SUCCINYLCHOLINE AND ACETAZOLAMIDE (DIAMOX) IN ANAESTHESIA FOR OCULAR SURGERY*

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SUCCINYLCHOLINE is the muscle relaxant of choice for tracheal intubation, and tracheal intubation is a requisite for a satisfactory general anaesthesia in intraocular surgery. However, succinylcholine is known to increase intraocular tension. In 1955 and 1957 there were reports in the literature of loss of vitreous occurring during surgery of the open eye when succinylcholine was used in anaesthesia,^{1,2} with a resulting loss of vision. Succinylcholine also represented a serious hazard to patients with glaucoma.³⁻⁷

A study was undertaken in the Department of Anaesthesia of the Winnipeg General Hospital to determine whether previous administration of acetazolamide (Diamox) would prevent the dangerous rise in intraocular pressure accompanying the use of succinylcholine in anaesthesia. If the results proved successful, then this valuable muscle relaxant could be safely employed in cataract extractions and corneal transplants, and in patients suffering from glaucoma.

The most important factor determining the internal pressure of the eye is the aqueous humour, the hydrostatic pressure of the blood accounting for only one-quarter of the total intraocular tension. Formed in the ciliary processes behind the iris by a combination of diffusion and active transport, in which the enzyme carbonic anhydrase plays an important role, the aqueous fills the posterior chamber and leaves the eye by the canal of Schlemm (Fig 1).⁸⁻¹¹

Rapid increases in intraocular pressure are due to interference with the outflow of the aqueous in most cases. The normal eye has a great capacity for compensating any increase in intraocular pressure, simply by increasing the rate of outflow of the aqueous. The osmotic pressure of the aqueous humour is higher than the osmotic pressure of the blood. If we compare the composition of the aqueous with that of blood, we observe that while the amount of protein of the aqueous is as low as 0.02 gm/100 ml, and the glucose, urea, and bicarbonate concentrations are lower than in blood, those of the chlorides, sodium, and lactate are higher. The aqueous is the only means of nutrition of the lens and cornea, since they are devoid of blood supply.¹²⁻¹⁴

The normal intraocular pressure has an accepted physiological range of 10 to 22 mm Hg above atmospheric pressure. There is a variation of 2 to 3 mm. Hg daily for each individual, the higher readings being obtained in the early hours of the morning, and the lower ones early in the evening. Position also accounts for a difference of 2 to 3 mm Hg, the reading being higher during recumbency than in a standing position.¹⁵

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The respiratory movements also affect intraocular pressure. Deep inspiration may lower it by as much as 5 mm Hg, while it is increased during expiration. The pulse beat produces a physiological oscillation of 1 to 2 mm Hg. Variations in arterial blood pressure are reflected in small but rapid changes in the ocular tension with a time delay of only one-tenth of a second. Obviously this is due to

FIGURE 1 The angle of the eye

changes in the volume of blood circulating through the eye, and not to over-production of aqueous humour. In sustained arterial hypertension, the ocular tension returns to its normal levels after a period of adaptation.

Obstruction to the venous return from the head increases the ocular pressure, and so does coughing, sneezing, or straining. This can be of importance during surgery of the open eye.^{16, 17}

If the outflow of the aqueous stops completely, the intraocular pressure should rise only to the effective filtration pressure of the capillary bed, which is about 30 mm Hg, and yet in closed angle glaucoma, readings above 80 and 90 have been reported. It is interesting to note in this connection that the hydrostatic pressure in the capillaries of the eye is 75 mm Hg, the osmotic pressure of the blood and the intraocular pressure being the only factors opposing it. When the circulation stops at the moment of death the intraocular pressure falls to 5 mm Hg and stays at this level for a short period, then gradually drops to zero. Hypoventilation, hypoxia, and hypercapnoea all elevate the tension in the eye. On the contrary, hyperventilation, high oxygen tension, and hypocapnoea lower the intraocular tension. Hypoproteinaemia has practically no effect.¹⁶

Endotracheal intubation by itself elevates the ocular pressure. Retrobulbar anaesthesia and digital pressure on the eye are two very effective means in the hands of the ophthalmologist for reducing the intraocular pressure.¹⁸⁻²⁴

Rapid ingestion of one litre of saline has no effect on the eye, but rapid ingestion of one litre of water elevates the pressure. There is no agreement as to

where control of the intraocular tensions lies, although the hypothalamus has been implicated. The role of the sympathetic and parasympathetic fibres is also controversial²⁵⁻³³

