Biochemical Pharmacology, Vol. 30, pp. 103–106.

0006-2952/81/0115–0103 $05.00/0

COMMENTARY

RECENT ADVANCES IN ANTIGLAUCOMA DRUGS*

GEORGE C. Y. CHIOU

Department of Medical Pharmacology and Toxicology, Texas A & M University College of Medicine, College Station, TX 77843, U.S.A.

Drugs used in the treatment of open-angle glaucoma may be grouped into three major categories based on their primary mode of action: (a) drugs that increase aqueous humor (AH) outflow without affecting AH formation, such as cholinergic agonists (pilocarpine and *N*-demethylated carbachol), cholinesterase inhibitors (physostigmine and echothiophate), and AH outflow resistance reducers (EDTA and cytochalasin B); (b) drugs that decrease AH formation without affecting AH outflow, such as carbonic anhydrase inhibitors (acetazolamide) and β-adrenergic blockers (timolol); and (c) drugs that affect both AH outflow and AH formation, such as adrenergic agonists (epinephrine and isoproterenol), and marijuana [1, 2].

Few advances have been made in the treatment of glaucoma since pilocarpine and physostigmine were first introduced in eye clinics over a century ago. It was not until 1977 that a breakthrough was made when timolol, a β-adrenergic blocker, was found to satisfactorily inhibit AH formation and to reduce intraocular pressure (IOP) [3–6]. Timolol was first put on the market by Merck Sharp & Dohme in 1978 with the trade name "Timoptic" [7].

At about the same time, considerable advances were also being made in the testing of a cholinergic agonist, *N*-demethylated carbachol (DMC), for use in glaucoma therapy. DMC increases AH outflow yet does not produce miosis, which is one of the major side effects of cholinergic drugs [8–11]. This drug is already in the phase I stage of clinical trials in two hospitals, one at National Taiwan University and the other at Louisiana State University [12, 13].

Medical trabeculocanalotomy is a novel approach for reduction of AH outflow resistance via disruption of actin microfilaments at the trabecular meshwork and at the inner wall of Schlemm's canal [14–17]. This approach has not yet progressed beyond the purely experimental stage, largely due to the toxicity of the drugs used for this purpose.

The use of marijuana in the treatment of glaucoma has drawn considerable attention recently [18–20]. The mechanism of action by which this drug reduces IOP is as mysterious as its central actions to exert euophoria.

Timolol

Timolol has been found to reduce IOP in both normal and glaucomatous eyes [3–6, 21, 22]. It produces rapid and potent hypotensive actions in glaucomatous eyes at concentrations between 0.1 and 1.0 per cent. The concentrations of timolol solutions used clinically are 0.25 and 0.5 per cent. Since the duration of timolol's action is longer than that of pilocarpine, timolol solution is instilled in the eyes only twice a day as compared to four times a day with pilocarpine. Timolol is a remarkably safe drug devoid of most of the side effects produced by pilocarpine, such as miosis, local irritation, headache, and ciliary spasm [21]. It also produces less conjunctival hyperemia than epinephrine [7]. Some instances of secondary glaucoma due to chronic uveitis are also controllable with timolol [23]. Because of these apparant advantages over other antiglaucoma drugs, enormous efforts have been made to screen other β-adrenergic blockers for antiglaucoma activities. The results obtained so far are rather disappointing. Timolol seems to be the only β-adrenergic blocker that exerts so potent an ocular hypotensive action [24, 25].

Based on the information available at present, it is quite clear that the antiglaucoma action of timolol has little relation to β-adrenergic blockade [26–28] because: (a) timolol is the only known β-adrenergic blocker that lowers IOP at low doses, whereas there are many potent β-adrenergic blockers that produce little ocular hypotensive actions; (b) both D- and L-isomers of timolol are equipotent in lowering the rate of aqueous humor formation, indicating that the sterospecificity of adrenergic receptors is not involved in this case; and (c) the ocular hypotensive actions of adrenergic agonists such as epinephrine are enhanced, rather than blocked, by timolol.

