Ocular hypotensive efficacy and safety of once daily carteolol alginate

Philippe Demailly, Catherine Allaire, Claude Trinquand, for the Once-daily Carteolol Study Group

Abstract

Backgroundaim—Carteolol is a β adrenoceptor antagonist used topically to reduce intraocular pressure, typically twice daily. In an effort to provide a once daily dosing regimen, carteolol was formulated with 1% alginic acid. The objective of this study was to evaluate the efficacy and safety of carteolol alginate solution in comparison with standard carteolol solution.

Methods—This was a double masked, parallel group, multicentre study. Patients with ocular hypertension or open angle glaucoma (n=235) were randomly assigned to receive either carteolol alginate four times daily or standard carteolol solution, twice daily. The masking was maintained through the use of a vehicle in the evening for the alginate group. Patients were evaluated at baseline, 15, 60, and 120 days.

Results—At 0900 (presumed trough) on day 60, mean reductions in intraocular pressure (IOP) from baseline were 6.09 (SD 2.97) and 6.49 (3.18) mm Hg for the standard carteolol and alginate, respectively. At 1100 (presumed peak), mean reductions were 6.51 (2.53) and 6.47 (2.76) mm Hg, respectively. Results were similar at other times (day 15 and day 120). The most common side effect was transient stinging on instillation of drops, which did not differ significantly between groups. There were no differences of note in other ocular or systemic signs or symptoms.

Conclusion—The new alginate formulation of carteolol 2% given once daily was as effective as standard carteolol 2% given twice daily with no meaningful differences regarding safety.

(Ophthalmology 2001;85:921–924)

Carteolol is a β adrenoceptor antagonist with intrinsic sympathomimetic activity. Applied topically in patients with elevated intraocular pressure (IOP), it elicits a dose related decrease in IOP, with a maximum at 2%.1,2 Applied twice daily, its ocular hypotensive efficacy has been reported to be similar to that of timolol.3,4

Glaucoma is for the most part an asymptomatic disease, and the treatments may elicit both local and systemic untoward effects. Thus, it is a classic disease for which patient adherence with a medication regimen may be low.5 In an effort to reduce the dosing frequency for topical carteolol from the standard twice daily to once daily, carteolol was formulated with alginic acid. Alginate solution exhibits a viscosity low enough to be compatible with topical administration without blurring effect. Sodium alginate is a natural polymer product with bioadhesive properties,6 used in many pharmaceutical preparations including those for reflux oesophagitis.7 In animals, an alginate formulation of carteolol 1% and 2% provides good intraocular delivery of carteolol, enhanced relative to standard solution.8 In a water loaded rabbit model of aqueous humour dynamics, the alginate formulation of carteolol had a longer duration of action than the standard solution.9 In a short term study in normal volunteers, the alginate formulation was found to be of similar comfort as the standard solution, with a possible longer duration of ocular hypotensive action.

The objective of this study was to evaluate the efficacy and safety of carteolol alginate administered once daily in comparison with standard carteolol solution administered twice daily in a long term study.

Methods

This was a double masked, randomised, multicentre study, comparing two parallel treatment groups. Enrolled were adult patients with open angle glaucoma or ocular hypertension in one or both eyes. Patients using ocular hypotensive medication were required to undergo a washout as follows: β adrenoceptor antagonists or sympathomimetics (3 weeks); latanoprost (1 week), pilocarpine, apraclonidine, or topical or oral carbonic anhydrase inhibitors (72 hours). For entry into the study the “study” eye(s) was (were) required to have an unmedicated IOP ≥ 23 at 0900 or 1100 and < 32 mm Hg at 0900 and 1100. This study was reviewed by an institutional review board, and all patients provided written informed consent. Excluded from the study were patients with angle closure, congenital, secondary glaucoma, or advanced glaucoma; contact lens wear during the study; any intraocular infection or inflammation, ocular trauma, ocular surgery, or laser trabeculoplasty within the previous 3 months; previous intolerance to carteolol; or contraindications to the use of β adrenoceptor antagonists (for example, asthma, chronic obstructive pulmonary disease, moderate to severe atrioventricular block unless a pacemaker was implanted, or bradycardia < 45 bpm, etc.). Ocular corticosteroid use during the study was prohibited. Patients who were using systemic medications such as adrenergic hypotension agents were allowed to participate if the condition and dosing regimen were stable. Also excluded were pregnant and lactating women.

