EFFECT OF METHOXYFLURANE ANAESTHESIA ON INTRAOCULAR PRESSURE*

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WITH THE INCREASING NUMBER of patients undergoing ophthalmological operations by methods other than local anaesthesia (intravenous, neuroleptanalgesia, inhalant agents), choice of the proper anaesthetic agent and technique of administration assumes greater importance in the successful performance of these operations. Most inhalant agents used have been shown to lower the intraocular pressure in proportion to the depth of anaesthesia.^{1,2}

Results of studies in dogs undergoing pentobarbital anaesthesia showed that hyperventilation produced a fall in intraocular pressure. The same study indicated a definite relationship between changes in ventilation, inspired P_{CO_2} , and intraocular pressure.³ Studies of the effect of various methods of anaesthesia on intraocular pressure in man, however, are wanting.

According to Davson, control of the intraocular pressure depends upon the same circulatory and respiratory factors as those which regulate the intracranial pressure.⁴ It can be inferred, then, that the method of ventilation, changes in blood gases, and arterial and central venous pressures may affect the ocular pressure during general anaesthesia. In evaluating the suitability of an anaesthetic for ocular surgery, a study must take into account all these factors, if it is to be adequate and informative. The present investigation was designed to be thorough by recording and analysing data on each of these variables.

The first objective of our study was to test the effectiveness of methoxyflurane in lowering the intraocular pressure. The second question we investigated was whether or not the method of administration plays a significant role in obtaining a maximum beneficial effect on the ocular pressure. Since the methods commonly employed in the use of inhalant agents are assisted and controlled ventilation, hyperventilation, and light and moderate anaesthesia, all these methods were studied in our investigation. Our third objective was to determine the conditions which would govern the selection of one of these methods.

METHOD

Thirty patients undergoing various non-ophthalmological operations with no known ocular abnormalities were studied. Their ages ranged from 13 to 76 years

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(mean: 43 ± 18). The patients were premedicated with 0.4 mg. of atropine and 25 to 50 mg. of meperidine administered intramuscularly 45 minutes prior to the induction of anaesthesia. The narcotic was not given to patients older than 65 years.

Following topical application of proparacaine hydrochloride ophthalmic solution (0.5%) to the cornea, the intraocular tension of both eyes was measured using a Schiotz tonometer with a 5.5 gm. weight load, and calibrated to zero before each measurement. Measurements were made before induction of anaesthesia with the patient in the supine position, during assisted and controlled ventilation, and in steady states of light and moderate anaesthesia. We obtained further measurements of intraocular pressure during the first 30 minutes of the arousal period before the patient's position was altered from the supine. In taking these measurements, we established the criteria for determining arousal stage: (1) rejection of the airway, (2) spontaneous opening of the eyes, and (3) response to simple commands. Measurements were short and frequent to avoid stimulation of outflow and irritation of the cornea.

Depth of anaesthesia was monitored with an electroencephaloscope (Neurological Amplifier A-103 Lexington) using fronto-occipital scalp leads. The instrument was calibrated at 100 microvolts and tracings were taken intermittently (Oscilloriter-Texas Instrument) at a speed of 25 mm. per second for better analysis of the wave forms. The EEG levels of anaesthesia were similar to those established by Andersen *et al.*⁵ Light anaesthesia was defined as the appearance of EEG levels 1 and 2; moderate anaesthesia was marked by the transition to EEG levels 3 and 4. Correlations were made with the clinical data of blood pressure, respiration, pupillary size, and muscular relaxation.

Following local anaesthesia with 1 per cent procaine, a 14-gauge, 24-inch radio-opaque polyethylene catheter was inserted into the brachial vein, advanced until its tip was well within the thoracic inlet, and connected to a water manometer. The position of the catheter was ascertained by the oscillations of the water column synchronized with the respiration. The arterial blood pressure was measured by the auscultatory method. For tabulation and analysis of the variances, these readings were converted to a mean blood pressure equal to $\frac{1}{3}(\text{systolic} + 2 \text{ diastolic})$.

