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A Randomised Double Blind Trial Comparing the Treatment of Episcleritis with Topical 2-(2-Hydroxy-4-methylphenyl) Aminothiazole Hydrochloride 0.1% (CBS 113A) and Placebo

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Summary

A randomised double blind trial of 2-(2-Hydroxy-4-methylphenyl) Aminothiazole Hydrochloride 0.1% (CBS 113A) versus placebo was carried out in 43 eyes with episcleritis. Our results show that CBS 113A is effective in reducing the signs of conjunctival and episcleral inflammation in mild episcleritis within the first week of administration of the drug (Day 3: Total Score $p = 0.0013$, Conjunctival Injection $p = 0.017$, Episcleral Injection $p = 0.0018$ and Day 7: Total Score $p = 0.01$, Conjunctival Injection $p = 0.014$, Episcleral Injection $p = 0.027$). CBS 113A was not effective against severe episcleritis. No significant side effects were found apart from a stinging sensation. There was no effect on intraocular pressure. The potential use of this new drug is discussed.

Episcleritis is a self limiting inflammatory disease requiring no treatment provided it does not become recurrent or develop associated scleral inflammation. The disease process is therefore a suitable model for the initial clinical assessment of the efficacy of new anti-inflammatory preparations.[1] It has two distinct clinical forms and may be simple or nodular.[2,3,4] The severity and duration of individual attacks is highly variable, but the condition itself is often sufficiently uncomfortable that many patients require some form of anti-inflammatory preparation. Topical steroids are commonly used and their efficacy for this condition is well known,[5,6,7] but these sometimes induce side-effects including a rise in intraocular pressure and cataract formation especially with prolonged use. These side effects are particularly relevant in recurrent episcleritis.

The search for alternative forms of treatment for ocular inflammation is a continuing process and most published work has been done on non-steroidal anti-inflammatory drugs (NSAIDS).[1,5,7–10] Double-blind studies using both systemic[9] and topical oxyphenbutazone[5] have shown that this agent is effective in reducing the inflammation in episcleritis. This drug is not satisfactory for routine use because the oral preparation has multiple side effects and topical treatment has to be used as an ointment.[5] Although systemic flurbiprofen[4,11] is effective in the treatment of episcleritis, topical treatment has little anti-inflammatory effect.[7]

The aim of this study is to determine the effectiveness of 2-(2-Hydroxy-4-methylphenyl) Aminothiazole Hydrochloride (CBS 113A) 0.1% drops, a new anti-inflammatory agent, for the treatment of episcler-

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itis. The pharmacological profile of CBS 113A is unique: it is a dual inhibitor of both cyclo-oxygenase and lipoxygenase, as well as being a potent free-radical scavenger.[12,13,14]

Materials and Methods

Patients

A randomised double blind trial was carried out at the Casualty Department of Moorfields Eye Hospital, London. Forty-three consecutive cases of episcleritis were recruited (38 patients including four patients with bilateral disease and one patient with two separate attacks) which were either first or recurrent attacks. Patients already on treatment with steroids or NSAIDS were excluded. Cases were randomly allocated to one of two groups. Patients allocated to the drug group (G. drug) were given CBS 113A 0.1% to be instilled one drop six times a day for the first week and four times a day for a further two weeks. This regime was suggested by Laboratoire Chauvin, based on results obtained from previous studies.[15,16] Patients in the placebo group (G. placebo) received the vehicle of the eye drops only, in a similar fashion. Neither the patients, surgeons or the pharmacists had any knowledge of the randomisation until the trial was completed. The study had the approval of the Hospital Ethical Committee and the informed written consent of all the patients.

Drug

The already randomised preparations of CBS 113A were provided by Laboratoire Chauvin S.A., Parc Euromédicine 104, rue de la Galéra, B.P. 1174 34009, Montpellier Cedex, France. A fresh preparation was made each week by reconstituting lyophilised powder with the provided solution in the Pharmacy Department of Moorfields Eye Hospital.

