

*****Copyright Notice*****

No further reproduction or distribution of this copy is permitted by electronic transmission or any other means.

The user should review the copyright notice on the following scanned image(s) contained in the original work from which this electronic copy was made.

Section 108: United States Copyright Law

The copyright law of the United States [Title 17, United States Code] governs the making of photocopies or other reproductions of copyrighted materials.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the reproduction is not to be used for any purpose other than private study, scholarship, or research. If a user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use," that use may be liable for copyright infringement.

This institution reserves the right to refuse to accept a copying order if, in its judgement, fulfillment of the order would involve violation of copyright law. No further reproduction and distribution of this copy is permitted by transmission or any other means.

4518215

Request # 4518215

OCT 01, 2001

Email (PDF) To: rmcueto@aol.com

Rebecca Cueto
10 Madonna Court
Belleville, IL 62223

LOANSOME DOC: Journal Copy Affiliated

Title: British journal of anaesthesia.
Title Abbrev: Br J Anaesth
Citation: 2001 Apr;86(4):519-22
Article: Ocular microtremor: a tool for measuring depth of
Author: Bojanic S; Simpson T; Bolger C;
NLM Unique ID: 0372541 ISSN: 0007-0912
PubMed UI: 11573625
Holding: Library reports holding vol/yr
Need By: N/A
DOCLINE: Yes
Patron UserID: RMCUETO@AOL.COM
Phone: 1.618.235-8609
Comments:
Received: 01-Oct-01 01:59 PM
Lender: Saint Louis University/ St. Louis/ MO USA (MOUSTL)

This material may be protected by copyright law (TITLE 17,U.S. CODE)

Ocular microtremor: a tool for measuring depth of anaesthesia?

S. Bojanic^{1*}, T. Simpson¹ and C. Bolger²

¹Department of Neurosurgery and ²Department of Anaesthetics, Frenchay Hospital, Bristol, UK

*Corresponding author: Department of Neurosurgery, The Radcliffe Infirmary, Woodstock Road, Oxford OX2 1HE, UK

Ocular microtremor (OMT) is a fine high frequency tremor of the eyes caused by extra-ocular muscle activity stimulated by impulses emanating in the brain stem. Several studies have shown that the frequency of this tremor is reduced in patients whose consciousness is reduced by anaesthesia or head injury. Therefore, OMT may possibly be used to determine depth of anaesthesia. Twenty-two unpre-medicated subjects undergoing surgery with general anaesthesia were studied. OMT activity was measured at admission using the open eye piezoelectric strain gauge technique. Anaesthesia was induced with propofol using a target controlled infusion delivery system (Diprifusor™). OMT activity was then recorded at predicted plasma propofol concentrations of 1, 2, 3 and 5 $\mu\text{g ml}^{-1}$. The patient's level of consciousness (response to command or stimulation) was assessed after each OMT measurement. OMT activity was reduced progressively at predicted plasma concentrations of propofol of 1 and 2 $\mu\text{g ml}^{-1}$ and then plateaued between 3 and 5 $\mu\text{g ml}^{-1}$. There was a significant difference between the last awake OMT recording and the first recording at loss of consciousness ($P < 0.001$). OMT recording holds promise as a practical indicator of the depth of anaesthesia.

Br J Anaesth 2001; **86**: 519–22

Keywords: anaesthesia, depth; equipment, piezoelectric strain gauge; anaesthetics i.v., propofol

Accepted for publication: November 17, 2000

At present the anaesthetist's main source of information on the depth of anaesthesia is the patients somatic and autonomic response to surgical stimuli. These responses are modified by neuromuscular block drugs and drugs affecting the autonomic nervous system. The presence or absence of these responses does not, however, correlate with conscious awareness¹ and they are inadequate indicators of a satisfactory depth of anaesthesia; therefore, the search for an adequate measure of the depth of anaesthesia continues.