There are two methods of measuring intraocular pressure: manometry, which involves placing a needle in the anterior chamber, and tonometry, used for recording the pressure necessary to depress the cornea. Tonometers are based on two different principles: indentation and applanation. The first depends on the fact that the impressibility of the cornea depends mainly on the ocular tension, while the corneal rigidity plays but a minor role. Indentation tonometers are suited for readings in the recumbent position. The Schiotz's tonometer is the most commonly used. Applanation tonometers are best used with the patient in the erect position.³⁴

Let us now review the effect of the anaesthetic agents on the intraocular pressure. Cyclopropane, diethyl ether, chloroform, halothane, trichlorethylene, and divinyl ether lower the intraocular pressure. The effect is more pronounced in deep planes of surgical anaesthesia, owing to the relaxation of the extraocular muscles and the consequent facilitation of aqueous outflow. Ethylene does not alter the tension, and nitrous oxide has been reported to raise it.^{28,35-39}

Morphine, meperidine, and the short-acting and ultra-short-acting barbiturates lower the intraocular tension by facilitating the aqueous outflow. Pre-anaesthetic medication at the usual doses of narcotic and atropine reduces the intraocular pressure of the normal eye by about 10 per cent.^{16,21,28,29,40-42} Atropine alone, when given systematically, produces a slight rise in intraocular pressure, owing to capillary dilatation. The concomitant mydriasis does not affect the normal eye, but in the patient with closed angle glaucoma it can produce an acute elevation of the intraocular pressure. For this reason atropine has been indiscriminately withdrawn from the pre-anaesthetic medication of glaucomatous patients. Actually it is only dangerous for the patient with narrow angle glaucoma.^{37,43}

There is no agreement as to the effects of scopolamine on the ocular pressure, but it is known to produce a greater degree of mydriasis than atropine. Acetylcholine and the anti-cholinesterases elevate the ocular tension by producing vasodilatation in the eye and by stimulating the contraction of the recti muscles. Epinephrine in small doses elevates the intraocular pressure by stimulating only the beta receptors, while at higher concentrations it reduces the tension by means of vasoconstriction produced when the alpha receptors are also stimulated.⁴⁴⁻⁴⁷

Finally, the non-depolarizing muscle relaxants, curare and gallamine, relax the extraocular musculature, bringing the intraocular pressure down, while the depolarizing agents, decamethonium and succinylcholine, elevate it.^{36,45,48-55}

It has been accepted for some time that the mechanism of this elevation is a sustained contraction of the extraocular muscles, and that they react to succinylcholine in a fashion different from the other skeletal muscles. While the latter suffer only momentary fasciculations followed by relaxation, the extraocular muscles respond with a sustained contraction, just as the belly muscles of birds and frogs do.^{1,28,52,53,56-61}

Electromyography of the human extraocular muscles has demonstrated that the motor unit of these fibres is much smaller than that of the skeletal muscles.

and also that it is much simpler, so it can fire at greater frequency. The innervation ratio of the soleus, for example, is 1 nerve fibre to 100 or 150 muscle fibres, compared to 1:5 for the extraocular muscles, and this ratio is characteristic of muscles used for precise and delicate movements. Skeletal muscle at rest shows no recordable potential, while the extraocular muscles are seldom electrically silent.⁶³⁻⁶⁵ To some authors this indicates that the extraocular muscles simply require a higher dose of succinylcholine to achieve the paralysis obtained in the skeletal muscle.³⁹

It has recently been shown that cutting the extraocular muscles does not prevent the rise in intraocular pressure caused by succinylcholine, and it is believed now that the direct vasodilatory effect of the depolarizing muscle relaxant on the intrabulbar vessels is the main factor responsible for the rise in intraocular pressure, while the contracture of the extraocular muscles is only secondarily responsible.⁶⁶⁻⁶⁸ Since the intraocular pressure is increased by succinylcholine, it seemed advisable to avoid its use during surgery of the open eye and in glaucoma. Some authors found that the use of succinylcholine was only dangerous if it was administered after the eye was open. Other investigators attempted to find a solution to this problem, some by using hexafluorenum (Mylaxen) to prevent the muscular fasciculations caused by succinylcholine, others by administering the drug very slowly, and still others by conducting the general anaesthesia in deep planes, or by injection of a local anaesthetic in the retrobulbar space and by applying pressure on the eye. The greatest reductions in intraocular pressure were achieved by the use of hypertonic solutions, thus intravenous Sorbitol, Dextran, and particularly urea and mannitol have been used with success in glaucoma.^{1-5, 20, 39, 65, 68-76} For other publications on the subject, see references 91 to 123.