It is obvious that timolol exerts its ocular hypotensive actions through reduction of AH formation [4, 28–32]. Its mechanism of action, however, is different from that of conventional drugs, such as acetazolamide which inhibits carbonic anhydrase [29]. The actual mechanism of action of timolol is still unknown.

Large scale clinical studies have revealed, however, that timolol eye drops do cause cardiovascular disturbances, including bradycardia and hypotension [33]. Therefore, it should not be used in patients who have inadequate cardiac reserve, A-V conduction disturbances, or peripheral vascular insufficiency. Timolol also causes some decrease in tear production [34] and occasional bronchospasm [35]. Thus, timolol therapy should be avoided in patients with a history of asthma or bronchitis. It is apparent that the efforts to find an ideal antiglaucoma drug should continue.

* Supported, in part, by research grants from the National Eye Institutes, NIH (EY-01624), and the Organized Research Funds, Texas A & M University.

N-Demethylated carbachol (DMC)

Currently, investigation is underway in our laboratory to develop a new drug, DMC, which, though it increases AH outflow in a fashion similar to pilocarpine, is devoid of the side effects of pilocarpine. DMC is a weak cholinergic agonist, approximately 1/300 as active as carbachol in contracting muscarinic preparations (guinea pig ileum, dog ciliary muscle, and circular muscle of dog iris) as well as nicotinic preparations (frog rectus abdominis muscle and chick biventer cervicis) in *in vitro* experiments. The potency of pilocarpine is equivalent to DMC in all the aforementioned muscarinic preparations, but it has no detectable actions in nicotinic preparations [8].

In studies *in vivo*, DMC elicits cholinergic effects with ED_{50} values that lie in a narrow range (1.7, 2.6 and 4.8 mg/kg, respectively) in cat superior cervical ganglion-nictitating membrane, dog chorda tympani-Wharton's duct, and rat blood pressure preparations. In contrast, pilocarpine is extremely potent in stimulating salivation (ED_{50} of 0.08 mg/kg on dog Wharton's duct preparations), but it is much weaker than DMC in lowering blood pressure (ED_{50} of 38.1 mg/kg on rat blood pressure preparation) [8].

In glaucomatous beagles, DMC eye drops penetrated ocular tissues effectively, lowered the IOP at solution concentrations of 4–8%, caused little miosis, and induced no observable side effects. The ocular hypotensive action is exerted via an increase in AH outflow and is not dependent on AH formation. These results indicate that DMC acts in a manner similar to the conventional drug pilocarpine but has few, or no, side effects, and, thus, it has a higher therapeutic index [10, 11].

The first clinical study of DMC was conducted at the Department of Ophthalmology, National Taiwan University, in May 1979. The preliminary results obtained were presented at the ARVO (The Association for Research in Vision and Ophthalmology) meeting in May 1980 [12]. Twenty patients, ages 18 to 71, with open-angle glaucoma were selected for this study. Diagnosis of open-angle glaucoma was based on typical visual field defects, abnormal cupping of the optic disc, elevated IOP, and openness of the anterior chamber angle. Patients with systemic hypertension, hepatic disease, or renal disease were excluded from the experiment. All previous medications for glaucoma were discontinued for 1 week before the study began. The experiment started at 8:00 a.m. for 5 consecutive days. IOP was measured with a Goldmann applanation tonometer. Pupil size, pulse pressure, and blood pressure were measured every 2 hr after medication for 8 hr. Tonography was performed again at 4:00 p.m. each day. On day 0, control measurements were made without medication. On the following days, patients received a single drop of one of three test solutions (6% DMC, 9% DMC, or 1% pilocarpine) in the treated eye and phosphate buffer in the other, placebo, eye. The order of drug administration was randomized.

It was shown that all three test solutions were ocular hypotensive. Maximal reductions of IOP obtained by 6% DMC, 9% DMC, and 1% pilocarpine were 14, 19, and 20 per cent from control IOPs of 23.8, 24.5, and 23.7 mm Hg respectively. All patients treated with pilocarpine showed strong miosis; those treated with DMC solutions showed neither miosis nor significant changes in heart rate or blood pressure.