A baseline examination was conducted, including measurements of heart rate and...
blood pressure, visual acuity, automated threshold visual field (if not performed within the previous 6 months), biomicroscopy, IOP measurement by Goldmann applanation at 0900 and 1100. After the last baseline IOP measurement, patients were assigned to receive, in a double masked fashion, either 2% carteolol alginate four times daily (~0900) or standard 2% carteolol solution (Carteol, Laboratories Chauvin, Montpellier, France), twice daily (~0900 and 2100). The randomisation code was prepared using the PROC RANUNI procedure (PC-SAS Version 6.12, SAS Institute, Cary, NC, USA) with a block size of four. The composition of carteolol-alginate was identical to that of market carteolol, with the exception of the addition of 1% alginate. The formulations were identical in toxicity and viscosity. The pH of the solutions was similar. The vehicle for the carteolol-alginate group was formulated the same as the carteolol-alginate formulation, with the exception of alginate. Patients used the medication in one or both eyes. The masking was maintained through the use of a vehicle in the evening for treatment in the other eye; bradycardia; and dizziness—all judged mild or moderate), cancellation of consent (one). In the alginate group a similar number of patients did not complete the trial: adverse events (three, tinnitus and watering of the eye; bradycardia; and dizziness—all judged mild or moderate), cancellation of consent (one), and poor compliance (one).

Patient demographics are shown in Table 1. The population was 58% male with a mean age of 61 years, with iris colour distributed among blue-green-grey, hazel, and brown irides. Most patients were white. Approximately two thirds of the patients were diagnosed with primary open angle glaucoma (63.4%, 149/235), including three patients with pigmentary glaucoma (one in standard group and two in the alginate group). There were no statistically significant differences between treatment groups (p > 0.22). Most (87%; 204/235) patients received treatment in both eyes. Also, most (64%, 151/235) patients were using at least one systemic medication. Before study entry, 51% of patients (120/235) were using an ocular hypotensive medication. For 102 of these patients, this medication was a topical β adrenoceptor antagonist.

Mean intraocular pressure at 0900 and 1100 is shown in Figures 1 and 2 respectively, and mean change from baseline in intraocular pressure in Tables 2 and 3. From a baseline of approximately 24–25 mm Hg, mean reductions ranged from 5.5 to 6.5

### Results

Entered into the study were 235 patients (115 standard and 120 alginate), plus one subject who did not return after day 0. In the standard group, five patients did not complete the study: lost to follow up (one), adverse events (two, dizziness, thorax pain and sweats of moderate intensity; and mild ocular irritation), worsening of disease (one), and cancellation of consent (one). In the alginate group a similar number of patients did not complete the trial: adverse events (three, tinnitus and watering of the eye; bradycardia; and dizziness—all judged mild or moderate), cancellation of consent (one), and poor compliance (one).

![Figure 1](http://bjo.bmj.com/)
mm to an IOP of approximately 18 mm Hg in both treatment groups. The ocular hypotensive efficacy of carteolol was slightly greater at 1100, 2 hours after the last instillation, relative to 0900, approximately 24 or 12 hours after the last instillation of alginate or standard, respectively. The IOP course was statistically significant within time (time effect: \( p = 0.0001 \) in the repeated measures analysis). There was no evidence of drift with either treatment. In the equivalence analyses, all measures were within the plus or minus 2 mm Hg interval for equivalence. There was no statistically significant difference between the two treatment groups (\( \chi^2 \), \( p = 0.20 \)). Similar results were seen at 0900 (141–144 mm Hg, and 81–82 mm Hg, respectively). Slight decreases in means were observed at follow up visits (up to 6 bpm, 73–74 bpm, and 141–144 mm Hg, respectively). No change was noted in distance visual acuity for 78.3% (90/115) of standard treated patients and in 70.0% (84/120) of alginate treated patients, without any statistically significant difference between the two treatment groups (\( \chi^2 \), \( p = 0.20 \)). Similar results were seen at 0900.

At day 120, visual fields were unchanged for 78.3% (90/115) of standard carteolol treated patients and by 98% of standard patients evaluated on day 120 (Table 4). Discomfort was reported by approximately 10% to 15% of patients in each treatment group at each visit (Table 5). These reports were similar in incidence in each group. The most frequent discomfort in both groups was a stinging sensation which generally lasted for a few seconds or a few minutes. The blurred vision discomfort was recorded in 3/120 patients of the alginate group and 2/115 patients of the standard group.

At baseline, mean heart rate, systolic and diastolic blood pressure was approximately 73–74 bpm, 141–144 mm Hg, and 81–82 mm Hg, respectively. Slight decreases in means were observed at follow up visits (up to 6 bpm, 8 mm Hg, and 3 mm Hg, respectively). There were no statistically significant differences between treatment groups (\( p = 0.607 \) to 0.852).

