THE EFFECT OF METOCURINE AND METOCURINE-PANCURONIUM COMBINATION ON INTRAOCULAR PRESSURE

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ABSTRACT

Maintenance of a normal to low intraocular pressure during ocular surgery is of critical importance. The prime considerations for anaesthetic management include adequate depth of anaesthesia, normal carbon dioxide and arterial oxygen tensions, stable cardiovascular status and avoidance of stimuli likely to raise central venous pressure. Non-depolarizing muscle relaxants are associated with a reduction in intraocular pressure. Metocurine, a non-depolarizing relaxant, formerly known as dimethyltubocurarine, has been recently reintroduced into clinical practice. Metocurine has been reported to be 1.8 times more potent than d-tubocurarine and has the clinically advantageous cardiovascular effects of stable heart rate and mean blood pressure with minimal associated histamine release. When combined with pancuronium, metocurine potentiates the neuromuscular blocking properties, so that small doses of both drugs in combination produce effective neuromuscular block. This study was designed to assess the suitability of metocurine $0.3 \text{ mg} \cdot \text{kg}^{-1}$ and metocurine $0.08 \text{ mg} \cdot \text{kg}^{-1}$ plus pancuronium $0.02 \text{ mg} \cdot \text{kg}^{-1}$ as muscle relaxants for ocular surgery. The results demonstrated that metocurine and metocurine-pancuronium combination in the above doses combined with sodium thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$ produced ideal conditions for intubation of the trachea in $4.45 (\pm 0.19 \text{ SE})$ minutes and $4.35 (\pm 0.16 \text{ SE})$ minutes respectively. In both treatment groups intraocular pressure was reduced below control values and a pattern of intraocular pressure stability ideal for ocular surgery was obtained during the 10 minutes observation period. The delayed onset of sufficient paralysis for tracheal intubation – $4.45 (\pm 0.19 \text{ SE})$ minutes for metocurine and $4.35 (\pm 0.16 \text{ SE})$ minutes for the combination – makes these techniques unsuitable for emergency ocular surgery because of the long interval when the airway is unprotected.

KEY WORDS: EYE, intraocular pressure; NEUROMUSCULAR RELAXANTS, metocurine, pancuronium.

THE PRIME considerations involved in the anaesthetic management of patients undergoing ocular surgery are a stationary eye, for safe surgical conditions; absence of coughing and vomiting during and after operation; avoidance of elevations in intraocular pressure, which can cause extrusion of globe contents; airway control and a stable cardiovascular system. The choice of muscle relaxant is of paramount importance. The ideal muscle relaxant for ocular surgery would be one that is potent, with a rapid onset, appropriate duration of action, and readily reversible. In addition, autonomic and cardiovascular side-effects should be minimal. Metocurine, a nondepolarizing neuromuscular blocking agent

formerly known as dimethyltubocurarine,¹ has been recently reintroduced into clinical practice. A trimethylated derivative of d-tubocurarine, metocurine has 1.8 times the potency of d-tubocurarine and in doses of $0.3 \text{ mg} \cdot \text{kg}^{-1}$ produces 96.1 per cent mean twitch depression within 4.8 ± 0.6 (SEM) minutes,² allowing easy tracheal intubation. In such doses, metocurine offers the clinically advantageous cardiovascular effects of stable heart rate and mean blood pressure and minimal associated histamine release.³⁻⁶

Combinations of metocurine and pancuronium potentiate the neuromuscular blocking effects,⁷ so that administration of small doses of both drugs (pancuronium $0.018 \text{ mg} \cdot \text{kg}^{-1}$ plus metocurine $0.072 \text{ mg} \cdot \text{kg}^{-1}$) produce clinically effective neuromuscular blockade, with stable haemodynamic parameters and rapid reversal of neuromuscular blockade.⁸

This study was designed to examine the effects of metocurine $0.3 \text{ mg} \cdot \text{kg}^{-1}$ and metocurine $0.08 \text{ mg} \cdot \text{kg}^{-1}$ plus pancuronium $0.02 \text{ mg} \cdot \text{kg}^{-1}$ combination on intraocular pressure when used in association with thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$ and to assess their suitability as muscle relaxants for patients undergoing ocular surgery.

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METHODS

Forty male and female subjects who had given informed consent and were undergoing elective minor surgical procedures were studied. The patients' ages ranged from 16–50 (mean age 35 years $\pm$ 2.0 SE). All patients were A.S.A. Class I or II and had no ocular disease. No patient had renal, hepatic or neuromuscular disease, nor was any patient receiving medication known to affect myoneural transmission. All subjects received a premedication of diazepam 0.2 mg·kg⁻¹ orally 90 minutes before operation. The patients were alternately allocated to two treatment groups.

