Southern African Journal of Anaesthesia and Analgesia. 2021;27(5):228-234
https://doi.org/10.36303/SAJAA.2021.27.5.2580

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

ORIGINAL RESEARCH

Minimum alveolar concentration of sevoflurane required to prevent Bell's phenomenon during examination of the eye under anaesthesia

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Background: Ophthalmological examination under anaesthesia (EUA eyes) in children is usually performed under sevoflurane anaesthesia. Adequate anaesthesia is required to immobilise the eye in a central position. Ocular stimuli at an insufficient depth of anaesthesia can result in Bell's phenomenon, with eyes turning cephalic, delaying the procedure. The aim of this study was to determine the minimum alveolar concentration (MAC) of sevoflurane which inhibits Bell's phenomenon (MACBell) in young children and the main stimuli eliciting this response.

Methods: A sequential experimental study was conducted using the up-and-down procedure or method. Children between the ages of 1 month and 10 years, scheduled for EUA eyes were included. Each patient received sevoflurane (in 40% oxygen/air) at a preselected end-tidal sevoflurane concentration that differed by 0.1%, depending on the response evoked in the preceding patient. The stimulus that elicited this response was recorded.

Results: Forty-three children were included in this study. The median age was 37.0 months (range 2–120 months). MACBell, determined by the average MAC at the midpoint of the 14 crossover pairs, was 1.74 (SD 0.19) and 1.81% by probit regression analysis (95% confidence interval 1.63–2.14). The main stimuli responsible for eliciting the reflex were forced traction on eye muscles (68% of responses) and lid speculum insertion (28%).

Conclusion: MACBell was 1.74 MACs of sevoflurane. A high concentration of sevoflurane is required for EUA eyes to prevent ocular movement. The most powerful stimulus during EUA eyes in children was traction on the eye muscles, followed by the insertion of the lid speculum. Administering other anaesthetic agents prior to the stimuli causing Bell's phenomenon should be considered to reduce sevoflurane requirements.

Keywords: up-and-down procedure, paediatric, eye, examination under anaesthesia, sevoflurane

Introduction

In children, examination of the eye involving uncomfortable instrumentation usually necessitates general anaesthesia. This facilitates relaxed extrinsic ocular muscles rendering the eyes immobile and in the central position.

In the 1920s, Arthur Guedel described the eye movements that occur as anaesthesia with ether deepens.[1] During stage 2 (excitement phase), muscular activity and eyeball movements increase. Entering stage 3 (surgical stage), however, muscular resistance to forced eye opening ceases. As anaesthesia deepens in stage 3, from plane I to II, eyeball activity abates and assumes a neutral position (Figure 1).[2] However, ocular stimulation may still cause upwards eyeball rotation (Bell's phenomenon), which is prevented by deeper planes of anaesthesia.[3]

Sir Charles Bell initially described Bell's phenomenon (BellP), in 1823, in a girl who could not close her eyes due to scar tissue. Attempted closure of her eyes was accompanied by an upward rotation of the eyes. He described this as a protective reflex, since this movement protected the eye from injury and promoted moistening of the cornea.[4] This phenomenon is also observed in most normal adults either in bilateral voluntary eyelid closure against resistance or in voluntary, but not spontaneous, blinking.[5] The presence of this reflex is ascertained before ptosis surgery since the absence of this reflex increases the risk of postoperative exposure keratopathy.[6] Premature neonates with brainstem immaturity exhibit this reflex less frequently, probably due to a lack of interaction between the facial nerve nucleus in the pons and the oculomotor nuclear complex in the midbrain.[7] Brain areas associated with voluntary eye movements are not involved.[8]

BellP may compromise ophthalmological surgical procedures (e.g. cataract extraction and squint surgery). Traction or stay sutures may be used to bring the deviated eyeball to a central position but may injure the eye. The anaesthetist may be requested to administer a neuromuscular blocking agent, although most cases resolve with deepening anaesthesia – albeit at the cost of increased procedure time.[3,9,10]

Paediatric ophthalmological examination under anaesthesia (EUA eyes) is usually performed using sevoflurane. The inspired concentration of sevoflurane is determined by the vapouriser dial setting. Apart from dial settings, several factors affect inspiratory and, consequently, end-tidal anaesthetic agent (ETAA) concentrations. These factors include type of anaesthetic system, fresh gas flow rate and duration of anaesthesia. ETAA represents alveolar vapour concentration and is regarded as close to brain (the biophase) concentration; it can be monitored and adjusted according to anaesthetic needs using the dial setting.

