Hazel/green/grey	3(15%)	2(10%)
Race		
White (%)	19(95%)	20(100%)
Non-white (%)	1(5%)	0
Diagnosis (%)		
POAG	20(100%)	20(100%)
Perimetry (%)		
Normal (%)	15(75%)	5(25%)
Vision loss		
both eyes	3(15%)	14(70%)
one eye	2(10%)	1(5%)

Figure 1 – 12 WEEK IOP COMPARISON
Betaxolol 0.5% vs l-bunolol 0.5%



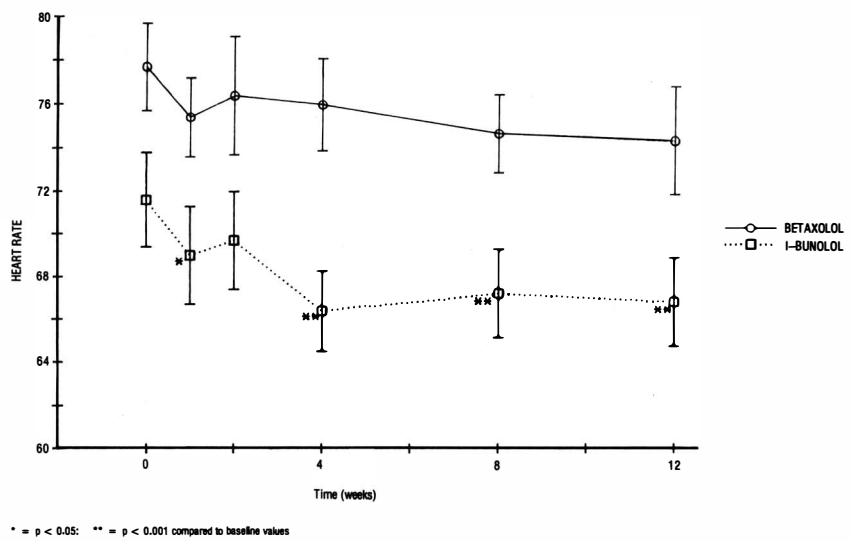
Systemic Evaluations:

Heart Rate: A significant reduction in the mean heart rate values was measured at weeks 1, 4, 8 and 12

TABLE 2
Visual acuity
Betaxolol treatment

	Pre-Therapy Exam.	12th Week Exam.
Patient nr. 7		
R.E.	20 / 60	20 / 40
L.E.	20 / 400	20 / 100
Patient nr. 8		
R.E.	20 / 40	20 / 30
L.E.	20 / 40	20 / 30

Figure 2 – Betaxolol 0.5% vs. Levobunolol 0.5% heart rate comparison twelve weeks



compared to mean baseline values in the Levobunolol treatment group (Figure 2), whereas no significant heart rate reduction was measured in the patients receiving Betaxolol.

Blood Pressure: No significant changes were observed with both drugs used.

Pulmonary System: No pulmonary changes were observed in the two groups, even for patients with chronic asthma that received Betaxolol.

Betaxolol is indicated for the treatment of all patients who need to control IOP. For its efficacy and safety on possible side effects, Betaxolol should be considered the drug of choice for patients who need ocular hypotensive medication and who suffer from chronic obstructive pulmonary disease, chronic asthma and chronic bronchitis.

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SUMMARY

This article shows a double masked study between Betaxolol 0.5% drops and Levobunolol 0.5% drops involving 40 glaucomatous patients.

20 randomized patients were given Betaxolol. And other 20 patients were given Levobunolol in a randomized way as well.

This work developed over a period of 12 weeks during which time the effects of the above mentioned drugs on the ocular were observed specially over the Intraocular Pressure as well as their possible systemic effects.

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