The expired minute volume was monitored by a Wright anemometer. Arterial blood samples for pH, Pco_2 , and Po_2 determinations were drawn intermittently into heparinized syringes using an in-dwelling 19-gauge scalp vein needle placed in the radial or brachial artery. The syringes were capped, iced, and the analyses performed within ten minutes of sampling. The pH, Pco_2 , and Po_2 were measured using an Instrumentation Laboratory electrode system maintained at 37° C. The instrument was calibrated before and after each determination with previously analysed gases and 7.384 buffer solution. The body temperature was measured rectally by means of a calibrated thermistor probe. Corrections were made for any temperature gradient in each sample.

When all control measurements were completed, patients were induced with a sleep dose of thiopental (150–250 mg.) and succinylcholine (40–60 mg.) and ventilated with oxygen. The trachea was intubated, and then methoxyflurane

inhalation was begun through a Heidbrink No. 8 vaporizer in five patients and a Pentec vaporizer in the other 25 patients, using a flow rate of 6 L./min. N₂O-O₂ in a 50:50 ratio in a partial rebreathing system. We waited ten minutes for the anaesthetic state to become stable before taking the first measurements.

The lungs of each patient were ventilated according to the respiratory patterns of assisted ventilation, controlled ventilation at normocarbica, and controlled ventilation at hypocarbica. Controlled ventilation at normocarbica was achieved by regulating the amount of minute volume which would keep the arterial PCO₂, as frequently monitored by blood gas analysis, between 35 and 45 mm. Hg. Controlled ventilation at hypocarbica was effected by increasing the tidal volume while leaving the respiratory rate unchanged. The minute volume ranged from 9 to 16 L./min. We controlled ventilation by two different methods: (1) IPPB in 15 patients manually or with a pressure generator ventilator (Emerson), and (2) PNPB in the other 15 patients using a timed-cycled pressure generator ventilator (Jefferson). During controlled ventilation, the respiratory rate was kept constant at 16 per minute and length of inspiration to expiration was a 1:1.5 ratio. Airway pressures were measured from the proximal end of the endotracheal tube connected to an aneroid manometer and read in centimetres of water.

Each phase of the investigation lasted 15 to 20 minutes except in the case of those patients in whom deepening of the anaesthetic stage caused a significant fall in blood pressure. In six patients in whom the depth of anaesthesia was maintained at EEG levels 3 and 4, the resulting arterial hypotension was corrected by a phenylephrine (Neosynephrine) infusion. The arterial, central venous, and intraocular pressures were measured intermittently before, during, and after the termination of infusion. This phase lasted approximately 15 minutes.

The data processing and statistical analyses were carried out on a 1620 IBM computer. At least 22 values were collected for each variable.

RESULTS

Control values for the intraocular pressure were unequal for the two eyes in ten patients. This difference ranged from 1.0 to 2.5 mm. Hg. The inequality subsided in most of these patients during the anaesthetic state. Occasionally it persisted to a similar degree throughout the anaesthesia, but this is considered within normal limits.⁶ In these cases, the values reported are the calculated averages between the two pressure readings.

Intraocular Pressure and the Stage of Anaesthesia

Changes in depth of anaesthesia and arousal from the anaesthetic state occurred without difficulty in the majority of patients. Fixation of the eyeball in the mid-line developed early and persisted through all planes of anaesthesia; pupils were miotic, and mid-dilatation was observed only during moderate anaesthesia (EEG 3, 4). Methoxyflurane was effective in reducing the intraocular pressure in the majority of patients. The extent of this fall ranged from 15.6 to 24.5 per cent of the control value. The decrease lasted throughout the first 30 minutes of the

arousal period, with an average fall of 9.4 per cent from the control value. Nausea and vomiting, which were observed in four patients, did not necessarily alter this reduction in ocular tension. Restlessness or efforts to remove an oral airway, however, was responsible for a pressure rise in two patients. As shown in Figure 1, the intraocular pressure falls markedly with each successive increase

FIGURE 1. The effect of depth of anaesthesia on intraocular pressure. The mean values and standard deviations for the intraocular pressure are represented on the ordinate. The stages of anaesthesia are arranged in order of increasing effect on intraocular pressure. Note: Deepening the anaesthesia from light to moderate yields only a slight further reduction in intraocular pressure.

in the depth of anaesthesia, but the change from light to moderate anaesthesia is not as significant as the fall from the control value to light anaesthesia and from the control value to the arousal stage, as compared to the fall from light to moderate anaesthesia. (See Fig. 1 and Table I.)