Ocular microtremor (OMT) is a small high frequency tremor of the eyes present in all individuals. This tremor is caused by high frequency extra-ocular muscle stimulation which originates in the oculomotor area of the brainstem.² The oculomotor neurons are 'embedded in the reticular formation' of the brainstem.³ However, neural activity from other areas outside of the brainstem impinge on the oculomotor nuclei. These include the frontal eye fields (areas 6 and 8),⁴ the inferior parietal cortex (area 7)⁵ and the cerebellum.⁶ The OMT signal appears as an irregular oscillatory movement with intermittent burst-like components. The peak-to-peak rotation involves a displacement

of the surface of the eye of between about 150 and 2000 nm.⁷ The mean OMT peak count frequency in the normal population is 84 Hz (SD 6).⁸

The initial interest in OMT was stimulated by its purported role in the visual process, as part of the dynamic theories of vision.⁹ More recently, the appreciation of OMT as a primarily neurological phenomenon has stimulated interest in its clinical applications.¹ Several studies have already shown that the frequency of this tremor is reduced in patients whose level of consciousness has been affected by head injury or anaesthesia.^{10–12} Both Coakley¹³ and Bolger¹² studied the effect of thiopental on OMT activity. Both studies showed a reduction in the high frequency components of OMT activity with a shift of the spectrum to the left, although the number of subjects studied was small. However, in the case of Coakley,¹³ a number of agents were used including neuromuscular block.

It would therefore seem possible that OMT recordings could be used to determine depth of anaesthesia. The present study was undertaken to show the effect of general anaesthesia induced with propofol on OMT. Assessment

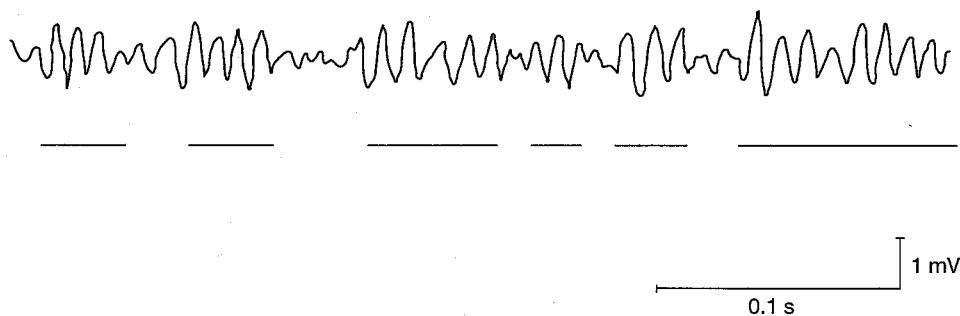


Fig 1 Example of a normal OMT recording in an alert individual. 'Bursts' are underlined and the period between the bursts is termed the baseline.

of the changes in OMT in the awake and unconscious state was also studied independent of the dose of propofol.

Methods

Subjects

After gaining local Ethics Committee approval and informed consent, 22 neurologically normal subjects undergoing general anaesthesia for general surgical procedures were studied. There were nine females and 13 males. The age range of the subjects was 38–71 yr. Subjects taking CNS depressant medication were excluded from the study. No pre-medication or opioid analgesia was given.

Recording session

OMT recordings were taken pre-operatively on the ward at admission using the piezoelectric strain gauge technique (baseline recording).¹⁴ This technique has been described in detail elsewhere⁷ and provides a reliable estimate of OMT activity.¹⁵ Briefly, the piezoelectric transducer is mounted in a Perspex rod and the protruding end is coated with rubber. The subject lies supine looking straight ahead wearing a headset. During anaesthesia this eye position may change but studies by Bolger¹² have shown there is no significant overall variation in OMT mean peak count frequency with eye deviation. The subject's eyelids are taped apart and the scleral surface is anaesthetized with 0.5% hydroxymethacaine hydrochloride. The piezoelectric probe is mounted in the headset and lowered so the rubber tip is just touching the scleral surface. Probe placement is judged by visual inspection and by listening to the signal being recorded using audiocassette headphones. The signal is processed in a conditioning unit and then recorded on an audiocassette recorder. A recording of between 30 and 60 s was taken.¹⁵ Analysis is performed on an IBM compatible PC with a special OMT processing package. An example of a normal OMT recording from an alert individual is shown in Figure 1.

Anaesthetic technique

The patients were monitored in the anaesthetic room with non-invasive arterial pressure, ECG and peripheral oxygen

saturation. The only drug administered during the duration of the study was propofol, which was infused using a target controlled infusion system (Diprifusor™). All patients received supplemental oxygen via nasal cannulae at 4 litre min^{-1} . The Diprifusor™ TCI system consists of a micro-processor driven infusion pump (Graseby 3500), controlling the infusion rate of propofol based on a three compartmental pharmacokinetic model, a specific set of pharmacokinetic parameters¹⁶ and algorithms for infusion control. The initial bolus required to reach the predicted blood concentration is given at 1200 ml min^{-1} . Thereafter the infusion rate is controlled to maintain the selected target concentration in the blood allowing for redistribution and elimination.