Parameters of assessment

At the initial attendance (Day 0 = D0), the severity of the episcleritis was assessed in terms of pain, conjunctival and episcleral injection, and the presence of nodules. Pain was graded subjectively and scored as being absent (0), mild (1), moderate (2) or severe (3). Conjunctival and episcleral injection were scored for each quadrant of the 'white of the eye' using the following scale: absent (0), very mild (0.5), mild (1), moderate (2) or severe (3). The presence of nodules were noted and each nodule received a score of three. The numerical sum of the above four parameters is the total score (TS) and gives an indication of the severity of the episcleritis. A full ocular and medical history was taken, including the duration of the current attack prior to presentation (duration of illness) and whether the attack was the first or a recurrence.

Cases were reassessed using the above four parameters on Days 3 (D3), 7 (D7), 14 (D14) and 21 (D21). In addition, the intraocular pressure was measured on each occasion. Any untoward side effects were recorded. In particular, enquiries were made about stinging on instillation of the eye drops (Absent (0), mild (1), moderate (2) and severe (3)). Patients who deteriorated clinically were withdrawn from the trial and were treated with prednisolone 0.3% eye drops and oral flurbiprofen for two weeks. Patients were assessed by the same surgeon (CSCL) throughout the study.

Statistical analysis

The following statistical tests were applied:

Age of patient and duration of illness with the t-test for independent samples.

Sex of the patient, history of allergies, whether first attack or recurrence, type and severity of the episcleritis with the Chi-square tabulation test.

Pain score and stinging score with the Mann-Whitney U test within and between groups.

Conjunctival and episcleral injection, nodules, total score and intraocular pressure by One way analysis of variance.

The percentage of patients free from inflammatory signs (i.e. conjunctival and episcleral injection and nodules) was also analysed by the Chi-square tabulation test.

Data were considered different when the statistical significance value was <0.05.

Results

Of the 43 eyes of 38 patients, 20 were allocated to G. placebo and 23 to G. drug. Thirty-

Table I *Patients withdrawn from the trial*

Group	*Case*	*D0*	*DW*	*DΩ*	*Reasons for withdrawal*
Placebo	W1	24	7	22	Lack of improvement +Pain
	W2	11	14	13	Peripheral Corneal Infiltrates Anterior chamber activity +Episcleral injection Chemosis
	W3	9	7	13.5	Nodule Formation +Conjunctival injection +Episcleral injection
	W4	11	7	10	+Pain +Episcleral injection
Drug	W5	16	7	25	+Pain +Conjunctival injection +Episcleral Injection
	W6	26	3	31	Development of 2 nodules
	W7	16	14	14	+Pain +Conjunctival Injection +Episcleral injection

D0 = Initial total score.
DW = Day of withdrawal.
DΩ = Final total score.
+ = Increase.

six patients completed the entire study. Seven patients were withdrawn (W) due to clinical deterioration: 4/20 (20%) from G. placebo and 3/23 (13%) from G. drug (Table I). Data from these seven patients were included in the analysis until the point of withdrawal.

The effects of drug treatment versus placebo were compared in all patients and in two sub-groups as follows:

(1) All patients: 20 patients from G. placebo and 23 patients from G. drug.
(2) Mild episcleritis: any patient with an initial total score of less than 15. This group consisted of 10 patients from G. placebo and 12 patients from G. drug.
(1) Severe episcleritis: any patient with an initial total score of 15 or more. This group consisted of 10 patients from G. placebo and 11 patients from G. drug.

All Patients

There was no significant difference between the age, sex, duration of illness, type and severity of the episcleritis and whether it was the first or a recurrent attack, although patients in the placebo group were younger (33.4 years c.f. 38.52 years, $p = 0.13$) and had a higher proportion of patients presenting with their first attack of episcleritis (80% c.f. 52%, $p = 0.11$). There were 21 Caucasians and two Black patients in the drug group and 17 Caucasians and three Black patients in the placebo group.