The minimum alveolar concentration (MAC) of an inhalational agent is a measure of its potency and varies according to environmental factors (e.g. atmospheric pressure) and patient factors (e.g. age). One MAC of an inhalational agent is the concentration at which 50% of the population will not move in response to a surgical stimulus during maintenance of anaesthesia at one atmospheric pressure. Modern anaesthetic machines calculate the effect of these variables and display the adjusted MAC of an agent according to the ETAA. The MAC required to reduce BellP increases with age in infants born at full term, but decreases with increasing prematurity.[11,12]

The researchers (GL and JdeB) noted that one MAC of sevoflurane was frequently inadequate to prevent eye movements for EUA eyes in children. A literature search for the optimal MAC to prevent BellP in children having an EUA only yielded the study by Yu et al.[12] in which preterm neonates required approximately one MAC of sevoflurane to prevent BellP. As prematurity reduces the occurrence of BellP, these results cannot predict the MAC needed to prevent BellP occurring in older babies and children.[7,11]

This study, therefore, aimed to establish the MAC multiple or submultiple of sevoflurane at which BellP was prevented during an EUA eyes in children. This will enable anaesthetists to use the appropriate dose for this procedure, avoiding both underdosing, which results in the occurrence of eye movements, and overdosing, which is associated with delayed emergence, prolonged procedure time and cardiorespiratory depression.

The study was done using the up-and-down procedure method, as this is frequently used in anaesthesia research when elucidating an appropriate dose.[13] As a secondary objective, the researchers investigated which of the stimuli occurring during an EUA elicited BellP, so that the anaesthetist will know at which stage of the procedure the anaesthesia should be at the deepest levels.

Methods

Approval to conduct the research was obtained from the local institutional ethics committee. Parents provided written informed consent and children gave assent where applicable. Data collection was performed in the ophthalmology theatre, Universitas Annex Hospital, Bloemfontein, South Africa. The same anaesthetic equipment was used throughout the study, including a sevoflurane vapouriser (TEC 5), a Datex Ohmeda anaesthetic machine (S/5 Datex Ohmeda Inc., Madison WI, USA) fitted with an M-CAiOV module for anaesthetic agent analysis and a paediatric breathing system.

A sequential up-and-down procedure was used to determine the MAC of sevoflurane at which 50% of patients did not elicit BellP on ocular stimulation (ED50), and was termed MACBell.

Children aged 1 month to 10 years presenting for EUA eyes during the study period (19 May to 31 August 2015) were included in this study. However, patients were excluded if they had a relevant co-morbid condition influencing the anaesthetic dose required or Bell's response. These included cardiac, neurological, muscular, hepatic and renal system disorders, obesity, or children who received medication with neurological effects. Children who pre- or intra-operatively received sedative, analgesic or anaesthetic agents, except sevoflurane and eye drops for ocular mydriasis, were also excluded.

Anaesthetic procedure

Anaesthesia was administered to all patients by the same anaesthetist (JdeB). Patients were fasted six hours for solids and two hours for clear fluids before surgery. No premedication was given.

Inhalational induction was performed with 8% sevoflurane in a 50% oxygen/air mixture and an intravenous line was inserted. After ascertaining jaw relaxation, a laryngeal mask airway (LMA) was inserted. Mechanical ventilation was started using synchronous intermittent mechanical ventilation with pressure support. Tidal volume, frequency and pressure support were adjusted to achieve an end-tidal carbon dioxide ($ETCO_2$) between 35 mmHg and 40 mmHg. Sevoflurane was reduced to a preselected MAC value for anaesthesia maintenance, in 40% oxygen/air, until a steady-state period of three minutes was achieved. The scrub sister then cleaned and draped the eyes. Before starting the EUA, inspired sevoflurane was adjusted to keep the predefined MAC stable for a further three minutes, with the eyeball in a neutral gaze position. Thereafter, the ophthalmologist started the EUA.