However, the model assumes immediate mixing in blood and takes no account of the delay required to achieve equilibration in the brain. Thus, a delay occurs between the time when a Diprifusor™ system indicates a target concentration has been reached and the time of maximum pharmacodynamic effect. Using a computer simulated model based on the Marsh pharmacokinetic parameters, it was clear that a period of 5 min would be long enough to allow steady state conditions to occur between the blood and effector site compartments.

The TCI infusion was started at a concentration of 1 $\mu\text{g ml}^{-1}$ predicted blood propofol concentration and after a period of 5 min, allowing for equilibration, OMT activity was recorded and then the patient's level of consciousness was assessed. They were deemed to have lost consciousness if there was loss of response to verbal command and no eyelash reflex present.

The reading taken before this point, at the lower predicted blood propofol concentration, was termed the 'last awake' recording. The process was then repeated at predicted blood propofol concentrations of 2, 3 and 5 $\mu\text{g ml}^{-1}$. When all the required recordings had been made either the patient's trachea was intubated or a laryngeal mask inserted and anaesthesia maintained appropriate for the intended surgery.

Analysis of records

Each subject had a baseline OMT record and then between two and four further recordings at each different predicted plasma propofol concentration. OMT recording was diffi-

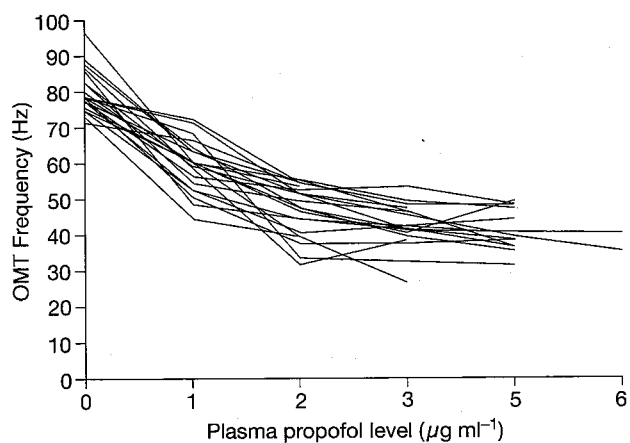


Fig 2 OMT (Hz) mean peak count frequency at different predicted plasma propofol concentrations.

cult in some subjects at different levels of awareness because of coughing or sneezing. Records were analysed using peak count analysis of dominant frequency. Comparison of peak count variables was performed using the Wilcoxon matched-pairs signed-ranks test.

Results

The mean peak count frequency of subjects before administration of propofol was 80.55 (SD 5.89) Hz and this fell to a mean frequency of 43.81 (7.33) Hz at loss of consciousness ($P < 0.001$). The mean peak count was reduced to a value of 60.05 (7.12) Hz when the plasma propofol concentration was $1 \mu\text{g ml}^{-1}$ ($P < 0.001$) and further reduced to a value of 47.77 (7.52) Hz at concentrations of $2 \mu\text{g ml}^{-1}$ ($P < 0.001$). This reduction plateaued between concentrations of 3 and $5 \mu\text{g ml}^{-1}$ as shown in Figure 2. There was a significant difference between the mean peak count frequency of the last awake reading (mean 53.67 (7.47) Hz) and the first OMT recording at loss of consciousness (mean 43.81 (7.33) Hz), $P < 0.001$. This is illustrated in Table 1. Ten subjects lost consciousness at a predicted plasma propofol concentration of $2 \mu\text{g ml}^{-1}$. The other 11 subjects lost consciousness at concentrations of $3 \mu\text{g ml}^{-1}$; in one subject readings were abandoned at $2 \mu\text{g ml}^{-1}$ because of coughing. However, there was no significant difference between the peak count frequency at loss of consciousness and the readings taken thereafter ($P < 0.83$ for $2 \mu\text{g ml}^{-1}$ and $P < 0.12$ for $3 \mu\text{g ml}^{-1}$ respectively) (Fig. 3).