TABLE I
DEPTH OF ANAESTHESIA AND INTRAOCULAR PRESSURE DURING
METHOXYFLURANE ANAESTHESIA

Stage of anaesthesia	Intraocular pressure (mm. Hg)	
	N	$\bar{X} \pm S.D.$
Control (awake)	30	15.66 $\pm$ 2.80
Arousal	30	14.18 $\pm$ 2.17
Light anaesthesia (EEG 2)	30	13.22 $\pm$ 2.73
Moderate anaesthesia (EEG 3, 4)	30	11.82 $\pm$ 3.17

N = number of patients.

$\bar{X}$ = mean value.

S.D. = standard deviation.

Effect of Neosynephrine Infusion

Since the fall in ocular tension was associated with a concomitant fall in arterial pressure, particularly during deeper anaesthesia, an attempt was made to reverse the arterial hypotension with a 0.1 per cent phenylephrine (Neosynephrine) drip infusion, while keeping the anaesthetic state unchanged (EEG 3, 4).

(N = 10; $\bar{X} \pm S.D.$)

FIGURE 2. Effect of phenylephrine (Neosynephrine) infusion during moderate depth of methoxyflurane anaesthesia. Relationship between arterial, central venous, and intraocular pressure represented in mean values with standard deviations. Note the sustained rise in CVP (two times the control value) during and for 25 minutes after termination of infusion. The depth of anaesthesia was steady moderate (EEG 3, 4).

In ten studies of patients whose average age was 28.5 ± 4.67 years, a transient rise in mean blood pressure occurring during the infusion was observed. Yet this rise was still below the control value. In the same patients, the central venous pressure rose to a value twice that of the control, and persisted after termination of the infusion. These changes in vascular pressures led to a rise in the intraocular tension from 11.13 ± 2.78 to 13.78 ± 2.60 mm. Hg during infusion. This rise came nowhere near the control value (mean 15.98 ± 1.75 mm. Hg), but remained steady at 13.31 ± 1.72 mm. Hg for the 25 minutes immediately following infusion (Fig. 2).

Effect of Method of Ventilation

For these studies, the minute volume and arterial blood gases were kept close to the control values. (See Table II.) The average airway pressure for controlled ventilation by IPPB was $+18.65/+1.53$ inspiration : expiration, and $+15.0/-7.07$ inspiration : expiration during PNPB.

Table III furnishes the values for mean blood pressure, central venous pressure, and intraocular pressure during assisted and controlled ventilation. An analysis of the variances indicated that assisted and controlled ventilation by IPPB or by PNPB were equally effective in lowering intraocular pressure. Both methods

TABLE II
VOLUME OF VENTILATION AND ARTERIAL BLOOD GAS MEASUREMENTS

Data	Awake (N = 30) ($\bar{X} \pm S.D.$)	Assisted ventilation (N = 30) ($\bar{X} \pm S.D.$)	Controlled ventilation (N = 30) ($\bar{X} \pm S.D.$)
MV	6.0 ± 1.6	7.6 ± 2.04	8.7 ± 2.12
pH	7.44 ± 0.03	7.42 ± 0.06	7.46 ± 0.05
P _a CO ₂ (in mm. Hg)	35.17 ± 4.52	35.54 ± 6.67	33.11 ± 5.20
P _a O ₂ (in mm. Hg)	78.00 ± 15.26	158.46 ± 83.88	162.56 ± 62.21

N = number of patients studied.

$\bar{X}$ = mean values.

S.D. = standard deviation.

MV = minute volume in L./min.

TABLE III
EFFECT OF METHOD OF VENTILATION ON INTRAOCULAR PRESSURE DURING
METHOXYFLURANE ANAESTHESIA (N = 30)

Data	Control ($\bar{X} \pm S.D.$)	Assisted ventilation ($\bar{X} \pm S.D.$)	Controlled ventilation ($\bar{X} \pm S.D.$)
IOP _x	15.66 ± 2.80	12.50 ± 2.29	12.45 ± 3.20
MBP _x	93.67 ± 15.64	77.00 ± 13.62	65.67 ± 13.05
CVP _x	7.44 ± 3.11	13.72 ± 4.19	14.62 ± 4.92

N = number of patients.