TREATMENT GROUP I

(n=20) Anaesthesia was induced with sodium thiopentone 5 mg·kg⁻¹ and metocurine 0.3 mg·kg⁻¹.

TREATMENT GROUP II

(n=20) Anaesthesia was induced with sodium thiopentone 5 mg·kg⁻¹ and metocurine 0.08 mg·kg⁻¹ plus pancuronium 0.02 mg·kg⁻¹.

A Professional Instruments Company NS-2A peripheral nerve stimulator was used to stimulate the ulnar nerve. The time interval between relaxant administration and complete peripheral nerve twitch suppression was recorded for both treatment groups and the degree of vocal cord relaxation at the time of tracheal intubation was classified as excellent, satisfactory, fair or poor using the criteria of Lund and Stovner.⁹

The conduct of anaesthesia was similar for both treatment groups. Following induction, anaesthesia was maintained with nitrous oxide-oxygen 4:2 litres/min and 0.5 per cent halothane, using a Bain non-rebreathing anaesthesia circuit. Controlled ventilation was employed in all cases and tracheal intubation was done when peripheral nerve twitch response was completely abolished. Blood pressure was recorded each minute and the electrocardiogram was monitored constantly. Arterial blood gas analysis was done at 5 and 10 minutes following administration to ensure normocarbida and normal arterial oxygenation.

An ophthalmologist (J.F.) measured the intraocular pressure of each subject using a Perkins hand-held applanation tonometer following the instillation of 0.5 per cent tetracaine in the left eye. Measurements were recorded at the following six time points: on arrival in the operating room (control) and every two minutes for a total of 10 minutes following administration of metocurine and metocurine-pancuronium combination (five measurements).

Data collected

The following data were collected for each patient: (1) age. (2) sex. (3) weight. (4) six intraocular pressure measurements (described above). (5) time interval between relaxant administration and complete peripheral nerve twitch suppression. (6) classification of vocal cord relaxation.

RESULTS

Age, sex, weight and ease of tracheal intubation had no apparent effect on intraocular pressure in either treatment group. Intubation conditions were recorded as excellent in 15 out of 20 patients receiving metocurine and 17 out of 20 patients receiving metocurine-pancuronium combination. The time interval between the administration of metocurine 0.3 mg·kg⁻¹ and complete peripheral nerve twitch suppression was 4.45 $\pm$ 0.19 (SE) minutes, while the interval was 4.35 $\pm$ 0.16 (SE) minutes for the metocurine-pancuronium combination.

Mean intraocular pressure values ($\pm$ SE) at each time point for the two groups are displayed in Table I. The values obtained at the five time points following induction are expressed as differences from control ($\pm$ SE) and also as percentage of control ($\pm$ SE). Following induction with thiopentone 5 mg·kg⁻¹ and metocurine 0.3 mg·kg⁻¹ intraocular pressure decreased to 69 per cent of control at two and four minutes and remained below control during the 10 minutes observation period $P < 0.05$ (Figure 1). For patients induced with thiopentone 5 mg·kg⁻¹ and metocurine 0.08 mg·kg⁻¹ plus pancuronium 0.02 mg·kg⁻¹ intraocular pressure decreased to 74 per cent of control at two minutes and 77 per cent of control at four minutes and remained below control during the 10 minutes observation period $P < 0.05$ (Figure 2). When the patterns of mean intraocular pressure values in the two

TABLE I
MEAN INTRAOCULAR PRESSURE VALUES

	Group I	Group II
Control	14.0 $\pm$ 1.1	12.6 $\pm$ 1.0
2 Min (A)	-4.4 $\pm$ 0.6	-3.3 $\pm$ 0.7
(B)	69 $\pm$ 4.0	74 $\pm$ 5.5
4 Min (A)	-4.4 $\pm$ 0.9	-2.9 $\pm$ 0.9
(B)	69 $\pm$ 6.5	77 $\pm$ 7.0
6 Min (A)	-3.3 $\pm$ 1.3	-1.6 $\pm$ 1.1
(B)	76 $\pm$ 9.5	87 $\pm$ 9.0
8 Min (A)	-4.2 $\pm$ 1.3	-3.1 $\pm$ 1.1
(B)	70 $\pm$ 9.0	75 $\pm$ 8.5
10 Min (A)	-4.9 $\pm$ 1.2	-3.5 $\pm$ 1.2
(B)	65 $\pm$ 9.0	72 $\pm$ 8.5

(A) Post induction difference from Control $\pm$ SE.

(B) Per cent of Control $\pm$ SE.

FIGURE 1 Treatment Group I (metocurine). Mean control intraocular pressure mmHg $\pm$ SE and per cent difference from control.

groups at the five time points following induction were assessed using a profile analysis technique,¹⁰ the pattern of values were similar and coincident.