Acetazolamide (Diamox) used intravenously is known to reduce intraocular pressure, starting to act within 2 minutes and reaching its greatest effect within 20 minutes. This potent drug, decreasing the aqueous flow by 50 per cent, is easy to employ in comparison with the cumbersome hypertonic solutions. Acetazolamide has no action on the pupil, nor does it alter the outflow of the aqueous. It completely inhibits the carbonic anhydrase activity of the ciliary body and iris, when given orally or intravenously. The carbonic anhydrase inhibition goes hand in hand with a noticeable reduction in the ocular tension.^{75, 77-89}

Acetazolamide is a non-bacteriostatic sulphonamide derivative. It produces diuresis and alkalization of the urine, inducing a state of mild acidosis. It results in renal loss of bicarbonate which carries with it water, sodium, and potassium. This is the reason for its indication in oedema, congestive heart failure, and obesity. In glaucoma it reduces the intraocular tension by slowing the rate of formation of aqueous humour. It interferes with the elimination of carbon dioxide by the lung, but this is of little concern, of course, in the anaesthetized patient whose respirations can be easily assisted. It is contraindicated in renal acidosis, dehydration, and sodium or potassium depletion. In large doses, or when given over long periods of time, it can produce drowsiness, disorientation, fever, leukopenia, and rashes. But these will not occur when a single dose of 500 mg. is administered. Acetazolamide in aqueous solution for intravenous use

is alkaline, so care must be taken to avoid extravasation, but it produces no slough of the subcutaneous tissues. It can be safely given intramuscularly^{75,80,90}

MATERIAL

The intraocular pressure of fifty anaesthetized patients was studied. The subjects were chosen at random. All were 20 years or older, and none of those included had glaucoma. The surgical procedures, all of which gave easy access to the eye, are listed in Table I.

TABLE I
SURGICAL PROCEDURES INCLUDED IN
THE STUDY

Surgical procedure	No. of cases
Ophthalmological	7
Gastro-intestinal	32
Orthopedic	6
E N T	3
Urological	2
Total	50

METHOD

Pre-anaesthetic medication consisting of meperidine 50 mg and atropine 0.6 mg was given intramuscularly one hour pre-operatively to each of the patients. Induction of anaesthesia was carried out with sodium thiopentone in doses of 200 to 500 mg to produce sleep. In 25 of the 50 patients (the test group) induction was preceded by a rapid injection of 500 mg acetazolamide dissolved in 5 to 10 ml sterile distilled water. The intraocular pressure was then measured with a Schiotz's tonometer with a 55 gm plunger load. Following this, the patient was oxygenated with a mask.

Two minutes after acetazolamide had been administered, a second reading was taken. Succinylcholine 60 mg was given intravenously, and the lungs were inflated with oxygen. A third reading was recorded at the peak of the fasciculations of the muscles of the face. Tracheal intubation followed, with manually controlled respiration using a mixture of oxygen at 3 litres per minute, nitrous oxide at 3 litres per minute, and halothane. A circle absorber system using the semi-closed technique and a Fluotec vaporizer outside the circle were employed in every case. Ocular tensions were then recorded every minute for at least 5 times. In the 25 patients not receiving acetazolamide (the control group), the intraocular pressure was taken after Pentothal induction and again two minutes later. Then succinylcholine was given, and the reading repeated at the peak of facial fasciculations, and every minute from then on for at least 5 times. Doses were as in the test group.

RESULTS

The mean values of each successive group of 25 observations were calculated. The standard deviations and upper limits were obtained for the basal tensions of the two series. The successive readings were compared to the upper limits. It was clear then that there were no significant deviations in the series with acetazolamide, but in the control series significant elevations over the upper limits were found in 19 out of the 25 observations made during fasciculations and in 17 out of the 25 made one minute later (Tables II and III). The mean estimates were obtained by adding all values obtained at similar moments and dividing the total by the number of observations. The standard deviations were obtained by subtracting the mean from each reading, squaring each difference, summing the resulting squares, dividing by one less than the number of values and taking the square root. Twice the standard deviation was added to mean estimate to give the upper limit, and subtracted to give the lower limit. Figure 2 shows the mean estimates for both series.