$\bar{X}$ = mean value.

S.D. = standard deviation.

IOP_x = intraocular pressure in mm. Hg.

MBP_x = mean blood pressure in mm. Hg.

CVP = central venous pressure in cm. H₂O.

were associated with arterial hypotension and an increase in central venous pressure (Fig. 3). When the individual cases were analysed, we found that the rise in central venous pressure (three to four times above the control), with or without high airway pressure, was associated with an increased ocular tension

(N=30; $\bar{x} \pm \text{S.D.}$)

FIGURE 3. Relationship between blood pressure, central venous pressure, intraocular pressure, and the method of ventilation. Each perpendicular line represents the data in mean values with standard deviations for 30 patients. Note the comparative effectiveness of assisted ventilation, IPPB, and PNPB, and also the steady rise in central venous pressure during the employment of these three methods.

unaffected by anaesthesia and hyperventilation. This was observed in patients 5 and 28. In patients 1, 3, and 27, however, the combination of hyperventilation by PNPB and deeper anaesthesia lowered the intraocular pressure, in spite of a sustained high central venous pressure (from 11 to 28 cm. H₂O).

Effect of Hyperventilation on Intraocular Pressure

The values for mean blood pressure, central venous pressure, and intraocular pressure are given in Table IV. In lowering the intraocular pressure, no significant difference was found between the normocarbic and hypocarbic groups. The effect on central venous pressure was similar in both groups, although the values differed from the control. The mean blood pressure was lower than the control value in the normocarbic group, and even lower in the hypocarbic group.

TABLE IV
EFFECT OF ALTERATION IN PaCO₂ ON INTRAOCULAR PRESSURE DURING
METHOXYFLURANE ANAESTHESIA

Data	Control (N = 30) ($\bar{X} \pm S.D.$)	Normocarbica (N = 24) ($\bar{X} \pm S.D.$)	Hypocarbica (N = 22) ($\bar{X} \pm S.D.$)
pH	7.44 $\pm$ 0.04	7.42 $\pm$ 0.02	7.51 $\pm$ 0.05
PaCO ₂	35.17 $\pm$ 4.52	35.58 $\pm$ 3.81	27.82 $\pm$ 3.30
IOP _x	15.66 $\pm$ 2.80	12.79 $\pm$ 3.00	11.92 $\pm$ 3.88
MBP _x	93.67 $\pm$ 15.64	72.50 $\pm$ 12.16	58.18 $\pm$ 7.95
CVP _x	7.44 $\pm$ 3.11	13.82 $\pm$ 4.65	15.06 $\pm$ 4.70

Legend as in Table III.

Another question pertinent to our study was the existence of a difference among the six modes of administration—assisted ventilation, controlled ventilation, controlled ventilation at normocarbica, hyperventilation, light anaesthesia, and moderate anaesthesia—all of which produced a fall in intraocular pressure. Analysis of the variances of these six methods employed under the present experimental conditions indicated that no differences existed among them ($F = .8386$ df 5,161). The evidence in Tables I, III, and IV, however, supports the conclusion that the order of fall in intraocular pressure under these conditions is maintained.

DISCUSSION

The data from our investigation tend to prove that methoxyflurane, like most other inhalant agents, lowers intraocular pressure during light, as well as moderately deeper, planes of anaesthesia. Its usefulness in ocular surgery is supported by the following additional findings.

1. Early fixation of the eyeball is maintained during all stages of anaesthesia. Akinesia, which is one of the fundamental requirements for cataract surgery, also facilitates operative procedures in the correction of strabismus.

2. We found that the lowering of intraocular pressure prolonged throughout the early arousal period reduces the dose of sedation required to keep the patient calm and to maintain a low ocular tension. The persisting decrease in pressure is presumably due to the relaxant effect of the anaesthetic agent upon the

muscular system and, consequently, upon the extraocular muscles, and to its continuing analgesia.^{7,8} In very elderly patients with severe pulmonary or vascular diseases, excessive sedation could result in circulatory or respiratory depression. The use of vasopressors and/or the presence of hypercapnia will definitely lead to an increase in intraocular vascular volume.