Similar results were obtained later at the Eye Center of Louisiana State University: 9% DMC was equipotent with 3% carbachol in lowering IOP of glaucoma patients [13]. No toxic signs and symptoms were observed in the DMC eyes. Those treated with carbachol complained routinely of eye pain, blurred vision, and local irritation and reddening of the eyes. There was a marked difference in pupil sizes. Patients treated with carbachol rapidly developed pinpoint pupils; those treated with DMC produced neither miosis nor mydriasis.

It is concluded that DMC is an effective drug in lowering the IOP of glaucoma patients. Although it may be slightly less potent than pilocarpine, it is remarkably non-toxic and produces none of the side effects that are typically associated with the use of pilocarpine or carbachol. This indicates that DMC has a higher therapeutic index and may become a better alternate drug in glaucoma therapy.

Medical trabeculocanalotomy

One of the major causes of elevated IOP in glaucoma patients is increased resistance to AH outflow occurring at the trabecular meshwork and at the inner wall of Schlemm's canal. At these sites there are cytoplasmic actin microfilaments that may be capable of contraction and, thus, may have a role in modulating outflow resistance [14–17].

Cytochalasin B is known to disrupt actin microfilaments and has been shown to cause marked reduction in outflow resistance when it is injected into the anterior chamber of the eye [36, 37]. It has been demonstrated to increase the numbers of transcellular AH pathways and to rupture the inner wall of the Schlemm's canal with separation of the endothelial cells.

It is well known that calcium is essential for cell adhesion. Removal of calcium from the tissue medium allows cells to be dispersed easily for preparation of a primary culture in tissue culture experiments [38]. It has been shown that removal of calcium from the anterior chamber by infusion of calcium-free AH-like solution or injection of a chelating agent, such as EDTA, results in a profound decrease in AH outflow resistance, marked reduction of IOP, and a "washout" phenomenon of debris similar to that noted with cytochalasin B [39, 40].

It is quite possible that less toxic calcium antagonists such as verapamil [41] and 6-(*N,N'*-diethylamino)-hexyl-3,4,5-trimethoxybenzoate (TMB-6) [42, 43] could be used to lower the IOP of glaucoma patients. This possibility is being investigated in our laboratory at present.

Marijuana

Marijuana is a mysterious drug that is, nevertheless, gaining wider and wider use in medicine, including glaucoma therapy. This drug lowers IOP by affecting both AH formation and AH outflow [18–20]. Although the actual mechanism of action is unknown, there is a good correlation between the ocular hypotensive effects of marijuana and its level

of central euphoria [19, 20]. Consequently, the antiglaucoma actions of marijuana might be induced centrally rather than locally.

The untoward effects produced by marijuana include conjunctival hyperemia and euphoria. If these side effects are separated from the ocular hypotensive actions, marijuana can become an acceptable antiglaucoma drug. For example, Δ^{10}-tetrahydrocannabinol (Δ^{10}THC), one of the active principles of marijuana, produces ocular hypotension with a lesser degree of euphoria than Δ^{9}-THC [20].

Comments of drug treatment of glaucoma

According to NIH statistics [44], more than a million people in the United States alone are suffereing from glaucoma. Among them, about 200,000 people have visual impairment and 56,000 individuals are legally blind. Every year, approximately 178,000 new cases of glaucoma are diagnosed. Statistically, women are affected more often than men. Each year, two million visits are made to eye clinics for diagnosis and treatment of glaucoma. Although some are treated with surgical operations, the great majority of them are treated with medications.