A MAC of 1.0 was chosen for the first patient. The preselected MAC each successive patient received was determined from the response of the previous patient and was either decreased by 0.1% if no Bell's response was elicited or increased by 0.1% if a Bell's response occurred. The stimulus responsible for a response was recorded as follows: (i) lid speculum insertion; (ii) eye muscles traction; (iii) scleral indentation; or (iv) other. When an eye response occurred, it was graded as either minimal (upward eye movement, centre of cornea remaining visible) or full (upward eye rotation, centre of cornea not visible).

Monitoring consisted of electrocardiography, pulse oximetry, non-invasive blood pressure, and inspired and expired concentration of carbon dioxide, oxygen and sevoflurane. The gas analysis monitor was preprogrammed to display the MAC multiples of sevoflurane, calculated from the end-tidal sevoflurane concentration (ETsevo), adjusted for altitude and each patient's weight and age. Temperature was monitored by a nasopharyngeal probe and a forced air-warming device maintained normothermia. The anaesthetist, in conjunction with the examining ophthalmologist, recorded the patient's, age, weight, gender, temperature, seniority of the ophthalmologist, MAC (as calculated by the anaesthetic machine from ETsevo), eye response during the examination, grading of eye response and stimulus responsible.

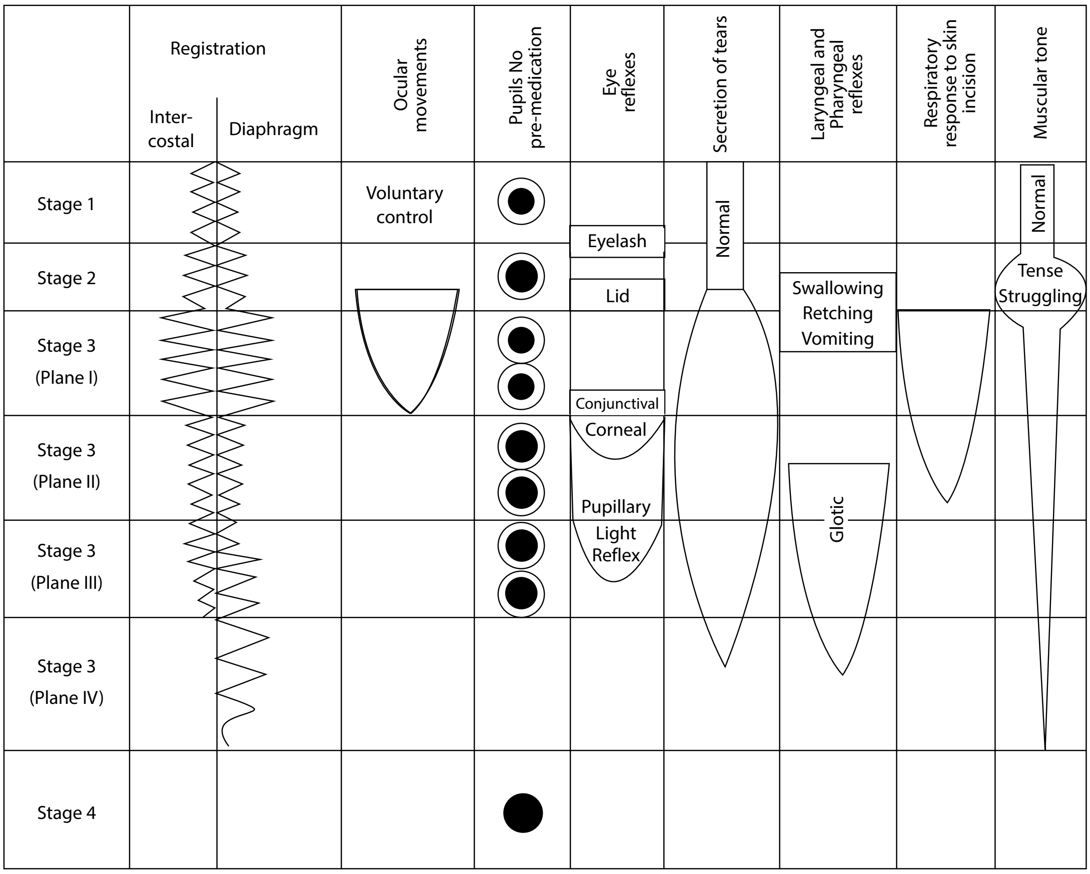

Figure 1: Adapted version of Guedel's 1927 description of eye signs according to stages and plane (stratum) of anaesthesia. Column 3 shows eyeball movements to be active in stage 2, with acquiescence during stratum (plane) I of stage 3