3. The incidence of nausea and vomiting with methoxyflurane is no greater than with other inhalant agents. In our study, these side-effects occurred in only four patients. Barbieri reported that nausea and vomiting were observed in 8 per cent of 275 patients undergoing ocular procedures.⁹ Tammisto *et al.*, in a study of the comparative usefulness of halothane and methoxyflurane in ocular surgery, found that methoxyflurane produced the smoother emergence from anaesthesia.¹⁰

Further findings in our study indicate that all methods employed were equally effective in lowering intraocular pressure. The presence of a mild to moderate hypotension and a rise in central venous pressure seem at variance with the established close correlation between venous pressure and level of intraocular pressure.¹¹ There are several explanations for this apparent discrepancy. It can be assumed that this rise in venous pressure was mutually compensated for by the arterial hypotension and a decreased inflow. Elevations and falls in arterial pressure are damped to a considerable degree by the outflow mechanism.⁴ Adams and Barnett reported a significant fall in intraocular pressure during halothane anaesthesia when the systemic pressure was lowered under 90 mm. Hg.¹² Investigations in animals, however, have failed to demonstrate a definite relationship between systemic arterial pressure and intraocular pressure.¹³

The second possibility, a predominant central action of the anaesthetic, as suggested by von Sallman and others, only partially holds true.^{14,15} In our study, although the intraocular pressure kept falling with the increasing depth of anaesthesia, the gain was not significantly greater than from the control value to light anaesthesia.

The third possibility is that the rise in central venous pressure was not sufficient to impede the outflow mechanism, nor did it cause an increase in intraocular vascular volume through capillary engorgement and vasodilatation. That an increase in intraocular vascular volume leads to high intraocular pressure is supported by these observations: (1) Experiments in dogs have shown that if the inspired CO₂ is increased, the intraocular pressure rises in all instances. Parallel changes in the opposite direction, however, cannot be achieved with hyperventilation. Our findings in the hypocarbic group agree with those of Duncalf and Weitzner.³ (2) Infusion of a vasopressor during the steady state of anaesthesia resulted in a sustained rise in central venous pressure and intraocular pressure. The rise in intraocular pressure was presumably the result of a change in the intraocular vascular volume, brought about by the more pronounced secondary effect of the vasopressor upon the central venous pressure.⁴ Since we deliberately avoided hypoventilation and hypercapnia, it can be assumed that the intraocular vascular volume did not increase.

Because several factors which may be mutually compensatory exert an influence on the intraocular pressure, the isolation of a single mechanism becomes difficult. On the basis of the data presented and the available literature, the most logical

explanation is that the rise in venous pressure was not sufficient to obstruct the outflow mechanism, and was mutually compensated for by the arterial hypotension and decrease in inflow (= alterations in aqueous humour dynamics).

The two questions most pertinent to clinical application are which method is more effective and what factors govern the choice of a particular method. That the order of effect on intraocular pressure is maintained (see Tables I, III, IV) allows a wider selection of method. The choice ultimately depends upon these interrelated factors: (1) subjective preference and experience, (2) availability of equipment, and (3) condition of the patient.

If ventilation is maintained within or above normal limits, and the venous pressure is not increased excessively, the intraocular pressure will fall during methoxyflurane anaesthesia. The use of these various methods, however, is limited by their consequent effects upon the intraocular vascular content and outflow mechanism, which may obviate the desired effects. Specifically, the decision to use a hyperventilation technique in a patient requiring a high inflation pressure could lead to an excessive rise in venous pressure (on occasion three to four times above the normal), engorgement of the episcleral veins, obstruction of the outflow, and finally, a sustained rise in ocular pressure. Yet, in spite of a high central venous pressure, hyperventilation by PNPB without excessive airway pressure, in conjunction with a deeper plane of anaesthesia, was effective in lowering the intraocular pressure in some of our patients. The development of bronchospasm, however, which could occur during light anaesthesia in patients with chronic lung disease, chronic bronchitis, or poor lung compliance, may lead to a sustained elevation in venous pressure and intraocular pressure, even after correction of the respiratory difficulty.¹⁶

The use of deeper planes of anaesthesia in patients with labile cardiovascular system also presents difficulties. Attempting to correct the subsequent hypotension with vasopressors will produce a more pronounced effect on the venous system and, consequently, on the intraocular pressure.