Although many antiglaucoma drugs are available, pilocarpine is almost the only drug that has been used for more than a century. The reason is that, although pilocarpine is a potent ocular hypotensive agent with some side effects, it was the least toxic drug among all antiglaucoma drugs until 1978. Pilocarpine produces side effects including miosis, headache, blurred vision, and local irritation. The marketing of timolol in October 1978 created a sensational acceptance of this new drug both by patients and ophthalmologists because of its remarkable efficacy and safety compared to pilocarpine. The advantages of timilol are many. Since it acts at the ciliary process to reduce AH formation (pilocarpine acts at the trabecular meshwork to increase AH outflow), timolol may be used: (a) to treat narrow-angle glaucoma; (b) to treat pilocarpine-resistant glaucoma; (c) to produce a further hypotensive effect after maximal responses are obtained by pilocarpine and epinephrine; and (d) to treat some secondary glaucomas.

Preliminary results obtained from clinical trials of DMC indicate that it is a promising new antiglaucoma drug for use in the near future. Although DMC is not as potent as pilocarpine, it is devoid of unpleasant side effects. It should be emphasized that it is the therapeutic index, not the potency of a drug, that determines its usefulness. As long as the drug is safe, doses can be raised high enough to produce desirable therapeutic actions. DMC may become particularly attractive (a) to young patients who tend to suffer from ciliary spasm when pilocarpine is used; (b) to senior cataract patients whose vision will be blocked when miotics are instilled; and (c) to glaucoma patients who are resistant to pilocarpine treatment.

The use of calcium-antagonists and cytochalasin B to lower AH outflow resistance and to reduce IOP is a unique approach to glaucoma treatment. Since cytochalasin B disrupts cytoplasmic microfilaments and alters the morphology and motility of many cell types, its use as an antiglaucoma drug requires further study. If the removal of calcium is responsible for the reduction in AH outflow resistance, well-established, safer drugs may be tried.

Marijuana has been used in many types of medical treatment, and the list of its applications is growing progressively longer. Unfortunately, the list of its undesirable actions is getting correspondingly longer and longer. Since it is still classified as a schedule one drug, its wide use by the general public is not feasible.

In conclusion, timolol is a new potent drug for glaucoma treatment with minimal side effects. If no better drug can be found, it may become the drug of choice for glaucoma. *N*-Demethylated carbachol is a promising new drug still in the developmental stage. Based on preliminary results, it may become an alternative to pilocarpine and timolol. Cytochalasin B and marijuana are new antiglaucoma drugs that have been tried clinically. Unfortunately, cytochalasin B is cytotoxic and not suitable for wide use and the availability of marijuana is limited by legal controls.

REFERENCES

1. C. Y. Chiou and T. J. Zimmerman, *Invest. Ophthal.* **14**, 416 (1975).
2. T. J. Zimmerman and C. Y. Chiou, *Curr. Concepts Ophthal.* **5**, 216 (1976).
3. I. M. Katz, W. A. Hubbard, A. J. Geston and A. L. Gould, *Invest. Ophthal.* **15**, 489 (1976).
4. L. Missotten and M. Goethals, *Ophthal. Res.* **9**, 321 (1977).
5. T. J. Zimmerman and H. E. Kaufman, *Archs Ophthal.* **95**, 601 (1977).
6. T. J. Zimmerman and H. E. Kaufman, *Archs Ophthal.* **95**, 605 (1977).
7. Merck Sharp & Dohme, *Summary of Basis of Approval of Timoptic.* FDA, Washington, DC (1978).
8. J. Trzeciakowski and C. Y. Chiou, *J. pharm. Sci.* **67**, 531 (1978).
9. C. Y. Chiou and J. Trzeciakowski, *Curr. Concepts Opthal.* **6**, 134 (1979).
10. J. Trzeciakowski and G. C. Y. Chiou, *J. pharm. Sci.* **69**, 332 (1980).
11. G. C. Y. Chiou, J. Trzeciakowski and K. N. Gelatt, *Invest. Ophthal. Vis. Sci.*, in press.
12. P. T. Hung, M. Y. Chang, L. K. Lin and G. C. Y. Chiou, *Invest. Ophthal. Vis. Sci.* (ARVO Suppl.), p. 197 (Abstr.) (1980).
13. T. J. Zimmerman, K. W. Olander and R. M. Mandelkorn, *Invest. Ophthal. Vis. Sci.* (ARVO Suppl.), p. 197 (Abstr.) (1980).
14. H. Inomata, A. Bill and G. K. Smelser, *Am. J. Ophthal.* **73**, 760 (1962).
15. I. Grierson and W. R. Lee, *Expl Eye Res.* **20**, 505 (1975).
16. I. Gopson and R. A. Anderson, *Invest. Opthal. Vis. Sci.* (ARVO Suppl.), p. 207 (Abstr.) (1978).
17. P. L. Kaufman, B. Svedbergh and E. Lütjen-Drecoll, *Ann. Ophthal.* **11**, 795 (1979).
18. K. Green, *Ann. Ophthal.* **11**, 203 (1979).
19. R. S. Hepler and I. R. Frank, *J. Am. med. Ass.* **217**, 1392 (1971).
20. M. C. Flom, A. J. Adams and R. T. Jones, *Invest. Ophthal.* **14**, 52 (1975).
21. R. L. Radius, G. R. Diamond, I. P. Pollack and M. E. Langham, *Archs Ophthal.* **96**, 1003 (1978).
22. R. Ritch, N. A. Hargett and S. M. Podos, *Acta Ophthal.* **56**, 6 (1978).