DISCUSSION

This study demonstrated that metocurine and metocurine-pancuronium combination with thiopentone are ideal muscle relaxants for patients undergoing elective ocular surgery. The low dose metocurine-pancuronium combination was as effective as metocurine alone in producing satisfactory conditions for intubation of the trachea.

Metocurine $0.3 \text{ mg} \cdot \text{kg}^{-1}$ produced smooth intubating conditions in 4.45 ± 0.19 (SE) minutes while the metocurine $0.08 \text{ mg} \cdot \text{kg}^{-1}$ plus pancuronium $0.02 \text{ mg} \cdot \text{kg}^{-1}$ produced similar smooth intubating conditions in 4.35 ± 0.16 (SE) minutes. Both treatment groups produced a pattern of intraocular stability which is highly desirable for patients undergoing ocular surgery. No undue hypotension (systolic blood pressure reduction to less than 70 per cent of control) or

stigmata of histamine release were noted in the metocurine group. The small dose metocurine-pancuronium combination appears to offer the advantages of adequate neuromuscular blockade, shorter duration of action and cardiovascular stability.⁷ Whether the combination of low dose metocurine-pancuronium combination exerts its action at a presynaptic or post-synaptic site or both is uncertain. A likely possibility is that of simultaneous pre- and post-synaptic receptor inhibition. Metocurine, like d-tubocurarine, may exert a predominant pre-synaptic action of reduced acetylcholine release while pancuronium in low concentrations appears to exert only a post synaptic effect.¹² These two non-depolarizing relaxants have different protein binding affinities,¹³ so their use in combination may alter the protein binding properties of each drug so that more free unbound drug is available at the neuromuscular junction.

Maintenance of normal to low intraocular pressure during intraocular surgery is of critical importance. If the eye is incised when the intraocular pressure is excessively high, the sudden decompression might cause rupture of a sclerotic long posterior ciliary artery and the resulting haemorrhage could lead to loss of the eye.¹⁴

Elevation of the intraocular pressure when the eye is open could lead to extrusion of uveal tissue, lens and vitreous. The two major categories of factors affecting intraocular pressure during surgery are extraocular pressure sources and intraocular aqueous humour fluid dynamics.

Extraocular pressure sources include the muscles surrounding the eye and orbit and central venous pressure. Contraction of the extraocular muscles and orbicularis oculi muscles can increase intraocular pressure. The depolarizing relaxant succinylcholine raises intraocular pressure by producing a slow and prolonged tonic contraction of the extraocular muscles.¹⁵ Increases in central venous pressure are transmitted directly to the eye, producing an elevation of episcleral venous pressure, which in turn impedes the aqueous humour outflow from the canal of Schlemm. The aqueous humour is a clear fluid which fills the anterior and posterior chambers. The volume of aqueous depends on its rate of formation and its rate of outflow through the trabecular meshwork and Schlemm's canal. Intraocular pressure rises when there is increased aqueous production or decreased outflow. Two-thirds of the aqueous is formed in the posterior chamber by the epithelial cells of the ciliary body in an active secretory process utilizing carbonic anhydrase. The remaining one-third of the aqueous is formed in the anterior chamber by simple filtration through the anterior

FIGURE 2 Treatment Group II (metocurine-pancuronium). Mean control intraocular pressure mmHg $\pm$ SE and per cent difference from control.

surface of the iris.¹⁶ From an anaesthetic viewpoint, control of the factors affecting pressure on the eye and extraocular muscle tone pose the major challenges. Adequate depth of anaesthesia, maintenance of normal carbon dioxide and arterial oxygen tensions¹⁷ stable cardiovascular status, avoidance of coughing and movement during operation will prevent vascular congestion from increasing intraocular pressure.

Control of the state of extraocular muscle tone through the use of neuromuscular blocking agents and the subsequent effect on intraocular pressure has been the subject of extensive investigation reported in the literature. The unique structure of the extraocular muscle is peculiar to this discussion. Two types of histological structures have been identified (A) Felderstruktur, which produces a slow tonic contraction when exposed to acetylcholine or depolarizing relaxants¹⁸ and (B) Fibrillenstruktur, which produces a twitch response. The effects of neuromuscular blocking agents on intraocular pressure depend on their action on these two muscles fibres. Succinylcholine, which has been shown to produce intraocular pressure rises of 18 mmHg in normal unanaesthetized individuals,¹⁹ in increasing doses produces an increase in extraocular muscle tension by its effect on the tonic Felderstruktur system. D-tubocurarine depresses the twitch response (Fibrillenstruktur) in the cat superior rectus muscle and lowers the intraocular pressure.²⁰ This is the likely mechanism of action of pancuronium²¹ and metocurine and other non-depolarizing relaxants in lowering intraocular pressure.