### Table 2: Intraocular pressure at 0900 (mm Hg); mean (SD) change from day 0 baseline

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Alginate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>No  Mean</td>
<td>SD</td>
</tr>
<tr>
<td>0</td>
<td>115  24.67 1.98</td>
<td>120  24.82 2.14</td>
</tr>
<tr>
<td>15</td>
<td>115  5.58 3.13</td>
<td>120  5.50 2.99</td>
</tr>
<tr>
<td>60</td>
<td>111  6.09 2.97</td>
<td>117  6.09 3.18</td>
</tr>
<tr>
<td>120</td>
<td>110  6.25 3.03</td>
<td>115  5.86 2.79</td>
</tr>
</tbody>
</table>

At each time of evaluation, the two unilateral \( t \) tests were significant (both \( p \) values < 0.005), showing the equivalence of both treatments.

### Table 3: Intraocular pressure at 1100 (mm Hg); mean (SD) change from day 0 baseline

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Alginate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>No  Mean</td>
<td>SD</td>
</tr>
<tr>
<td>0</td>
<td>115  24.31 1.83</td>
<td>120  24.42 2.63</td>
</tr>
<tr>
<td>15</td>
<td>113  6.07 2.27</td>
<td>119  6.06 2.72</td>
</tr>
<tr>
<td>60</td>
<td>111  6.51 2.53</td>
<td>116  6.47 2.76</td>
</tr>
<tr>
<td>120</td>
<td>110  6.47 2.40</td>
<td>115  6.18 2.84</td>
</tr>
</tbody>
</table>

At each time of evaluation, the two unilateral \( t \) tests were significant (both \( p \) values < 0.005), showing the equivalence of both treatments.

### Table 4: Number and percentage of patients with very good or good tolerance upon instillation

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Alginate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>No  %</td>
<td>No  %</td>
</tr>
<tr>
<td>15</td>
<td>114  99.1</td>
<td>119  99.2</td>
</tr>
<tr>
<td>60</td>
<td>112  100.0</td>
<td>116  99.2</td>
</tr>
<tr>
<td>120</td>
<td>109  98.2</td>
<td>114  99.1</td>
</tr>
</tbody>
</table>

At baseline, mean heart rate, systolic and diastolic blood pressure was approximately 73–74 bpm, 141–144 mm Hg, and 81–82 mm Hg, respectively. Slight decreases in means were observed at follow up visits (up to 6 bpm, 8 mm Hg, and 3 mm Hg, respectively). There were no statistically significant differences between treatment groups (\( p = 0.607 \) to 0.852).

### Discussion

Evaluated at both peak and trough, at an initial, middle, and long term stage, the new alginate formulation once daily was equivalent in ocular hypotensive efficacy to the standard solution formulation given twice daily. While a vehicle control would have been desirable, it is not possible to use in a chronic glaucoma study for ethical reasons. The positive control, standard carteolol solution, was similarly effective in the present study (reduction of ~6 mm Hg or ~25%) to that observed in previous studies. Thus, the efficacy of the positive control, and the high power of the study (95% to detect a 2 mm Hg difference) supports the statement of equivalency.
Special attention is directed towards the 0900 hour measurement. This is ~24 hours after the last dose of carteolol alginate, and yet the mean IOP is similar to the standard solution given 12 hours previously.

The ocular tolerance of the alginate was good. Again, it was similar to the standard formulation, which itself has been reported to be well tolerated. Thus, the finding of no substantial comfort problems is also a positive attribute of the alginate. In particular, the incidence of blurred vision (less than 3% in each group) is much lower than what has been reported with timolol in gel forming solution.

With regard to safety, there was no significant difference between both treatment groups for all studied safety variables.

Both treatment groups experienced a slight decrease in mean heart rate and blood pressure. The intrinsic sympathomimetic activity of carteolol could explain the relatively small impact of carteolol on the cardiovascular function: carteolol has been shown to cause less bradycardia than timolol at night. In our study, cardiovascular parameters were measured only once per visit, 1 hour after the morning instillation. Thus, it is not possible to discuss what occurred at other times for the 24 hours.

The relatively few adverse events were similar to those previously reported for this class of compounds.

In conclusion, the new alginate formulation of carteolol 2% given once daily was as effective as standard carteolol given twice daily with no meaningful differences regarding safety.