23. P. J. Airaksinen, *Acta Opthal.* **57**, 425 (1979).
24. P. Vareilles, D. Silverstone, B. Plazonnet, J. C. LeDonarec, M. L. Sears and C. A. Stone, *Invest. Ophthal. Vis. Sci.* **16**, 987 (1977).
25. T. J. Zimmerman and W. P. Boger, III, *Survey. Ophthal.* **23**, 347 (1979).
26. A. H. Neufeld, *Surv. Ophthal.* **23**, 363 (1979).
27. G. C. Y. Chiou, H. K. Liu and J. Trzeciakowski, *Life Sci.*, in press.
28. H. K. Liu and G. C. Y. Chiou, *Expl Eye Res.*, in press.
29. H. K. Liu, G. C. Y. Chiou and L. C. Garg, *Archs Ophthal.* **98**, 1467 (1980).
30. R. L. Coakes and R. F. Brubaker, *Archs Ophthal.* **96**, 2045 (1978).
31. M. D. Yablonski, T. J. Zimmerman, S. R. Waltman and B. Becker, *Expl Eye Res.* **27**, 135 (1978).
32. S. Sonty and B. Schwartz, *Surv. Opthal.* **23**, 381 (1979).
33. M. E. Kosman, *J. Am. med. Ass.* **241**, 2301 (1979).
34. N. V. Nielsen and J. S. Eriksen, *Acta Ophthal.* **57**, 418 (1979).
35. F. L. Jones and N. L. Ekberg, *New Engl. J. Med.* **301**, 270 (1979).
36. P. L. Kaufman and E. H. Barany, *Invest. Ophthal. Vis. Sci.* **16**, 47 (1977).
37. B. Svedbergh, E. Lütjen-Drecoll, M. Ober and P. L. Kaufman, *Invest. Ophthal. Vis. Sci.* **17**, 718 (1978).
38. A. Allen and C. Snow, *Biochem. J.* **117**, 32 (1970).
39. G. I. Kaye, C. M. Fenoglio, F. B. Hoefle and J. Fischbarg, *J. Cell Biol.* **61**, 537 (1974).
40. G. I. Kaye, S. Mishima, J. D. Cole and N. W. Kaye, *Invest. Ophthal.* **7**, 53 (1968).
41. D. Krikler, *Eur. J. Cardiol.* **2**, 3 (1974).
42. C. Y. Chiou and M. H. Malagodi, *Bri. J. Pharmac.* **53**, 279 (1975).
43. C. Y. Chiou, M. H. Malagodi, B. V. R. Sastry and P. Posner, *J. Pharmac. exp. Ther.* **198**, 444 (1976).
44. U. S. Department of Health, Education and Welfare, *Vision Research, A National Plan: 1978–82*, p. 97. HEW, Washington, DC (1978).