There was no difference in outcome between the two groups in terms of the mean total score, pain score, mean scores of conjunctival and episcleral injection, and mean score for nodules. However within each group, there was a significant reduction in pain comparing D7, D14 and D21 with D0 in both groups, and also D3 with D0 in the placebo group. A higher percentage of cases in the drug group were free from conjunctival and episcleral injection but statistical significance was not reached (Fig. 1).

Bilateral cases

Four patients had bilateral disease. Two of these received different treatment to each eye (placebo eye drops to one and CBS 113A eye drops to the other). Both these patients were convinced that the two eyes were treated differently, complaining of stinging on instillation of the active drug. With the other two patients, both eyes were treated with the active drug (Table II).

Recurrent case

One patient (W4, Table I) received both the

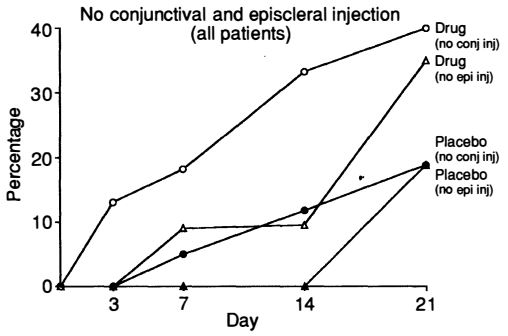

Fig. 1. *Combined graph demonstrating the percentages of patients with no conjunctival injection and of patients with no episcleral injection (All patients).*

active drug and placebo eye drops in the same eye during separate attacks. During his first attack, he was treated with placebo drops and he was withdrawn from the trial because of clinical deterioration. He developed a recurrent attack having been without symptoms and signs for one week. He was re-entered into the trial and was on the second occasion allocated to the active drug group. He went through the whole trial on this occasion and the score decreased from 7 at D0 to 1.5 at D21.

Side Effects

Stinging was reported by 20/23 (86.9%) of patients treated with the active drug but only by 7/20 (35%) of patients in the placebo group. All patients on the active drug who complained of stinging reported moderate to severe stinging whereas none of the patients on placebo reported severe stinging. Intraocular pressure: there was no significant variation along the study in either group. In addition, the intraocular pressure remained under 21 mm Hg in all patients throughout the study.

Other untoward reactions

Placebo group:

One patient developed a small subconjunctival haemorrhage.

Drug group:

One patient developed lower lid oedema at D7 which disappeared by D21, and granularity of the corneal epithelium at D14 which also disappeared by D21. This patient had a history of allergy to aspirin and co-trimoxazole.

One patient developed cheek oedema at D3 which gradually decreased and disappeared by D21. In this case there was no history of allergy to medications.

Mild Episcleritis

Patients in the drug group were on average older (37.08 years c.f. 30.9 years, $p = 0.121$), had shorter duration of illness prior to presentation (3.4 days c.f. 11.7 days, $p = 0.08$) and a higher proportion of patients with simple episcleritis (92% c.f. 70%, $p = 0.45$). Patients in the placebo group had a higher proportion of patients presenting with their first attack (90% c.f. 50%, $p = 0.12$). These differences were not statistically significant.

The evolution of the averaged total scores, and scores for conjunctival and episcleral injection of the drug and placebo groups are shown in Figs. 2 and 3. Patients treated with the active drug recovered faster. The differences were significant at D3 (Total score $p = 0.0013$; Conjunctival injection $p = 0.017$; Episcleral injection $p = 0.0013$; Conjunctival injection $p = 0.017$; Episcleral injection $p = 0.0018$) and D7 (Total score $p = 0.01$; Conjunctival injection $p = 0.014$; Episcleral injection $p = 0.027$), but not on Days 14 and 21. The percentage of patients free from conjunctival and episcleral injection were higher in the drug treated group but statistical significance was not achieved (Fig. 4).

Severe Episcleritis

The characteristics of the patients in the drug

Table II *Total scores of patients with bilateral episcleritis*

Case	*Eye*	*D0*	*DΩ*
1	A	22.0	8.0
	B	19.0	14.0
2	A	19.0	10.0
	B	15.0	9.0
3	B	8.0	6.0
	B	15.0	10.0
4	B	10.0	0.0
	B	5.5	0.0

A = Placebo eye drop.
B = Drug eye drop.
D0 = Initial total score.
DΩ = Final total score.