Discussion

Plomley was the first, in 1847, to define depth of anaesthesia.¹⁷ He described three stages: intoxication, excitement and deeper levels of narcosis. Since then, many descriptions of the depth of anaesthesia have been published including Guedel's¹⁸ classic description of the clinical signs of ether anaesthesia. A variety of clinical monitors has been tested in

Table 1 Ocular microtremor (OMT Hz) mean peak count frequency at last awake and at loss of consciousness

Subject	Age	Last awake OMT (Hz) reading	First OMT (Hz) reading at loss of consciousness
1	52	61	54
2	53	52	48
3	45	59	32
4	63	73	55
5	51	40	27
6	65	55	50
7	57	45	40
8	44	53	45
9	71	53	41
10	71	49	45
11	56	47	41
12	49	51	38
13	70	53	54
14	47	69	34
15	45	52	46
16	68	48	40
17	36	52	42
18	53	56	50
19	63	48	42
20	64	55	49
21	62	56	47
Mean	57	53.67	43.81
SD	10	7.47	7.33
P		0.001	

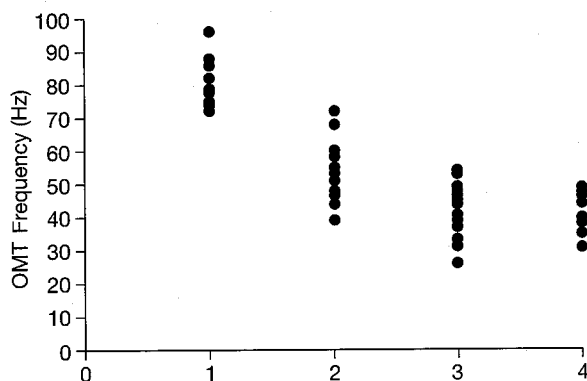


Fig 3 OMT (Hz) mean peak count frequency of the subjects studied at baseline (1), at the last awake (2), at first loss of consciousness (3) and when deeply anaesthetized (4).

order to assess depth of anaesthesia, including autonomic signs, EEG, isolated forearm technique, auditory evoked responses, oesophageal contractility and surface EMG, but each has its limitations.¹⁹

Anaesthetic agents appear to have a predilection for the reticular activating system even if they do also act more diffusely in the brain. Recent studies by Rampil and colleagues²⁰ in rats support the hypothesis that anaesthetics have a primary action within the midbrain or lower. OMT is a high frequency tremor caused by impulses emanating from the oculomotor area in the brain stem. The oculomotor neurons are embedded in the reticular activating system.³ Therefore, we would expect that agents affecting this area would also influence OMT activity.

This study confirms that ocular microtremor activity is affected by propofol. Previous studies by Coakley¹³ and Bolger¹² also showed that OMT activity is affected by thiopental. In the study by Coakley¹³ a number of agents were used, including neuromuscular block, and in all but two cases recordings were made with a closed eye transducer. The report by Bolger¹² studied only five patients. However, neither study gave details of induction times or assessment of levels of awareness.

This study has shown that the mean OMT peak count frequency is reduced progressively at predicted plasma propofol concentrations of 1 and 2 $\mu\text{g ml}^{-1}$ and then plateaued between 3 and 5 $\mu\text{g ml}^{-1}$. Significantly, in this study no subject was conscious at predicted plasma concentrations of 3 $\mu\text{g ml}^{-1}$ and at these concentrations none of the subjects had a peak count frequency above 55 Hz. After loss of consciousness, OMT activity remained below this level (55 Hz). There was no significant difference between mean peak count frequency at loss of consciousness and readings taken thereafter, even at increasing predicted plasma propofol concentrations. There is a significant difference between the last awake OMT recording and the first recording taken at loss of consciousness ($P < 0.001$). The actual frequency at which subjects lost consciousness, however, was very variable—ranging from 27 to 55 Hz. It may be that a better predictor of the actual mean peak count frequency at which there was loss of consciousness in each subject would be to calculate a percentage of the baseline frequency for each subject. In this study, if we set a value of 45% of the baseline frequency for each subject, then 17 out of the 21 subjects had lost consciousness at this predicted OMT frequency (81%).

