EVALUATION OF SUSTAINED-RELEASE ACETAZOLAMIDE*†

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CARBONIC anhydrase inhibitors are extensively utilized in all forms of glaucoma therapy (Becker, 1954; Grant and Trotter, 1954). However, long-term administration of such drugs in effective doses is limited by undesirable systemic effects in a considerable number of patients (de Carvalho, Lawrence, and Stone, 1958; Muirhead and Scheie, 1960). Consequently, efforts have been made to alter the absorption pattern of the medicament so as to achieve sustained blood levels with less frequent administration.

Several recent studies of a sustained-release form of acetazolamide (Diamox) have indicated some benefit over conventional therapy with this drug (Drance and Carr, 1961; Garner, Carl, and Ferwerda, 1961). This communication reports an evaluation of this form of medication in a rigidly controlled study with particular reference to perilimbal suction cup analysis of changes in aqueous flow.

Material and Methods

Patients were obtained from the Glaucoma Research Service of the New York Hospital-Cornell Medical Centre. All were glaucomatous and were being treated solely with miotics, which were not discontinued during the course of this study. No form of epinephrine had been administered to any of the patients at any time. Patients were so chosen that their weights were reasonably similar, as were their pre-treatment levels of intra-ocular pressure and outflow facility.

At the inception of each period of study applanation measurements of intra-ocular pressure were obtained and the patients were subjected to tonographic and perilimbal suction cup analysis. All patients had been well acclimatized to both procedures during previous studies. In each individual patient all procedures were carried out at the same time of day and at a constant interval from the time of administration of medication.

Tonographic tracings were made with the Mueller electronic tonometer, and values for outflow facility were taken from the tables of Moses and Becker (1958). Calculations of ocular rigidity were made at all phases of this study, but were found to be non-pertinent. The perilimbal suction cup technique has been previously described by several authors (Rosengren, 1956; Ericson, 1958) as well as by workers in this laboratory (Galin, Baras, and Mandell, 1961; Galin, Baras, and McLean,

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1962; Galin, Baras, and Nano, 1962). Fifty mm. of negative pressure obtained from the difference in height of two mercury columns were created and attached to a perilimbal suction cup with a scleral flange having a radial curvature of 15 mm. A schematic diagram of the system is shown in the Figure.

FIGURE.—Schematic diagram of perilimbal suction cup applied to the eye at 50 mm. Hg suction.

This system creates sufficient force to close the episcleral and intra-scleral venous plexi so that anterior egress of aqueous is essentially terminated. If aqueous secretion continues, intra-ocular pressure will rise. After 15 minutes of suction, the change in intra-ocular pressure induced by the suction is measured by applanation tonometry. The increase in ocular volume necessary to have caused the increase in intra-ocular pressure is obtained from a modification of Friedenwald's Tables (1954) of pressure-volume relationships.

After these baseline data were obtained, patients were started on 500 mg. acetazolamide* by mouth every 8 hours and after 2 weeks of therapy the studies were repeated. At this time sustained-release acetazolamide* (sequels) was substituted at the same dosage and frequency. This level of medication represented approximately 20 mg./kg. acetazolamide per day. Since this is approximately the maximal effective level of therapy, it was thought that comparative data would be more meaningful at this than at lower levels.

After 3 weeks of sequels therapy, the studies were repeated and the patients were placed on 1 g. sequels per day. After 3 weeks of therapy at this dosage level, tonographic and perilimbal suction cup data were again obtained and the dosage of

* Kindly supplied by Lederle Laboratories, Pearl River, New York.

sequels reduced to 500 mg. per day. In 3 weeks the baseline studies were repeated, and the patients were instructed to discontinue all acetazolamide therapy. The studies were again repeated 3 weeks later.

Results

At the outset it should be noted that individual patients commonly show moderate variations in tonographically obtained values of outflow facility. Furthermore, since carbonic anhydrase inhibitors primarily influence flow, spontaneous or induced alterations in outflow facility are not too meaningful for this study. Tonographic calculations of flow are open to serious theoretical question, and, therefore, have not been listed. Perilimbal suction cup estimates of flow are comparatively useful when studied in the same patient and are, therefore, included.

The Table lists the intra-ocular pressure, outflow facilities, and flow measurements (perilimbal suction cup technique) for all patients at the various

TABLE
INTRA-OCULAR PRESSURE, OUTFLOW FACILITY, AND FLOW (PERILIMBAL SUCTION CUP TECHNIQUE) AT DIFFERENT LEVELS OF ACETAZOLAMIDE SEQUELS ADMINISTRATION AND AT ONE LEVEL OF REGULAR ACETAZOLAMIDE ADMINISTRATION