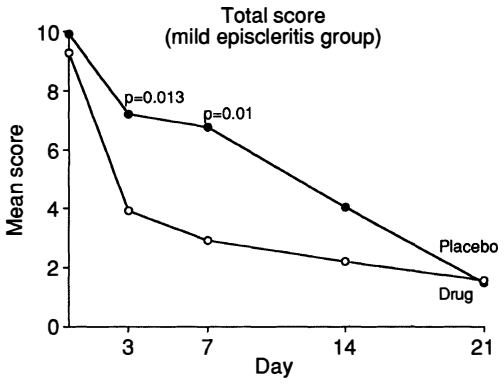

Fig. 2. *Graph showing mean total scores of patients with mild episcleritis.*

group and the placebo group were comparable. There were no differences in outcome (mean total scores, scores for pain, conjunctival injection, episcleral injection and for nodules) of the two groups.

Discussion

The anti-inflammatory activity of the majority of NSAIDS is primarily attributed to inhibition of distinct steps in the arachidonic acid cascade, particularly the cyclo-oxygenase pathway.[17] 2-(2-Hydroxy-4-methylphenyl) Aminothiazole Hydrochloride (CBS 113A) is unique in that it is a dual inhibitor of both cyclo-oxygenase and lipoxygenase as well as being a free radical scavenger.[12–14] From arachidonic acid, cyclo-oxygenase activity leads to the production of prostaglandins whereas the lipoxygenase pathway leads to the production of leukotrienes. Free radicals are generated at sites of inflammation by leukocyte phagocytosis and by the presence of ischaemia-reperfusion injury.[18] Prostaglandins, leukotrienes and free radicals are all mediators of inflammation.[19]

Glucocorticoids are potent anti-inflammatory agents. They exert some of their effects by inhibiting the enzyme phospholipase A thus preventing the release of arachidonic acid from membrane phospholipids. By acting at a higher level than NSAIDS, glucocorticoids decrease the synthesis of both prostaglandins and leukotrienes. The effects of CBS 113A therefore closely mimic those of glucocorticoids in that it inhibits both the cyclo-oxygenase and lipoxygenase pathways while ordinary NSAIDS inhibit the cyclo-oxygenase pathway only.[17] This dual inhibition is a real advantage in controlling inflammation as many NSAIDS actually increase leukotriene production by diverging arachidonic acid metabolism to the lipoxygenase pathway.[19,20]

The pharmacological activity of CBS 113A has been shown both *in vitro*[12] and *in vivo*.[13–16] It was shown to inhibit cyclo-oxygenase activity in platelets and 5-lipoxygenase activity in leukocytes. In addition its free radical scavenging activity was demonstrated. CBS 113A was also shown to inhibit oxygen burst in stimulated leukocytes and the release of Interleukin I-like compound from vascular endothelial cells in culture.[12] *In vivo*, it inhibited inflammation in experimental conjunctivitis and uveitis induced by various agents. The experimental animals were mostly pre-treated with the drug before the insult. It was also shown that CBS 113A did not have a worsening effect on experimental

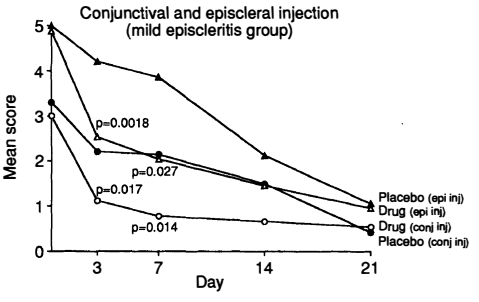

Fig. 3. *Combined graph of mean scores of conjunctival and of episcleral injection in patients with mild episcleritis.*

