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Main Article

Influence of anaesthetic agents on transient evoked otoacoustic emissions and stapedius reflex thresholds

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Abstract

This aim of this study was to determine the effect of anaesthetic agents on stapedius reflex (SR) thresholds and transient evoked otoacoustic emissions (TEOAE). Fifty patients who were scheduled for operation and who had normal hearing were included in the study. All were given midazolam for premedication and propofol for induction. Anaesthesia was maintained in five different ways in each group of 10 patients. Groups I–IV received inhalational anaesthesia: group I received 70 per cent N_2O plus 30 per cent O_2, group II sevoflurane, group III desflurane and group IV halothane. Group V received total intravenous anaesthesia with propofol plus sufentanil. The SR and TEOAE of the patients were measured four times: on the day before surgery (first measurement), after premedication (second measurement), after induction of anaesthesia (third measurement) and during maintenance of anaesthesia (fourth measurement). Midazolam significantly increased ipsilateral and contralateral SR thresholds and decreased TEOAE wave reproducibility. Propofol significantly increased only the SR thresholds. The other anaesthetic agents significantly increased only the contralateral reflex thresholds. Of these, the highest increase was seen after sevoflurane and the lowest after halothane. The changes in TEOAE wave reproducibility due to anaesthetic agents used for maintenance were not significant. We concluded that midazolam premedication may affect audiological evaluation with SR and TEOAE tests, and sevoflurane should not be used when it is necessary to measure SR under general anaesthesia.

Key words: Otoacoustic Emissions, Spontaneous; Reflex, Acoustic; Anaesthetics, General; Halothane; Propofol

Introduction

The stapedius reflex (SR) threshold is of considerable diagnostic significance in otolaryngology,[1,2] being used to evaluate audiological function in both children and adults. It is also an objective method for the assessment of auditory function in children and neonates.[1] Transient evoked otoacoustic emission (TEOAE) has been reported to be very effective in screening applications, particularly in neonates,[3] and measurement of TEOAE is increasingly used as an objective hearing test. Because of lack of cooperation, children may sometimes be tested under sedation or general anaesthesia.[4] Drugs used for general anaesthesia often act on neurotransmitters or neuromodulators, some of which have been shown to be present in the cochlea.[5–7]

During cochlear implantation, the SR is evoked electrically under anaesthesia and is important for assessment of the individual dynamic spectrum of the implanted speech processor.[1] In addition, otoacoustic emissions can be used to monitor cochlear function during acoustic neuroma surgery.[8,9] Therefore, it is necessary to know the effects of anaesthetic agents on SR thresholds and otoacoustic emissions so that more accurate results can be obtained. In this study we aimed to determine the effect of anaesthetic agents on the TEOAE and SR thresholds.

Materials and methods

After approval by the Ethics Committee and informed consent being obtained, 50 patients

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(15 women and 35 men) who were scheduled for operation under general anaesthesia were assigned to this prospective study. Their average age was 31.5 years (range 12–61 years). To participate in the study the patients had to have an anaesthesia score level of I or II according to the American Society of Anesthesiologists (ASA) risk classification,[10] a normal pure tone audiogram (hearing thresholds should be better than 20 dB in the frequency range 250–4000 Hz), a type A tympanogram, a normal SR threshold and positive TEOAE in both ears. For the first measurements, the patients were directed to the ENT Department by an anaesthesiologist, who evaluated them on the day before surgery. In the ENT Department the patients, who were normal according to physical and otoscopic examination, were tested with audiometry, impedance audiometry and TEOAE.

Pure tone audiometry was performed with a clinical audiometer AC 40 (Interacoustics, Assens, Denmark) in a soundproofed room and impedance audiometry with an AZ 7 impedance audiometer (Interacoustics, Assens, Denmark). The acoustic stimulus was applied by a TDH-39P earphone (Telephonics, New York, USA) at 1000 Hz. The frequency of the probe tone was 220 Hz. The stimulus intensity of the acoustic signal was increased in 5 dB increments up to a maximum of 110 dB hearing level (HL), both ipsilaterally and contralaterally. The TEOAE test was performed using the Otodynamic Analyser ILO 88 (Ver. 4.20B) (Otodynamics Ltd, Hatfield, Herts, UK) in a silent room. Rectangular pulses of 80 μsec were used as click stimuli with a peak intensity of 80 ± 5 dB sound pressure level (SPL), and stability was more than 80 per cent. The rejection threshold was less than 50 dB, and the quiet : noise rate was over 50 per cent. Transient responses were averaged 260 times and analysed during the first 2.5–20 μsec interval after the stimulus onset. Wave reproducibility of 50 per cent or higher was seen as a 'positive' result. If this reproducibility ratio was not obtained after the acquisition of 260 subsets, this constituted a 'negative' result.[11]