Statistical analysis

Descriptive statistics, namely medians, percentiles and interquartiles (IQR), were calculated for non-normally distributed continuous data. For normally distributed data, the means and standard deviations (SDs) were calculated. The MAC and weight variables were normally distributed. Frequencies and percentages were calculated for categorical data. A sequential up-and-down experimental method was used to determine the MAC of sevoflurane at which 50% of patients did not elicit BellP on ocular stimulation (ED50) and was termed MACBell. The ED50 (MACBell) was calculated from the mean of the midpoint concentrations of crossover pairs. Analysis was done by the Department of Biostatistics, Faculty of Health Sciences, University of the Free State. Probit regression analysis was performed using the MedCalc statistical software.

Table I: Age, weight, intra-operative temperature and MAC* values (n = 43)

Variable	Median (IQR)	Range
Age (months)	37.0 (15–58)	2–120
Temperature (°C)	36.2 (36.0–36.4)	34.9–37.1
	Mean (SD)	
Weight (kg)	13.7 (4.6)	4.8–25.0
MAC	1.7 (0.3)	1.0–2.2

*Minimum alveolar concentration

Results

Forty-nine patients were recruited for this study but six patients were later excluded for not meeting the inclusion criteria. Data of the remaining 43 patients were analysed.

Patients were aged between 2 and 120 months (median 37.0 months). Slightly more than half of the patients (n = 17; 53.1%) were female. The median nasopharyngeal temperature was 36.2 °C and the mean weight was 13.8 kg (Table I). The majority of procedures (n = 39; 90.7%) were performed by an ophthalmology registrar and the remainder by a consultant.

The up-down progression is shown in Figure 2. Initially, four children had a Bell's response from one MAC up to 1.4 MAC. The highest MAC at which a response still occurred was 2.1 MAC. A Bell's response occurred in 25 (58.1%) patients, with no Bell's response in 18 (41.9%) patients. In 18 (72.0%) of the 25 patients, the response was minimal, while a full response occurred in seven (28.0%) patients. The most common stimulus (n = 17; 68%) responsible for Bell's response was traction of eye muscles, followed by eye speculum insertion (n = 7; 28%). Only one patient responded to scleral indentation.

There were 14 crossover pairs (consecutive patients with opposite Bell's responses). The turning point estimator, that is, the mean of the midpoint MAC multiple of these crossovers, was 1.74 (SD 0.194). Probit regression analysis gave a population ED50 of 1.81 MAC (95% confidence interval [CI] 1.63–2.14) (Figure 3).