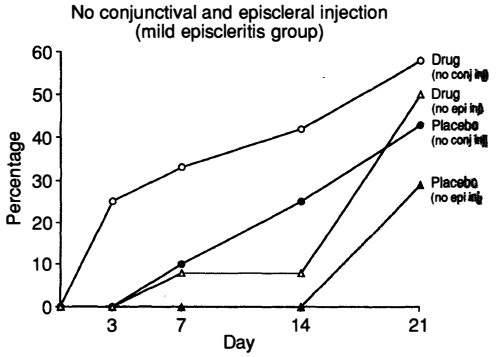

Fig. 4. *Combined graph demonstrating the percentages of patients with no conjunctival injection and of patients with no episcleral injection (Mild episcleritis).*

herpetic keratitis. CBS 113A was devoid of any anti-inflammatory activity when administered orally. Because of a very short half-life in plasma, it would not be suitable for intravenous administration either.[13] Preliminary clinical studies on patients with 'acute conjunctivitis' (of allergic and viral aetiology)[15] and post-cataract extraction patients[16] have shown CBS 113A to be effective in reducing ocular inflammation. No toxic effect to the epithelium was reported.

We have shown CBS 113A to be effective in reducing the signs of inflammation within the first week of administration of the drug in mild but not severe episcleritis. The differences were significant at D3 (Total score $p = 0.0013$; Conjunctival injection $p = 0.017$; Episcleral injection $p = 0.0018$) and D7 (Total score $p = 0.01$; Conjunctival injection $p = 0.014$; Episcleral injection $p = 0.027$), but not on Days 14 and 21. That significant values were not achieved at D14 and D21 can be explained by the self-limiting nature of the disease. The percentage of patients free from conjunctival and episcleral injection were also higher in the drug treated groups although statistical significance was not achieved (Figs. 1 and 4). Given such a broad pharmacological profile, it was surprising that CBS 113A was not effective against severe episcleritis as well. This might have been due to a number of reasons.

Comparing the severity of the episcleritis of our patients with those in previous studies with nearly identical scoring system, our patients had particularly severe disease. Our mean initial total score for the drug group was 13.5 (c.f. Lloyd-Jones *et al.*:[6] 9 (betamethasone group) and 10 (clobetasone group)) and for the placebo group 14.3 (c.f. Lloyd-Jones *et al.*:[6] 8). Our mean initial score for episcleral injection for the drug group was 6.7 (c.f. Watson *et al.*:[5] 4.27 (betamethasone) and 3.60 (oxyphenbutazone); Lyons *et al.*:[7] 3.7 (flurbiprofen) and 3.8 (prednisolone)) and for the placebo group 6.6 (Watson *et al.*:[5] 3.31; Lyons *et al.*:[7] 3.1). In fact, most of the patients from the studies quoted would have been mild disease by our definition, and would probably have done as well with CBS 113A as with steroids. It may be that more frequent instillation of CBS 113A is necessary for severe disease. A higher concentration of CBS 113A may also be of help, especially if the conjunctiva and episclera are much thickened.

We initially suspected that early treatment may be necessary for a good therapeutic response. In the mild episcleritis sub-group, CBS 113A was very effective in rapidly reducing inflammation. The drug treated group had a much shorter history (3.4 days) than the placebo group (11.7 days) prior to presentation ($p = 0.08$), nearly reaching statistical significance. However, on plotting a graph of the efficacy of CBS 113A against the duration of illness of all our patients (not shown), no such relationship could be shown.

Lack of compliance is a possible reason for a poor response but we do not believe this to be the case. Compliance was always enquired for at each follow up visit. None of the patients except one admitted to non-compliance. This patient used his eye-drops two or three times a day instead of four times a day for one week because it was inconvenient to instill eye-drops at work.

All the cases withdrawn from the CBS 113A treated group had severe disease to begin with. This is in contrast to patients withdrawn from the placebo group with three out of the four patients presenting with mild disease. We would agree with Lyons[7] that some cases of episcleritis do progress to scleritis. The possibility of progression was noted earlier by Duke-Elder.[21] It is conceivable that CBS 113A may have prevented such progression of initially mild disease.