All patients were premedicated with intramuscular midazolam 0.07 mg/kg 30 minutes before they were taken to the operating room. After standard monitoring (non-invasive blood pressure, heart rate, electrocardiography lead II, pulse oximetry), anaesthesia was induced with propofol 2 mg/kg intravenously. After loss of consciousness and the eyelash reflex, all subjects were ventilated with 30 per cent oxygen in air via a face mask. Patients were then divided into five groups of 10 persons each, according to the anaesthetic agent they had been given. The results of otologic measurements were not considered when the patients were distributed to the groups. In group I, patients received 30/70 per cent O_2/N_2O; group II received 1.5 MAC sevoflurane 30 per cent oxygen in air; group III received 1.5 MAC desflurane in 30 per cent oxygen in air; group IV received 1.5 MAC halothane in 30 per cent oxygen in air; and the patients in group V were administered total intravenous anaesthesia (TIVA) with an intravenous infusion of propofol (10 mg/kg/hr) and sufentanil (0.5 μg/kg/hr) with 30 per cent oxygen in air for the maintenance of anaesthesia.

Neither muscle relaxants nor endotracheal intubation was used in any of these subjects. The anaesthesia equipment used was Draeger Cato (Lübeck, Germany).

Except for the first measurements (audiogram, impedance audiometry, TEOAE), which helped us decide whether or not to include the patients in the study, SR and TEOAE measurements were performed three times on one ear in the operating room. As regards the contralateral SR threshold, we took care in choosing the ear that would be tested: if the SR thresholds were equal in both ears, the ear to be tested was chosen at random; if there was a difference between the two ears, the ear with the lower contralateral SR threshold was chosen. All the measurements were performed by the same ENT specialist using the same equipment in the operating room. Optimum silence was provided during the TEOAE measurements. The artefact rejection values were lower than 50 dB SPL. In addition, there was no difference in noise level between the first measurement, which was performed in the silent room, and the other measurements, which were performed in the operating room ($p > 0.05$).

The second measurements were performed 30–40 minutes after premedication, the third measurements were performed after the propofol induction when the eyelash reflex was lost, and the fourth measurements were performed during the maintenance of anaesthesia. To make this last measurement we waited for certain criteria, i.e. regular and periodic respiration; stable blood pressure and heart rate; loss of orbicular motion and light reflex; myotic pupils; and no lacrimation or swallowing. Thus, the fourth measurements were performed after 10–15 minutes of steady-state anaesthesia in groups I and V, and when the end-tidal concentration of volatile anaesthetics reached 1.5 MAC in groups II, III and IV. No surgical manipulation was made until we had completed our last measurement.

Results were analysed by paired samples *t*-test, the Kruskal–Wallis test and the Mann–Whitney U test. $p \leq 0.05$ was accepted as the level of significance.

Results

Compared to the first measurements, there was an elevation of the contralateral and ipsilateral SR thresholds and a reduction in TEOAE wave reproducibility values at the second, third and fourth measurements, which were done in the operating room (Figures 1–3). Tympanograms showed that N_2O (group I) caused a moderate increase in middle-ear air pressure up to 50 daPa during the fourth measurements, but neither elevation nor reduction was found in the other groups.

To evaluate the effect of midazolam, which was administered for premedication before the second measurements, we compared mean values of contralateral and ipsilateral SR thresholds and the