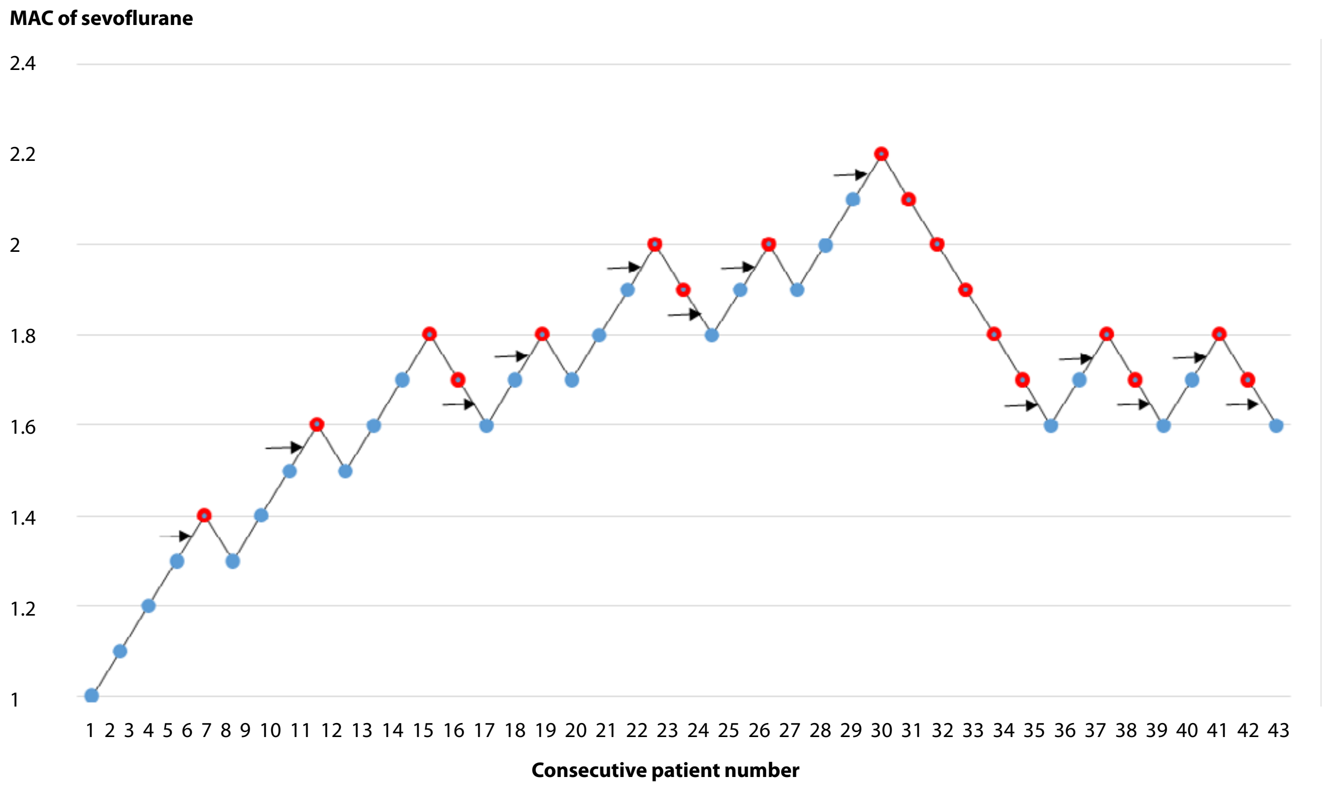

Figure 2: MAC of sevoflurane for consecutive patients. The blue markers indicate when a Bell's response occurred, and the following patient was given a MAC of sevoflurane 0.1% more. The red markers indicate when no Bell's response occurred and the following patient received 0.1% less. Arrows indicate midpoint of crossover pairs[2]

Discussion

The main finding of this study was that MACBell is equal to 1.74 MAC, as determined by the turning point estimator, and 1.81 MAC using probit regression analysis. The most common stimulus causing a Bell's response was traction on eye muscles, followed by lid speculum insertion. Reaction to scleral insertion only evoked a response in one patient.

The study used the up-and-down method (UDM), whereby the medication dose given to a participant is altered according to the response of the previous participant. UDM requires the effect of the medication to be swiftly apparent, characteristic of many anaesthetic drugs, rendering UDM a useful technique to conduct dose-finding studies in anaesthesia.[13] Several studies to determine the MAC of inhalational agents at other thresholds, for example, MAC-awake or MAC to insert or remove a supraglottic airway, have also used this method.[14]

The required sample size cannot be accurately predicted using UDM, since the data distribution is unknown before performing the study. Therefore, rather than deciding on a sample size, a time interval is set during which the study is performed. Typically, UDM does not require a large sample size, typically between 20–40 participants, with a minimum of six crossover pairs.[15] These recommendations were exceeded in this study, with a sample size of 43 patients and 14 crossover pairs.

When employing the UDM, the turning point estimator is commonly used and considered reliable in anaesthesia studies to determine the ED50s. This result is therefore used in further calculations discussing this study. Probit regression analysis for up-and-down studies' data has been used in order to obtain confidence intervals and an ED95. However, inherent flaws with "traditional" UDM, particularly with regard to accuracy at upper and lower quartiles, suggest that unless the UDM is modified (e.g. to a biased coin design), results of probit regression analysis may be flawed, particularly when calculating the ED95.[13] The utility of the ED95 seems logical, since this dose ensures that most, rather than only half, of patients do not respond to the stimulus tested. However, owing to the steep dose-response relationship in the region of the ED50 for most inhalational agents, and their relative safety, it is considered acceptable to determine only the ED50 and then "give a little more".[16]