Conflict of interest: Professor Demailly serves as a consultant to Laboratories Chauvin, but has no proprietary interest. Drs Allaire and Trinquand are employees of Laboratoires Chauvin. The Once-daily Carteolol Study Group consisted of 23 French clinical centres and one Swiss clinical centre: Y. Lachkar, MD, H. Gracies, MD, Hôpital St Joseph, Paris (Study Coordinator: Pr Ph Demailly); J-P. Adenis, MD, Ph Bertin, MD, CHRU Dupuytren, Limoges; JC. Descomps, MD, Lyon; J. Flamant, MD, J Siewarczyk, MD, Hospices Civils, Strasbourg; H. Hoang-Uyen, MD, N. Belavici, MD, Hôpital Necker, Paris; G. Kretz, MD, Paris; MJ Le Rebeller, MD, Ph Cousin, MD, GH Pellegrino-Tripode, Bordeaux; G. Leseur, MD, Albi; M. Monnard, MD, F. Mao, MD, CHU Jean Minjoz, Besançon; A. Raspiller, MD, L. Malax, MD, X Portrat, MD, Hôpital Central, Nancy; Ph Renard, MD, P. Delacour, MD, Institut Arthur Ver- nes, Paris; D. Serbat, MD, Strasbourg; G. Bouat, MD, S. Vinet, MD, JP Ghipponi, MD, Hôpital Militaire Laveran, Marseille; L. Pernod, MD, P. Hérit, MD, CHA René Le Bas, Cherbourg; C. Rousse, MD, C. Chopin, MD, Hôpital Louis Pasteur, Dole; JL George, MD, P. Leslie, MD, Hôpital de Brabois, Vandoeuvre- les-Nancy; J. Perraton, MD, Clinique Charcos, Ste-Foy-les- Lyon; A. Brézin, MD, O. Rivoul, MD, A. Lefrancois, MD, Hôpital Cochin, Paris; G. Arrosas, MD, Djon; JD Orange, MD, L. Kodjikian Hôpital de la Croix Rousse, Lyon; JL Kovalski, MD, Y. Dordain, MD, R. Macarez, MD, D. Salabert, MD, HIA “Clermont-Tonnerre”, Brest; P. Daubas, MD, G. Fillion, MD, Hôpital Sainte-Anne, Toulouse; AG Arredez, MD, Polyclinique Sévigné, Cesson-Sévigné; A. Mermoud, MD, F. Achache, MD, A Chabari, MD, Hôpital Jules Gomin, Lausanne (Swiss).

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Coordinating centre: Catherine Allaire, MD, Sandrine George, MS, Anne Combe, MS, Florence Bernard, MS, Ghzel El Hamdi, PhD (San Rafael, CA, USA).

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LETTER TO THE EDITOR

Analysis of publication trends in two internationally renowned ophthalmology journals

EDITOR,—International journals represent a forum for exchange of current information with contributions from all over the world. High standards are essential. In this report, we compared the publishing trends of two internationally renowned ophthalmology journals—the British Journal of Ophthalmology (BJO) and the American Journal of Ophthalmology (AJO).

METHOD AND RESULTS

Using the public Medline facility provided by the National Institutes of Health, the numbers of prospective studies and case reports published in the AJO and the BJO from January 1980 to December 1999 were determined. These were done using the following keyword searches: “prospective” and “case report.” The countries of origin of the articles were counted manually for the years 1990 and 1999, and were taken as the addresses of the corresponding author. Keyword searching was not possible owing to the non-uniformity of the way the addresses were registered.

The total number of publications remained fairly constant in the AJO over the two decades (Fig 1A). The percentage of prospective studies increased greatly from 1% to 12% (Fig 1B). Case reports, on the other hand, constituted 34–45% of the published articles (Fig 1C) with no obvious trend.

In comparison, there was a steady increase in the total number of articles (Fig 1A) in the BJO. The trends in the percentages of prospective studies and of case reports were similar to that in the AJO (Fig 1B and C).

The native countries (that is, the countries in which the journals are published) were the major contributors of articles for their respective journals (Fig 2A). The United States made a considerably larger contribution to the BJO than the United Kingdom did to the AJO (Fig 2B). Comparing 1990 with 1999, the contribution from foreign countries had risen significantly from 40% to 60% in the BJO and from 14% to 36% in the AJO. The top few foreign countries contributing to the respective journals are shown in Figures 2C and D.

COMMENT

In an ideal world, all studies will be randomised and controlled. In reality, however, this is often not the case for various reasons. In our present study, we arbitrarily and simplistically chose the prospective design as an indicator of a good quality publication. In both the BJO and the AJO, there had been an increasing percentage of prospective studies published (from 3% to 6% and from 1% to 12% respectively) over the past two decades. This is an encouraging sign but the percentages remain small, especially in the BJO, when compared with other types of publications. This is not necessarily the fault of the journals but merely a reflection of the research work done during that period.