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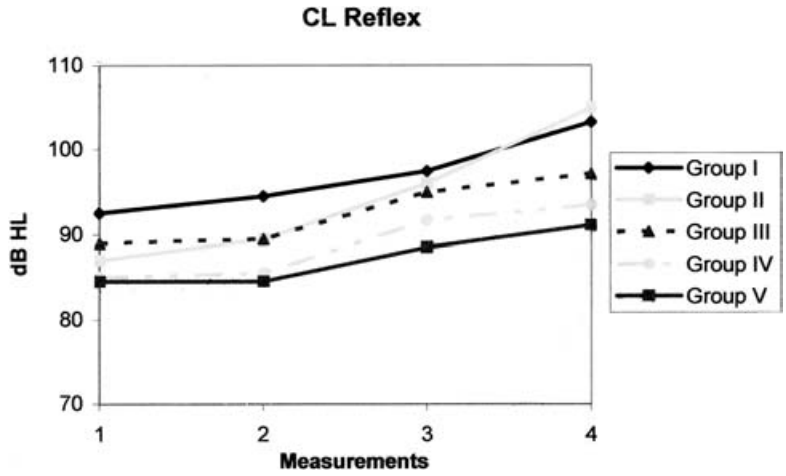

FIG. 1
Change in contralateral SR thresholds in each group at each measurement.

reproducibility of the second TEOAE measurement with those of the first measurement in all 50 patients, and found a significant difference for each test (Table I). Thus, we determined that midazolam causes an elevation of contralateral and ipsilateral SR thresholds and a reduction in TEOAE reproducibility.

To evaluate the effect of propofol, which was administered for induction, we compared mean values of contralateral and ipsilateral SR thresholds and the reproducibility of the third measurement of TEOAE with those of the second and first measurements in all 50 patients. Although we did not find a significant difference between the second and the third measurements for TEOAE, we found significant differences between the first and the third, and between the first and the second TEOAE values. Compared to the first measurement, the contralateral and ipsilateral SR values increased at the second and third measurements (Table I).

No significant difference was found with respect to contralateral SR thresholds among the five groups at the first, second and third measurements. On the other hand, there was a significant difference with respect to mean values of contralateral SR thresholds at the fourth measurement in all five groups ($p = 0.028$) (Table II). The highest value was obtained in group II (105 dB); the lowest was in group V (91 dB). In group II the contralateral SR values were higher than in groups IV and V ($p = 0.011$, $p = 0.031$, respectively). In group I, the contralateral SR values were higher than in groups IV and V ($p = 0.028$ and $p = 0.041$, respectively).

The mean values of ipsilateral SR thresholds at the fourth measurement were greater than those of the third measurement in all groups, but the difference was not statistically significant. Also, a reduction was found for mean values of TEOAE at the fourth measurement in groups III and IV, but this reduction was not significant.

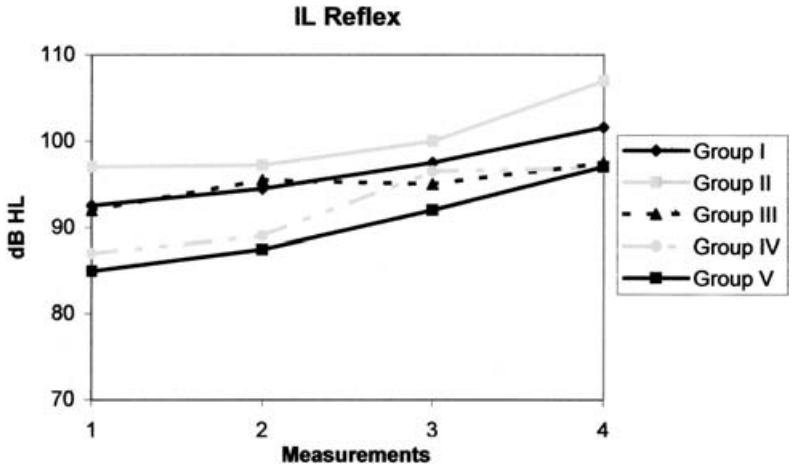

FIG. 2
Change in ipsilateral SR thresholds in each group at each measurement.

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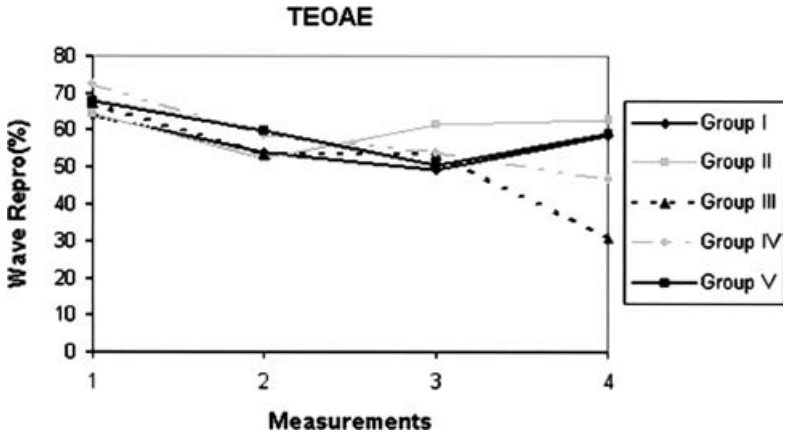

FIG. 3
Change in TEOAE reproducibility in each group at each measurement.