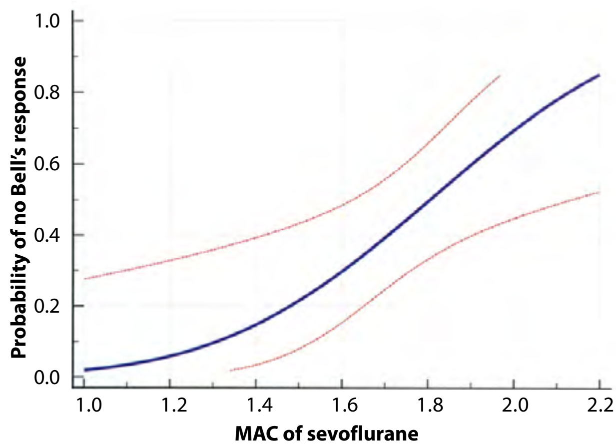

Figure 3: Dose response curve plotted from probit regression analysis for the probability of Bell's phenomenon occurring at different MACs of sevoflurane. The dotted lines indicate confidence intervals

A shortcoming of the UDM[15] is that by starting at a lower dose than the MACBell, the ED50 may be slightly biased towards a lower estimate. In this study, this effect was offset by the relatively large sample size. To reduce the effect of interindividual variability, an up-down study requires at least six crossovers. The 14 crossover pairs in this study limited inaccuracies related to the potential problem of interindividual variability. Furthermore, this is the result from only one experiment; a simulation study on UDM demonstrated that the accuracy of this result may only be in the order of 10%, to more than 25%, higher or lower.[15] Therefore, MACBell may vary from less than 1.74 – 0.435 = 1.3 MAC to more than 1.74 + 0.435 = 2.2 MAC.

Accuracy of the anaesthetic gas analyser may contribute to the inaccuracy of the results. According to manufacturer specifications, the accuracy of sevoflurane measurement in this study was ± (0.15 vol% + 5% of reading).

Interobserver variation in data recording was minimised by limiting data collection to one researcher (JdeB). However, during UDM investigation, the observer is not blinded to results, which may give rise to observer bias. The examining ophthalmologist could not be limited to a single person and variation regarding strength of stimuli during the EUA eyes could have occurred.

Age has a major impact on MAC as it declines with age.[17] Five of the study subjects were younger than one year of age. The majority of subjects were between the ages of one to four years. According to the findings of Lerman et al.,[18] the MAC of sevoflurane for babies between one and six months is approximately 3.2%, while it is approximately 2.5% for children between one and four years.

The anaesthetic gas analyser displays an age- and altitude-corrected MAC value. Therefore, MACBell was recorded, not the ETAA at which BellP was prevented. To compensate for age-related differences, the anaesthesia machine was programmed with the patient's age in order to calculate the MAC, rather than only record the end-tidal concentration at which BellP occurred. Regarding age correction, the monitor is programmed with the Eger II formula.[19]

According to Eger II, MAC normalised to the age of 40 years (MAC 40) for anaesthetic vapours, is given by the following formula:

$$\mathbf{MAC_{40} = 1.32 \times 10^{(-0.00303 \times Age)}}$$

This formula gives MAC values similar to values demonstrated by Lerman et al.[18]

The machine was calibrated for an altitude of 1 400 meters above sea level. The concentration of anaesthetic agent is derived from its partial pressure and instead of using MAC, it has been argued that a more appropriate term to use is "minimum alveolar partial pressure" (MAPP), which reflects more accurately the effect of altitude, making altitude-corrected MAC unnecessary.[20]

The potential inaccuracies of this study's results are not major and demonstrate that MACBell is considerably higher than the MAC of sevoflurane required for surgery which may be unexpected for anaesthetists inexperienced in giving general anaesthesia for EUA eyes. As the procedure is without surgical incision, anaesthetists may not expect that a deep level of inhalational anaesthesia is required to prevent eye movements.

MAC is reduced by sedative premedication and intraoperative use of opiates. Since EUA eyes is usually a day-case procedure, these agents are frequently omitted to facilitate emergence and discharge home. Withholding preoperative sedation may contribute to preoperative anxiety, which increases anaesthetic requirements, which itself can lead to a higher intraoperative MAC being required. These factors result in the inhalational agent often being the sole anaesthetic medication given for EUA eyes, with a higher MAC required to obtain an appropriate depth of anaesthesia, compared to other surgical procedures on eyes.