Contributions from abroad appeared to be on the increase in both journals when comparing 1990 with 1999 with the BJO.
NOTICES

Oncocerciasis
The latest issue of Community Eye Health (No 38) discusses onchocerciasis and the impact of interventions, with an editorial by Bjorn Thyfors, former director of the Programme for the Prevention of Blindness and Deafness, WHO. For further information please contact Community Eye Health, International Centre for Eye Health, Institute of Ophthalmology, 11–43 Bath Street, London EC1V 9EL. (tel: (+44) (0) 20-7608 6909/6910/6923; fax: (+44) (0) 20-7608 3207; email: eyeresource@ucl.ac.uk) Annual subscription £25. Free to workers in developing countries.

International Centre for Eye Health
The International Centre for Eye Health has published a new edition of the Standard List of Medicines, Equipment, Instruments and Optical Supplies (2001) for eye care services in developing countries. It is compiled by the Task Force of the International Agency for the Prevention of Blindness. Further details: Sue Stevens, International Centre for Eye Health, 11–43 Bath Street, London EC1V 9EL, UK (tel: (+44) (0) 20-7608 6910; email: eyeresource@ucl.ac.uk).

Second Sight
Second Sight, a UK based charity whose aims are to eliminate the backlog of cataract blind in India by the year 2020 and to establish strong links between Indian and British ophthalmologists, is regularly sending volunteer surgeons to India. Details can be found at the charity website (www.secondsight.org.uk) or by contacting Dr Lucy Mathen (lucy.mathen@yahoo.com).

Specific Eye Conditions (SPECS)
SPECS is a not for profit organisation acting as an umbrella organisation for support groups of any conditions or syndrome with an integral eye disorder. The SPECS website (www.eyeconditions.org.uk) acts as a portal to support groups, and is a valuable resource for professionals and may also be of interest to people with a visual impairment or who are blind. Further details: Kay Parkinson, SPECS development officer. (tel: +44 01803 524 238; email: k@eyeconditions.org.uk).

41st St Andrew's Day Festival Symposium on Therapeutics
The 41st St Andrew’s Day Festival Symposium on Therapeutics will be held on 6–7 December 2001 at the Royal College of Physicians of Edinburgh. Further details: Ms Eileen Straw, Symposium Co-ordinator (tel: 0131 225 7324; fax: 0131 220 4393; email: e.straw@rcpe.ac.uk; website: www.rcpe.ac.uk).

4th International Conference on the Adjuvant Therapy of Malignant Melanoma
The 4th International Conference on the adjuvant therapy of malignant melanoma will be held at The Royal College of Physicians, London on 15–16 March 2002. Further details: Conference Secretariat, CCI Ltd, 2 Palmerston Court, Palmerston Way, London SW8 4AJ, UK (tel: + 44 (0) 20 7720 0600; fax: + 44 (0) 20 7720 7177; email: melanoma@confcom.co.uk; website: www.confcom.co.uk/Melanoma).

EUPO 2002 Course Retina
A course on retina will be held on 15–17 March 2002 at Erlangen, Germany, where European professors will teach European residents. Further details: Priv Doz Dr Ulrich Schonherr, Friedrich-Alexander-University of Erlangen-Nuernberg, Department of Ophthalmology, Schwabachanlage 6 (Kopfflinikum), D-91054 Erlangen, Germany (tel: +49 9131-853-4379; fax: +49 9131-853-4332; email: ulrich-schonherr@augenmed.uni-erlangen.de).

International Society for Behçet’s Disease
The 10th International Congress on Behçet’s Disease will be held in Berlin 27–29 June 2002. Further details: Professor Ch Zouboulis (email: zoubbere@zedat.fu-berlin.de).

Singapore National Eye Centre 5th International meeting

CORRECTIONS

In a paper published by Minassian et al in the July issue of the BJO (2001;85:822–9) two authors who made significant contributions to the project were omitted. They are Sunny Kaushal, research optometrist, Oxford Eye Hospital, and Nicholas Wingate, research optometrist, Moorfields Eye Hospital. We apologise for this omission.

A translation error occurred in the article by Demaily et al which appeared in the August issue of the BJO (2001;85:921–4). In the abstract (p 921 line 16) and the text (p 922, line 8) the dose for carteolol alginate was once daily. We apologise for this error.