These results are encouraging and indicate that in the subjects studied OMT activity varies with awareness. With regards to depth of anaesthesia, we could postulate that any increase in OMT above the mean peak count frequency noted at loss of consciousness could indicate lightening of anaesthetic depth. It is interesting that studies of the effect of propofol on the auditory evoked response have shown no significant effect on the amplitude and latency of the brain stem waves.²¹ In our study there is a clear effect on OMT, which has been shown to be an indicator of brain stem function.¹ However, if this is to be used in the clinical setting, more information is required on the effect of other agents on OMT activity such as opiates, neuromuscular block agents and, in particular, surgical stimulus. For continuous monitoring during anaesthesia, recordings will need to be made through the closed eyelid. These points are currently being investigated.

Acknowledgements

The authors wish to thank the Royal College of Surgeons of England for the Lang Research Fellowship, which funded this study, and Dr A. Minara for his advice in preparing this manuscript.

References

- 1 Hugg CC. Lipid solubility, pharmacokinetics and the EEG; are you better off today than you were four years ago? *Anesthesiology* 1985; **62**: 221–6
- 2 Coakley D. *Minute Eye Movement and Brain Stem Function*. Florida: CRC Press, 1983; 49–56
- 3 Carpenter RHS. *Movements of the Eyes*. Pion: London, 1988
- 4 Leichnetz GR, Spencer RF, Smith DJ. Cortical projection to nuclei adjacent to the oculomotor complex in the medial diencephalic tegmentum in the monkey. *J Comp Neurol* 1984; **228**: 359–87
- 5 Sakata H, Shibutani H, Kawanok S. Spatial properties of visual fixation neurones in posterior parietal association cortex of the monkey. *J Neurophys* 1980; **43**: 1654–72
- 6 Precht W. Cerebellar influences of eye movements. In: Lennerstrand G, Bach P, Rita Y, eds. *Basic Mechanism of Ocular Motility*. Oxford: Pergamon Press, 1978; 261–80
- 7 Sheahan NF, Coakley D, Hegarty F, Bolger C, Malone J. Ocular microtremor measurement system: design and performance. *Med Biol Eng Comp* 1993; **31**: 205–12
- 8 Bolger C, Bojanic S, Sheahan N, Coakley D, Malone J. Dominant frequency content of ocular microtremor in normal subjects. *Vision Res* 1999; **39**: 1911–5
- 9 Ratcliff F. Role of physiological nystagmus in monocular activity. *J Exp Psychol* 1952; **43**: 163–72
- 10 Shakhnovich AR, Thomas JG, Dubova SB, Milovamova LS. The prognosis of the outcome of comatose states. *Resuscitation* 1980; **8**: 243–55
- 11 Golda V, Petr R. OMT and the level of vigilance. *Sb Ved Pr Lek Fak Karlovy Univer Hvada Kralow* 1981; **24**: 77
- 12 Bolger C. *Ocular microtremor: reliability of measurement, physiological variation and neurogenic origin*. PhD Thesis 1994, Trinity College Dublin, Ireland
- 13 Coakley D, Thomas JG, Lunn JN. The effect of anaesthesia on ocular microtremor (abstract). *Br J Anaesthesia* 1981; Proceedings of the Anaesthetic Research Society: 1122–23
- 14 Bengi H, Thomas JG. Three electronic methods for recording ocular tremor. *Med Biol Eng* 1968; **6**: 171–8
- 15 Bolger C, Sheahan N, Coakley D, Malone J. High frequency eye tremor: reliability of measurement. *Clin Physics Physiol Measurement* 1992; **13**: 151–9
- 16 Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model-driven infusion of propofol in children. *Br J Anaesth* 1991; **67**: 41–8
- 17 Plomley F. Operations upon the eye (letter). *Lancet* 1847; **1**: 134
- 18 Guedel AE. *Inhalational Anaesthesia; A Fundamental Guide*. New York: Macmillan, 1937
- 19 Jones GJ. Awareness under anaesthesia. *Anaesthesia Rounds* (21). Oxford: The Medicine Group (Education) Ltd, 1989
- 20 Rampil I, Mason P, Singh H. Anaesthetic potency (MAC) is independent of forebrain structures in the rat. *Anesthesiology* 1993; **78**: 707–12
- 21 Thornton C, Konieczko DM, Knight AB, et al. Effect of propofol on the auditory evoked response and oesophageal contractility. *Br J Anaesth* 1989; **63**: 411–7