The anaesthetic technique of induction with thiopentone and metocurine or metocurine-pancuronium combination, followed by controlled ventilation with nitrous oxide/oxygen and halothane 0.5 per cent, as employed in this study, ensures optimal surgical conditions for ocular surgery – a stationary eye, absence of coughing and movement during operation, stable cardiovascular status, airway control, adequate depth of anaesthesia, lowered intraocular pressure levels, appropriate duration of neuromuscular blockade and easy reversibility with anticholinesterases.

The delayed onset of sufficient paralysis for tracheal intubation – 4.45 ± 0.19 (SE) minutes for metocurine and 4.35 ± 0.16 (SE) minutes for the combination makes these anaesthetic techniques unsuitable for emergency ocular surgery because of the long time interval when the airway is unprotected. For such emergency open-eye, full stomach cases succinylcholine offers the advantages of rapid onset of relaxation (the time interval from bolus administration of $1 \text{ mg} \cdot \text{kg}^{-1}$ succinylcholine to abolition of twitch response is 63 ± 5.1 seconds²²) smooth intuba-

tion conditions and short duration of action. Following pretreatment with diazepam $0.1 \text{ mg} \cdot \text{kg}^{-1}$ and in combination with thiopentone $3\text{--}5 \text{ mg} \cdot \text{kg}^{-1}$, succinylcholine will produce only minor rises in intraocular pressure²³ and this is a rational anaesthetic technique for the emergency ocular surgery case. Other reports suggest that the prior administration of the carbonic anhydrase acetazolamide²⁴ or hexafluorenum²⁵ or pretreatment with the non-depolarizing agents d-tubocurarine or gallamine²⁶ will inhibit the rise in intraocular pressure produced by succinylcholine.

The new neuromuscular blocking agents ORG NC45 (Norcuron), BW33A (Atracurium) and BWA 444U currently under investigation offer the exciting promise of shorter duration of action, significant lack of cardiovascular effects and less cumulative tendency than the currently popular non-depolarizing relaxants.²⁷ Unfortunately, in the initial clinical studies of the monoquaternary pancuronium homologue ORG NC45, the major disappointing feature is that the drug, like the currently used non-depolarizing relaxants, has a slow onset of neuromuscular blockade. Using an intubating dose of $0.02 \text{ mg} \cdot \text{kg}^{-1}$, the onset time to 76 ± 6 per cent twitch suppression was 6.0 ± 0.31 minutes.²⁸

What is required for the emergency open eye case is a relaxant with the speed of onset of the depolarizing agent succinylcholine and the intraocular pressure reducing action of the non-depolarizing agents pancuronium and metocurine.

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RÉSUMÉ

La chirurgie oculaire nécessite le maintien de pressions intraoculaires basses ou normales. Une bonne conduite anesthésique inclut une profondeur suffisante, une normocarbie et une oxygénation adéquate, un état cardiovasculaire stable et la prévention de tout stimulus susceptible d'augmenter la pression veineuse centrale. Les antidépolarisants ont l'avantage de produire une baisse de la pression intraoculaire. La métocurine, agent antidépolarisant connu aussi sous le nom de diméthyltubocurarine a récemment été réintroduite en anesthésie. La métocurine est 1.8 fois plus puissante que la d-tubocurarine tout en procurant des bénéfices cardiovasculaires certains: stabilité de la fréquence cardiaque et de la pression artérielle moyenne avec décharge minime d'histamine. Lorsqu'on l'associe au pancuronium, la métocurine potentialise le blocage musculaire de sorte que de petites doses des deux produits peuvent produire une myorésolution efficace. Cette étude a été conçue pour évaluer l'efficacité de doses de métocurine $0.3 \text{ mg} \cdot \text{kg}^{-1}$ et $0.08 \text{ mg} \cdot \text{kg}^{-1}$ associées au pancuronium $0.02 \text{ mg} \cdot \text{kg}^{-1}$ comme myorelaxants pendant la chirurgie oculaire. Les résultats ont démontré que la métocurine et l'association métocurine-pancuronium aux doses déjà mentionnées avec thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$ produisent des conditions idéales pour l'intubation en $4.45 (\pm 19 \text{ SE})$ minutes et $4.53 (\pm 16 \text{ SE})$ minutes respectivement. Dans les deux groupes, la tension intra-oculaire a été réduite sous le niveau des valeurs de contrôle et un état de stabilité tensionnelle intraoculaire idéale pour la chirurgie oculaire a été obtenue pendant la période d'observation de 10 minutes. Le délai nécessaire à l'obtention d'une paralysie suffisante pour l'intubation trachéale, $4.45 (\pm 0.19 \text{ SE})$ minutes pour le métocurine et $4.35 (\pm 0.16 \text{ SE})$ minutes pour l'association des deux antidépolarisants, rend ces techniques inadéquates pour la chirurgie oculaire d'urgence à cause de la longueur de l'intervalle au cours duquel les voies respiratoires restent sans protection.