Before Diamox			1500 mg. Diamox			1500 mg. Diamox Seq.			1000 mg. Diamox Seq.			500 mg. Diamox Seq.			Diamox Discontinued		
I.O.P.	C	F ₁₅	I.O.P.	C	F ₁₅	I.O.P.	C	F ₁₅	I.O.P.	C	F ₁₅	I.O.P.	C	F ₁₅	I.O.P.	C	F ₁₅
22	·27	12	15	·13	8	15	·22	9	17	·15	10	22	·20	10	21	·24	11
28	·21	10	22	·12	7	19	·17	9	19	·17	9	24	·18	10	25	·15	9
26	·08	15	19	·10	11	22	·08	13	23	·10	14	25	·08	13	24	·10	14
27	·09	17	23	·10	13	20	·12	14	22	·07	12	20	·07	11	23	·09	17
24	·07	9	22	·05	7	20	·09	6	20	·10	7	22	·04	7	28	·10	12
26	·10	6	22	·11	5	20	·03	3	22	·08	5	26	·02	5	30	·09	11
32	·09	12	27	·10	8	28	·11	9	28	·10	10	34	·08	12	36	·07	14
28	·10	11	22	·12	8	24	·09	9	26	·07	9	30	·07	10	33	·08	12
22	·14	15	14	·11	9	16	·10	9	18	·12	10	22	·14	12	24	·14	15
20	·18	17	16	·15	12	14	·12	10	17	·17	11	19	·17	10	23	·19	14
23	·20	9	15	·27	7	14	·17	6	14	·08	4	15	·18	8	23	·14	7
24	·12	7	15	·16	8	14	·11	6	12	·11	6	19	·13	7	24	·13	7
30	·05	8	22	·08	6	23	·10	7	27	·07	8	32	·04	7	34	·06	7
17	·12	14	15	·08	7	16	·11	7	15	·14	11	19	·03	10	20	·11	12
22	·18	12	17	·14	8	14	·10	8	17	·12	9	19	·14	12	20	·12	12
24	·17	15	19	·13	10	17	·14	11	18	·15	10	20	·18	12	20	·14	14
23	·09	10	18	·12	7	21	·12	7	24	·08	8	25	·12	9	26	·10	11
24	·08	14	18	·08	11	21	·09	10	24	·10	10	27	·12	12	27	·07	10
22	·12	8	20	·15	8	24	·09	8	25	·09	8	24	·10	9	25	·10	9
22	·19	10	19	·13	7	20	·12	7	20	·11	7	20	·12	8	24	·14	11

I.O.P. = Intra-ocular pressure;
C = Tonographically computed outflow facility;
F₁₅ = 15-minute measurement of flow calculated by the perilimbal suction cup technique.

dosages of acetazolamide sequels and for the single dosage level of acetazolamide. It is apparent that intra-ocular pressure is not significantly reduced by the sequels as compared with regular acetazolamide at maximum dosage levels. Furthermore, reduced dosages of sequels do not influence intra-ocular pressure as favourably as maximum levels of regular acetazolamide.

Discussion

The purpose of delayed-action medication may be condensed into two broad categories. The first is that a single large dose should replace multiple administration, since slow release should theoretically permit longer therapeutic levels of medication. The second is that a desirable plateau of blood concentration should be achieved, eliminating multiple peaks and troughs with their corresponding toxicity and lack of response respectively. However, clinical comparisons of regular and delayed-action medications in the same and in different individuals are open to considerable criticism unless the more obvious variables of weight, prandial status, time of administration, and time of recording results are controlled. Furthermore, with respect to studies of intra-ocular pressure, the measurement of mean reductions following the administration of drugs such as acetazolamide means little unless starting pressures are reasonably similar. A small reduction in flow at high levels of intra-ocular pressure will result in a significantly larger reduction than will the same reduction in flow at a lower initial pressure. The study herein reported attempted to consider these variables, and may therefore explain some of the difference in results reported by other investigators (Drance and Carr, 1961).

Of more significance in studying delayed-action medication, are assays of blood and urine (Campbell, Chapman, and Chatten, 1957; Chapman, Chatten, and Campbell, 1957; Campbell, Nelson, and Chapman, 1959). Plasma and blood concentrations of acetazolamide in the sequel and regular forms have been analysed, and these assays further substantiate the clinical observations made in this study (Personal communication). It has been noted that plasma concentrations in $\mu\text{g./ml.}$ reach substantially higher levels with oral doses of 500 mg. regular acetazolamide than with sequels. Despite this, however, the plasma decay for regular acetazolamide is not unlike that for sequels for approximately the first 8 hours. Urinary excretion studies essentially mirror the plasma findings (Personal communication).

On both clinical and experimental grounds, a more suitable form of acetazolamide for maximum dosage therapy is not yet available. It is conceivable that, when only small effects are desired, the plasma concentration plateau obtained from sequels may be of some advantage and, theoretically, might reduce toxicity. However, for the more usual case in which acetazolamide is administered in significant dosage, this new form of the agent does not appear to have any advantage.

Summary

A sustained-release form of acetazolamide has been compared in various dosages with maximum dosage therapy of regular acetazolamide and does not appear to offer any major advantages.

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