TABLE I
THE FIRST, SECOND AND THIRD MEASUREMENT MEAN VALUES OF THE SR THRESHOLDS AND TEOAE WAVE REPRODUCIBILITY

	Measurement values (mean)			$p^{*(1-2)}$	$p^{*(1-3)}$	$p^{*(2-3)}$
	First	Second	Third			
Contralateral SR (dB)	87.2 ± 8.1	88.7 ± 8.8	93.7 ± 8.8	<0.05	<0.01	<0.01
Ipsilateral SR (dB)	90.1 ± 8.7	92.6 ± 8.5	95.8 ± 9.3	<0.01	<0.01	<0.01
TEOAE wave reproducibility (%)	68.1 ± 12.0	55.4 ± 20.4	53.5 ± 28.8	<0.01	<0.01	>0.06

*Paired samples *t*-test.

TABLE II
COMPARISON OF THE FOURTH MEASUREMENT MEAN VALUES OF CONTRALATERAL SR THRESHOLDS IN EACH GROUP

Group (*n*)	Contralateral 4		
	Mean	Min	Max
I (9)	103.33 ± 8.29	90.00	110.00
II (7)	105.00 ± 5.77	95.00	110.00
III (7)	97.14 ± 8.59	85.00	110.00
IV (10)	93.50 ± 9.44	75.00	105.00
V (9)	91.11 ± 13.64	70.00	110.00

$p = 0.028$; Kruskal–Wallis test.

Discussion

The SR is an autonomic reflex that protects the inner ear against very loud noises. The first nuclear connection of the cochlear nerve is at the brain stem and the neurotransmitters involved are not precisely known, but aspartate, glutamate, acetylcholine and noradrenaline (norepinephrine) have been suggested. The same neural mediators have been found in the efferent nuclei of the stapedial reflex arch. The transmitter in the motor endplate is acetylcholine. Because of its neuroanatomical structure, anaesthetic agents, which have a sedative or depressive effect on the central nervous system, may affect the SR.[12]

Borg and Moller[13] showed the depressive effect of ethanol and pentobarbital on the ipsilateral and contralateral SR, and Robinette *et al.*[14] showed that secobarbital increased the SR threshold. In the present study, we established that all the anaesthetic agents increased both ipsilateral and contralateral SR thresholds. Whereas midazolam and propofol increased both ipsilateral and contralateral SR thresholds significantly, 70 per cent N_2O plus 30 per cent O_2, sevoflurane, desflurane, halothane and propofol combined with sufentanil increased only the contralateral SR threshold.

Gnadeberg *et al.*[15] established that after intravenous injection of midazolam and methohexital the SR threshold increased slightly, and propofol and thiopental significantly increased acoustically evoked SR thresholds. In addition, isoflurane and propofol combined with fentanyl strongly increased electrically evoked SR thresholds. Bissinger *et al.*[1] established that oral ingestion of 0.01 mg/kg flunitrazepam for premedication slightly increased SR thresholds, intravenous midazolam and alfentanil in combination caused an elevation of SR threshold more contralaterally than ipsilaterally, but a midazolam–ketamine combination has very little effect on either.

Bissinger *et al.*[1] showed that thiopental caused a more prominent and significant elevation of SR threshold contralaterally than ipsilaterally. Inhalational anaesthetics such as halothane, enflurane and isoflurane, with or without N_2O, abolished SR. Dinc and Nagel[16] established a prominent elevation of SR threshold with dihydrobenzperidol and fentanyl in their study.