The required depth of anaesthesia for EUA eyes is at least plane II of stage 3 of Guedel's levels of anaesthesia. Guedel considered plane I optimal for surgery, as here the body movements cease.[1] However, this plane is characterised by eccentric eyeball movements and increasing depth to plane II, characterised by central pupils, is required for EUA eyes. Yu et al.[21] investigated preterm neonates undergoing EUA eyes and found central pupils a better sign than absence of body movements to indicate an adequate depth of anaesthesia. For central pupils, the average inspired concentration of sevoflurane of 3.5% was 0.5% higher than when body movements ceased.[21]

Preterm neonates frequently undergo EUA eyes to screen for retinopathy of prematurity and, in these patients, pain during insertion of the lid speculum can be attenuated with topical anaesthetic eye drops.[22] Similarly, topical anaesthesia has been shown to reduce BellP in awake adults.[23] Therefore, it can be speculated that the BellP that occurred in 28% of patients during insertion of the lid speculum might have been prevented by instilling topical anaesthesia in conjunction with general anaesthesia. This could decrease the MACBell.

The order of the various steps of the EUA eyes, and thereby the order in which the eyes were subjected to the various noxious stimuli, was not recorded in this study, although in practice, the lid speculum insertion is generally first. The order of the steps may, however, have varied according to the ophthalmologist or presenting complaint of the child. In this study, the most powerful stimulus was forced traction of the eye muscles, while scleral indentation evoked a Bell's response in only one patient. Consideration should therefore be given to the sequence of examination. Traction on eye muscles should be performed last to prevent a Bell's response from interfering with the rest of the examination. The sevoflurane dose can be increased to 1.8 MAC (MACBell) before traction on the eye muscles to prevent this reflexive eye movement, or a low dose of propofol can be given to transiently deepen the anaesthesia.

Another ocular reflex, which results from non-ocular noxious stimuli, is pupillary dilatation. This reflex is controlled by the autonomic nervous system and as with BellP, also requires a considerably higher MAC (MACpup) to prevent than surgical MAC. Bourgeois et al.[24] found MACpup for sevoflurane to be 4.8% in prepubertal children and 3.4% in postpubertal children, and the value for MACBAR, the amount of sevoflurane required to prevent autonomic cardiovascular responses to pain, is similar to MACpup.[24] These results concur with this study as both demonstrated that substantially different amounts of sevoflurane are required to reduce responses to stimuli, in different areas of the central nervous system. In addition, MACpup was remarkably close to MACBell. For prepubertal children, one MAC of sevoflurane is approximately 2.5%, therefore, one MACBell would be 1.74 × 2.5% = 4.4% (the Parisian hospital of the Bourgeois et al. study is approximately at sea level).[24] Alternatively, MACpup can be expressed as 4.8/2.5 = 1.9 × MAC, which is similar to the finding in this study that MACBell = 1.74 × MAC.

MACBell (1.74 MAC) is a high dose of sevoflurane. Side-effects can result from this, and Bourgeois et al.[24] noted epileptiform movements in two patients when concentrations exceeding 5% were used. Since high doses of volatile agents, including sevoflurane, decrease intraocular pressure, intraocular pressure measurements may be unreliable.[25] However, as the potency of different anaesthetic vapours is compared using MAC, a different inhalational agent such as isoflurane, could probably be used for maintenance during EUA eyes, at a similar MACBell to prevent BellP. Although this is at the cost of the side-effects from high doses specific to the alternative agent.

Conclusion

The MAC of sevoflurane needed to prevent BellP occurring during an EUA eyes in children was 1.74 × MAC (MACBell). This is a relatively high concentration, so co-administration of other anaesthetic agents should be considered to prevent this reflex at a lower concentration of sevoflurane, particularly prior to the common noxious stimuli associated with this procedure of traction on the eye muscles and insertion of the lid speculum.

Acknowledgements

Dr Edwin Turton and Prof. Johann Diedericks, Department of Anaesthesiology, University of the Free State, for professional advice received; Prof. Carl Lombard, South African Medical Research Council, for advice and assistance with the probit regression; and Dr Daleen Struwig, medical writer/editor, University of the Free State, for technical and editorial preparation of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding was required.

Ethical approval

Approval to conduct the research was obtained from the University of the Free State Ethics Committee (ECUFS NR. 59/2014).

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