TABLE II
INTRAOCULAR PRESSURES, CONTROL SERIES PROTOCOL

Basal IOP	2 min later	S ch fascic	1 min later	2 min later	3 min later	4 min later	5 min later
Recorded values							
14 6	12 2	20 6	18 9	17 3	17 3	14 6	14 6
12 2	10 2	17 3	20 6	17 3	18 9	14 6	10 2
17 3	17 3	24 4	24 4	20 6	14 6	17 3	15 9
10 2	8 5	20 6	24 4	18 9	14 6	10 2	12 2
12 2	12 2	24 4	24 4	17 3	18 9	14 6	10 2
15 9	12 2	20 6	18 9	13 4	18 9	18 9	18 9
18 9	18 9	24 4	20 6	20 6	15 9	14 6	14 6
11 2	15 9	24 4	20 6	15 9	14 6	11 2	11 2
15 9	17 3	26 6	29 0	18 9	14 6	14 6	14 6
14 6	14 6	22 4	34 5	24 4	17 3	14 6	15 9
17 3	15 9	18 9	18 9	17 3	17 3	14 6	14 6
14 6	15 9	34 4	29 0	18 9	18 9	17 3	12 2
13 4	15 9	15 9	15 9	14 6	15 9	15 9	14 6
15 9	15 9	14 6	17 3	14 6	15 9	15 9	15 9
14 6	15 9	20 6	18 9	14 6	14 6	14 6	14 6
17 3	17 3	24 4	24 4	20 6	18 9	18 9	17 3
10 2	10 2	14 6	17 3	13 4	13 4	11 2	11 2
11 2	10 2	20 6	20 6	18 9	13 4	11 2	10 2
20 6	18 9	29 0	26 6	20 6	14 6	14 6	14 6
15 9	17 3	26 6	20 6	24 4	17 3	14 6	12 2
17 3	18 9	34 5	26 6	20 6	17 3	18 9	15 9
13 4	13 4	17 3	17 3	13 4	13 4	13 4	12 2
13 4	13 4	24 4	26 6	17 3	12 2	12 2	12 2
15 9	17 3	29 0	26 6	14 6	13 4	13 4	12 2
17 3	17 3	29 0	26 6	18 9	18 9	18 9	18 9
Mean values							
14 8	14 4	23 1	22 7	17 8	16 0	14 8	13 8

Standard deviation 2 74

Upper limit 20 38

Lower limit 9 22

TABLE III
INTRAOCULAR PRESSURES, TEST SERIES PROTOCOL

Basal IOP	Diamox effect	S ch fascic	1 min later	2 min later	3 min later	4 min later	5 min later
Recorded values							
15 9	15 9	18 9	18 9	18 9	17 3	10 2	12 2
20 6	20 6	20 6	17 3	18 9	17 3	17 3	17 3
17 3	15 9	15 9	17 3	15 9	15 9	15 9	15 9
20 6	20 6	17 3	18 9	17 3	15 9	15 9	17 3
14 6	13 4	15 9	12 2	13 4	11 2	12 2	13 4
17 3	17 3	17 3	17 3	15 9	15 9	10 2	12 2
15 9	15 9	10 2	10 2	15 9	15 9	14 6	14 6
17 3	15 9	17 3	18 9	14 6	15 9	17 3	17 3
17 3	14 6	14 6	14 6	13 4	12 2	12 2	12 2
10 2	12 2	12 2	8 5	10 2	5 9	7 1	5 9
12 2	10 2	10 2	11 2	8 5	8 5	10 2	9 4
12 2	10 2	11 2	9 4	9 4	11 2	10 2	12 2
17 3	14 6	17 3	18 9	18 9	17 3	18 9	18 9
10 2	7 1	14 6	17 3	14 6	12 2	14 6	14 6
14 6	14 6	17 3	12 2	14 6	12 2	10 2	12 2
12 2	12 2	8 5	8 5	10 2	12 2	12 2	12 2
13 4	13 4	17 3	13 4	10 2	10 2	8 5	8 5
14 6	10 2	12 2	14 6	10 2	12 2	12 2	12 2
15 9	17 3	17 3	14 6	14 6	10 2	10 2	12 2
17 3	15 9	18 9	15 9	15 9	15 9	17 3	17 3
11 2	10 2	10 2	10 2	10 2	7 1	8 5	10 2
10 2	10 2	12 2	12 2	8 5	10 2	10 2	10 2
11 2	15 9	15 9	12 2	10 2	8 5	11 2	11 2
13 4	13 4	10 2	12 2	12 2	10 2	12 2	12 2
13 4	12 2	12 2	13 4	13 4	13 4	13 4	13 4
Mean values							
14 6	13 9	14 6	14 0	13 4	12 9	12 4	13 0