SUMMARY

The effect of methoxyflurane anaesthesia on intraocular pressure was investigated in 30 patients. This inhalant agent effectively reduced the intraocular pressure throughout the first 30 minutes of the arousal period, as well as during light and moderate anaesthesia. Although a further decrease in pressure occurred with increasing depth of anaesthesia, this reduction was not as significant as the initial one from control value to light anaesthesia.

Analyses of variances failed to demonstrate any statistical difference between the various methods investigated: assisted ventilation, controlled ventilation by IPPB and by PNPB, light and moderate anaesthesia. Similarly, hyperventilation did not differ significantly from the other methods studied. The order of fall in intraocular pressure under these conditions, however, is maintained, with the greatest falls occurring during moderately deep anaesthesia and during hyperventilation, and the smallest during light anaesthesia. In all the methods investigated, the ventilatory parameters were kept within or above normal limits.

Selection of a particular method of ventilation is influenced by its concomitant side-effects which may tend to cancel out the desired lower ocular tension. The use of vasopressors to correct arterial hypotension leads to a rise in intraocular pressure; an excessive rise in venous pressure could increase intraocular pressure by impairing the outflow or by elevating the intraocular vascular content.

Our conclusion, that all six methods employed clinically are effective in lowering intraocular pressure during methoxyflurane anaesthesia, is soundly supported by statistical evidence, provided that ventilation is maintained within or above normal limits, that the venous pressure is not unduly increased, and that the steady state of anaesthesia is achieved without respiratory difficulties.

RÉSUMÉ

Nous avons étudié, chez trente malades, l'effet de l'anesthésie au méthoxyflurane sur la pression intraoculaire. De fait, cet agent anesthésique par inhalation a diminué la pression intraoculaire au cours des premières trente minutes de la période d'induction aussi bien que durant l'anesthésie légère et durant l'anesthésie modérément profonde. Bien qu'un approfondissement plus marqué de l'anesthésie ait entraîné une diminution plus sensible de la pression, cette dernière réduction de pression n'a pas été aussi importante que la diminution initiale à partir de la valeur du point de contrôle à celle de l'anesthésie légère.

Des analyses des variations n'ont pas réussi à mettre en évidence une différence statistique entre les diverses méthodes étudiées: la ventilation assistée, la ventilation contrôlée à l'aide de IPPB ou de PNPB, l'anesthésie légère et l'anesthésie plus profonde.

Ainsi en a-t-il été de l'hyperventilation qui n'a pas apporté de variations marquées comparativement aux autres méthodes étudiées. Dans ces différentes circonstances, l'importance de la chute de la pression intraoculaire s'est toutefois maintenue et les diminutions les plus importantes sont survenues au cours de l'anesthésie plus profonde et de l'hyperventilation, alors que les diminutions les moins importantes ont été observées au cours de l'anesthésie légère. Dans toutes les méthodes que nous avons étudiées, nous avons maintenu les paramètres de la ventilation au-dessus ou dans les limites de la normale.

Le choix d'une méthode particulière de ventilation est influencé par ses effets secondaires concomitants qui peuvent avoir tendance à neutraliser la tension oculaire inférieure désirée. L'usage de vasopresseurs pour corriger l'hypotension entraîne une augmentation de la pression intraoculaire; une élévation marquée de la tension veineuse pourrait augmenter la pression intraoculaire soit en modifiant la sortie des liquides de l'œil soit en augmentant le contenu intravasculaire de l'œil.

Nous en venons à la conclusion que toutes les six méthodes employées cliniquement sont efficaces pour diminuer la pression intraoculaire au cours de l'anesthésie au méthoxyflurane; l'évidence statistique confirme cette assertion, à la condition que la ventilation conserve des valeurs au-dessus ou dans les limites de la normale, que la tension veineuse ne soit pas indûment élevée et que l'on maintienne un niveau d'anesthésie égal sans difficultés respiratoires.

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