Stinging from CBS 113A is a feature of the compound. Stinging was reported by 20/23 (86.9%) of patients treated with the active drug but only by 7/20 (35%) of patients in the placebo group. In addition, patients with bilateral disease treated with CBS 113A in one eye and placebo in the other complained of quite significant but short-lived stinging from what turned out to be the active drug. Although non-compliance has not been a problem with our study patients, stinging may contribute to non-compliance in less committed patients. A change in formulation may help. Reducing the need to instill frequently will also help with compliance.

CBS 113A did not cause any significant variation in intraocular pressure. None of our

patients had an intraocular pressure of over 21 mm Hg at any time. This is important as prostaglandins are increasingly recognised to have a regulatory effect on intraocular pressure.[20,22–24]

The corneal epithelial irregularity in one of the patients treated with CBS 113A may just have been part of the disease, rather than a side effect of the drug, as corneal involvement occurs in 15% of patients with episcleritis.[3] One patient developed lower lid oedema and another developed cheek oedema. Both patients completed the trial with spontaneous resolution of the oedema, making an allergic type rection to the drug extremely unlikely.

Given our results, we would recommend the use of CBS 113A for the treatment of milder cases of episcleritis. Rapid relief of congestion in the conjunctiva and episclera would benefit the patient enormously as it is the redness of the eye which patients with episcleritis so often complain of. CBS 113A would also be of help with frequent bouts of attacks, being free from the serious side-effects of steroids eye drops. By the same argument, a trial of CBS 113A may be worthwhile in known steroid responders and in patients with a history of herpetic keratitis, even if the episcleritis is severe.

CBS 113A may by its own actions complement steroids and thus have a steroid sparing effect. This is the case with diclofenac-sodium drops[1] and with sodium cromoglycate in the treatment of vernal keratoconjunctivitis.[25] Its action as a free radical scavenger may also be of help in alkali burns and in uveitis.[26] Further studies will be required in these areas.

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Key Words: CBS 113A, episcleritis, free radicals, NSAIDS, 2-(2-Hydroxy-4-methylphenyl) Aminothiazole Hydrochloride.

References

[1] van Husen H: Lokale Behandlung mit Diclofenac-Na-Augentropfen bei Erkrankungen der vorderen Augenabschnitte. *Klin Mbl Augenheilk* 1966, **188:** 615–9.

[2] Watson PG, Hayreh SS, Awdry PN: Episcleritis and Scleritis I. *Br J Ophthalmol* 1968, **52:** 278–9.

[3] Watson PG and Hayreh SS: Scleritis and Episcleritis. *Br J Ophthalmol* 1976, **60:** 163–91.

[4] Watson PG: Diseases of the Sclera and Episclera. In Duane TD ed. *Clinical Ophthalmology*, Philadelphia: Harper and Row 1987: Chapter 23, Volume 4.

[5] Watson PG, McKay DAR, Clemett RS, Wilkinson P: Treatment of Episcleritis. A Double-blind trial comparing Betamethasone 0.1%, Oxyphenbutazone 10% and Placebo Eye Ointments. *Br J Ophthalmol* 1973, **57:** 866–70.

[6] Lloyd-Jones D, Tokarewicz A, Watson PG: Clinical Evaluation of Clobetasone Butyrate Eye Drops in Episcleritis. *Br J Ophthalmol* 1981, **65:** 641–3.

[7] Lyons CJ, Hakin KN, Watson PG: Topical Flurbiprofen: an Effective Treatment for Episcleritis? A randomised double-blind trial comparing Gutt. prednisolone 0.3%, Gutt. flurbiprofen 0.03% and Gutt. saline 0.5% in the treatment of episcleritis. *Eye* 1990, **4:** 521–5.

[8] Hersh PS, Rice BA, Baer JC, Wells PA, Lynch SE, McGuigan LJB, Foster S: Topical Nonsteroidal Agents and Corneal Wound Healing. *Arch Ophthalmol* 1990, **108:** 577–83.