Standard deviation 3 059

Upper limit 20 71

Lower limit 8 48

DISCUSSION

Readings subsequent to those obtained within the five-minute interval proved to be unnecessary because in all cases observed the intraocular tensions did not revert to high readings after five minutes. This fact has been repeatedly corroborated by previous publications of different authors who have found that the maximal effect of a single dose of succinylcholine on intraocular pressure occurs within twenty to thirty seconds and lasts from two to five minutes^{1,2}

Although a perusal of Figure 2 may lead one to believe that the intraocular tension never rose after acetazolamide was given, 12 patients did show some rise in ocular tension after succinylcholine despite the carbonic anhydrase inhibitor, as can be seen in Table III. But these elevations were not significant since they did not go above the calculated upper limits. These results therefore appear to prove the significant value of acetazolamide as a means of preventing the elevations in ocular pressure produced by succinylcholine. But if a practical conclusion has to be drawn from this study, the anaesthesiologist would do better administering the carbonic anhydrase inhibitor intravenously 20 to 30 minutes before the muscle relaxant, and limiting the succinylcholine dose to 20 or 30 mg. A more reliable control of the intraocular tension can be achieved in

this manner. The fact that glaucomatous patients have not been included in the study precludes extension of these conclusions to them.

FIGURE 2 A = Basal IOP B = Two minutes later C = Succinylcholine facial fasciculations

The sequence of events here is as follows: in A, acetazolamide and Pentothal were given and the eye tension was recorded when the patient was asleep. In B, two minutes after A, the intraocular pressure was taken and succinylcholine given. In C, the ocular tension was measured during muscular fasciculations of the face. Then the patients were intubated and given halothane, nitrous oxide, and oxygen while the intraocular pressure was taken every minute for 5 minutes. Between A and B, and between B and C, the patients were given oxygen by mask.

SUMMARY

A review of the physiology and pharmacology of intraocular pressure as related to anaesthesia has been presented. A study has been undertaken to determine whether previously administered acetazolamide would prevent the dangerous rise in intraocular pressure accompanying the use of succinylcholine in anaesthesia, so that succinylcholine might be safely employed in cataract extractions and corneal transplants, and in patients suffering from glaucoma.

The ocular tensions of two series of 25 anaesthetized patients have been studied. Acetazolamide (Diamox) and succinylcholine were given to the test group, and succinylcholine only to the control group. The mean values of the successive readings, the standard deviations, and the upper and lower limits of the basal observations have been calculated. The results are given in tables and the mean values are expressed graphically to facilitate their comparison.

Significant deviations have been found after succinylcholine alone, but not when acetazolamide was given before the succinylcholine. The readings in the test group remained within the accepted normal limits for the intraocular tension.

This study therefore indicates the practical value of acetazolamide as a means of avoiding the significant elevations in intraocular tensions produced by succinylcholine.

RÉSUMÉ

Nous avons présenté une revue de la physiologie et de la pharmacologie de la pression intraoculaire en rapport avec l'anesthésie. Nous avons entrepris une étude pour préciser si l'administration préalable d'acétazolamide (Diamox) pourrait prévenir l'élévation dangereuse de la pression intraoculaire qui accompagne l'usage de la succinylcholine au cours de l'anesthésie. De cette façon, il serait possible d'employer la succinylcholine, en toute sécurité, au cours de l'extraction de cataractes, de greffes de cornée et chez les malades qui souffrent de glaucome.

Nous avons étudié les tensions oculaires de deux séries de 25 malades anesthésiés. Nous avons donné l'acétazolamide (Diamox) et la succinylcholine au groupe à l'étude et la succinylcholine seule au groupe contrôlé. Nous avons calculé les valeurs moyennes des lectures successives, les déviations standards, les limites supérieures et inférieures des observations de base. Nous donnons les résultats sur les tableaux et, pour faciliter leur comparaison, nous exprimons les valeurs moyennes par des graphiques. Nous avons observé des variations importantes lorsque la succinylcholine était employée seule, mais non dans la série de sujets étudiés, chez qui l'acétazolamide avait été donnée avant la succinylcholine. Chez ce dernier groupe, les lectures sont demeurées dans les limites normales acceptées pour la tension intraoculaire.

En conséquence, il semble bien que cette étude prouve la valeur pratique de l'acétazolamide (Diamox) comme moyen d'éviter les élévations importantes intraoculaires produites par la succinylcholine.

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