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In our study, sevoflurane increased SR threshold the most of the anaesthetic agents we used. N_2O plus O_2, propofol plus sufentanil, desflurane and halothane followed. We therefore concluded that sevoflurane had a more muscle-relaxing effect than desflurane and halothane. On the other hand, desflurane had a more muscle-relaxing effect than halothane. There are studies that support the muscle-relaxing effect of sevoflurane. Tracheal intubation could therefore be performed without using muscle relaxants in these studies.[17–19] We thought that N_2O, which had no muscle-relaxing effect, had an effect on the SR thresholds as a result of crossing the stapedius reflex arch and different central mechanisms. There was an increase in middle-ear pressure of up to 50 daPa in the group given 70 per cent N_2O plus 30 per cent oxygen, but there was no prominent pressure difference in the others. It is known that N_2O diffuses rapidly into air-containing cavities. Middle-ear pressure increases because nitrogen gas cannot diffuse rapidly out of the tympanic cavity, which causes a decrease in stapedius muscle reflex response and compliance of the tympanic membrane for impedance audiometry.[16] Middle-ear pressure height is important because of its effect on SR measurement. Patterson and Bartlett[20] observed a pressure increase up to 450 daPa during N_2O anaesthesia in their study, but they found no pressure increase during halothane or ethrane anaesthesia without N_2O.

It has been reported in the literature that inhibition of the enzyme aldehyde reductase, which ensures normal neuronal transmission or cell membrane stabilization in neurons, could be a factor in the increase of SR threshold.[13] Jevtovic-Todorovic *et al.*[21] established that N_2O could block the excitator glutamate receptors. The attack points were defined for benzodiazepines, inhalational anaesthetics and barbiturates on the nicotinic acetylcholine receptors of the neuromuscular endplate.[22–24] We could find no study in the literature about the effect of sevoflurane, desflurane or sufentanil on the SR.

We found no significant differences in TEOAE measurements after the use of anaesthetic agents, except for midazolam, but established a significant reduction in TEOAE wave reproducibility after the use of midazolam for premedication. Hess *et al.*[25] found a slight influence on TEOAE reproducibility after administering flunitrazepam, but when they compared otoacoustic emissions before and after drug intake they found no difference. Hauser *et al.*[4] could determine no significant differences in amplitude or wave reproducibility after premedication with 0.05–0.1 mg/kg midazolam hydrochloride and/or 0.01 mg/kg atropine.

In our study, we found a slight reduction in TEOAE reproducibility after induction with 2 mg/kg propofol, but this was not significant. Ferber-Viart *et al.*[26] sought the effect of propofol and isoflurane on TEOAE. During the first 20 minutes of anaesthesia both agents caused a reduction in TEOAE amplitude, and after 20 minutes it continued to decrease with isoflurane but increased with propofol. However, this reduction was not statistically significant.

In our study we found increases or decreases in TEOAE wave reproducibility after administering N_2O, sevoflurane, desflurane, halothane or propofol plus sufentanil. A decrease occurred in the group administered desflurane or halothane. The others caused an increase. However, all of the reproducibility values were lower than the values established before anaesthesia, and none of the differences was significant.

Hess *et al.*[25] determined increases or decreases in TEOAE wave reproducibility values with isoflurane plus N_2O or enflurane. Hauser *et al.*[4] found a decrease in reproducibility in patients who received N_2O, but observed almost no difference in those who did not. Harel *et al.*[27] observed a significant increase in otoacoustic emission amplitudes in chinchillas given ketamine or pentobarbital.

We also could find no study in the literature regarding the effect of sevoflurane, desflurane or sufentanil on otoacoustic emissions.

In conclusion, midazolam may cause a significant elevation in ipsilateral/contralateral SR thresholds and a significant reduction in TEOAE reproducibility, and propofol may lead to a significant elevation in SR thresholds only. On the other hand, N_2O, sevoflurane, desflurane, halothane and propofol plus sufentanil may cause significant elevation in contralateral reflex thresholds only. Among these agents, sevoflurane may increase the threshold the most, but halothane may not have an effect. For this reason, inhalational anaesthetics (i.e. halothane or desflurane) and propofol plus sufentanil TIVA should be preferred instead of sevoflurane, and midazolam should be avoided for premedication when it is necessary to measure SR under general anaesthesia.

- **This study investigates the effects of anaesthetic agents on stapedius reflex thresholds (SR) and transient evoked otoacoustic emissions (TEOAE)**
- **Midazolam significantly increased SR thresholds and decreased TEOAE reproducibility. Propofol significantly increased SR thresholds but did not effect TEOAE reproducibility**
- **The effect of anaesthetic agents on audiometric parameters will need to be taken into account when assessing the results of testing under sedation and general anaesthesia**

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