[9] Watson PG, Lobascher DJ, Sabiston DW, Lewis-Faning E, Fowler PD, Jones BR: Double-blind Trial of the Treatment of Episcleritis-Scleritis with Oxyphenbutazone or Prednisolone. *Br J Ophthalmol* 1966, **50:** 463–81.

[10] Chan CC, Ni M, Miele L, Cordelle-Miele E, Ferrick M, Mukherjee AB, Nussenblatt RB: Effects of antiflammins on Endotoxin-Induced Uveitis in Rats. *Arch Ophthalmol* 1991, **109:** 278–81.

[11] Watson PG: Doyne Memorial Lecture 1982. *Trans Ophthalmol Soc UK* 1982, **102:** 257–81.

[12] Bonne C, Muller A, Latour E, Tissie G, Emerit I, Modat G, Dornan J, Roch M, Giroud JP, Griswold DE, Marshall PJ, Coquelet C: 2-(2-Hydroxy-4-methylphenyl) aminothiazole Hydrochloride as a Dual Inhibitor of Cyclooxygenase/Lipoxygenase and a Free Radical Scavenger: 1st Communication: In vitro studies. *Arzneimittel-Forschung/Drug Research* 1989, **39, 10:** 1242–5.

[13] Bonne C, Latour E, Muller A, de Kozak Y, Faure J-P, Malet F, Colin J, Tissot M, Giroud J-P, Maghni K, Sirois P, Griswold DE, Coquelet C: 2-(2-Hydroxy-4-methylphenyl) aminothiazole Hydrochloride as a Dual Inhibitor of Cyclooxygenase/Lipoxygenase and a Free Radical Scavenger: 2nd Communication: Anti-inflammatory activity. *Arzneimittel-Forschung/Drug Research* 1989, **39, 10:** 1246–50.

[14] Bonne C, Tissie G, Trong HN, Latour E, Coquelet C: Free radical scavenging capacity and anti-inflammatory activity of CBS-113A. *Adv Exp Med Biol* 1990, **264:** 257–9.

[15] Raspiller A: Rapport CBS 113A dans les Conjonctivites Aiguës, une Étude en Double Aveugle. Document held in file, Laboratoire Chauvin.

[16] Chaine G: Étude de L'Action du CBS 113A dans les États Inflammatoires Post-Chirurgicaux. Document held in file, Laboratoire Chauvin.

[17] Ku EC, Lee W, Kothari HV and Scholer DW: Effects of Diclofenac on the Arachidonic Acid Cascade. *Am J Med* 1986, **80 (suppl 4B):** 18–23.
[18] McCord JM: Oxygen-derived radicals: a link between reperfusion injury and inflammation *Federation Proc* 1987, **46:** 2402–6.
[19] Malmsten CL: Prostaglandins, Thromboxanes, and Leukotrienes in Inflammation. *Am J Med* 1986, **80 (suppl 4B):** 11–7.
[20] Bito LZ: Prostaglandins. Old Concepts and New Perspectives. *Arch Ophthalmol* 1987, **105:** 1036–8.
[21] Duke-Elder S: Textbook of Ophthalmology. London. Kimpton, 1938: Volume 2, pp. 2051–4.
[22] Lee P-Y, Shao H, Xu L, Qu C-K: The Effect of Prostaglandin F2α on Intraocular Pressure in Normotensive Human Subjects. *Invest Ophthalmol Vis Sci* 1988, **29:** 1474–7.
[23] Goh Y, Nakajima M, Azuma I, Hayaishi O: Prostaglandin D2 reduces intraocular pressure. *Br J Ophthalmol* 1988, **72:** 461–4.
[24] Villumsen J and Alm A: Prostaglandin F2α-isopropylester eye drops: effects in normal human eyes. *Br J Ophthalmol* 1989, **73:** 419–26.
[25] Wright P: External Diseases. In Sir Stephen Miller ed. *Clinical Ophthalmology,* Bristol: Wright 1987: 122.
[26] Rao N, Romero JL, Fernandez MAS, Sevanian A and Marak GE Jr: Role of Free Radicals in Uveitis. *Surv Ophthalmol* 1987, **32:** 209–13.