Relationship between awareness and middle latency auditory evoked responses during surgical anaesthesia

P. Aceto, A. Valente, M. Gorgoglione, E. Adducci and G. De Cosmo*

Department of Anaesthesiology and Intensive Care, Catholic University of Sacred Heart, Rome, Italy
*Corresponding author: Department of Anaesthesiology and Intensive Care, Policlinico A. Gemelli, L.go A. Gemelli 8, I-00168 Rome, Italy. E-mail: gdecosmo@rm.unicatt.it

Background. Some studies support the view that meaningful auditory input can be processed by the brain during apparent surgical anaesthesia. Consequently, patients may be able to remember some information implicitly after anaesthesia as well through a ‘dream-like process’ (subconscious awareness). The aim of this study was to investigate the presence of subconscious awareness during anaesthesia and to examine its relationship to the mid-latency auditory evoked responses (MLAERs).

Methods. We studied 40 patients, ASA I–II, undergoing laparoscopic cholecystectomy. General anaesthesia was induced with thiopental 5 mg kg⁻¹, fentanyl 3 μg kg⁻¹, and vecuronium 0.08 mg kg⁻¹. For the maintenance of anaesthesia, patients were randomly assigned to one of four anaesthetic regimen groups: sevoflurane+air in oxygen 40%; sevoflurane+nitrous oxide 60%; isoflurane+air in oxygen 40%; and isoflurane+nitrous oxide 60%. MLAERs were recorded before anaesthesia, at 1 MAC of inhaled anaesthetic and then 30 min after awakening. An audioclip with one of four stories was played immediately after intraoperative MLAER recording. Explicit and implicit memory was assessed 24 h after awakening.

Results. None of the patients had explicit recall. One of the patients from the isoflurane–air group showed implicit memory of listening to the audioclip. A dream-like process, in which they remembered implicitly the story played during anaesthesia, occurred in one of the patients from the sevoflurane–nitrous oxide group. In the patients with subconscious awareness, MLAERs were similar to that of the awake state with a Pa latency increase of less than 8.87. When there was a marked increase in Pa latency during anaesthesia, no subconscious awareness was observed. No statistically significant differences were found between Pa latency before and after anaesthesia.

Conclusions. MLAERs may help to predict subconscious cerebral processing of auditory inputs during anaesthesia.

Br J Anaesth 2003; 90: 630–5

Keywords: memory; monitoring
Accepted for publication: January 17, 2003

Some studies support the view that meaningful auditory input can be processed by the brain during apparent surgical anaesthesia (hypnosis, analgesia, and neuromuscular block). Consequently, patients may be able to remember some information implicitly after anaesthesia (subconscious awareness). Awareness can be defined as ability to recall, with or without prompting, events that occurred while the patients were considered to be unconscious. Subconscious awareness, on the other hand, is a state in which information registered by the brain does not enter consciousness. It seems that surgical anaesthesia produces a memory impairment similar to amnestic syndromes: explicit memory for auditory information perceived during anaesthesia is impaired after wakening, although implicit memory may sometimes be preserved. Implicit memory can be demonstrated by letting the subjects undertake actions which facilitate access to unconscious memory (priming). Perceptual priming may be induced by using a lexical decision task which consists of reading a word list. Conceptual priming, which reflects prior processing of
stirning effects. Inspection of records of awareness is a complication of anaesthesia which has potential adverse consequences. In non-obstetric and non-cardiac cases, it has been estimated that awareness may occur in 0.2% of cases. 

Evidence for cognitive processing includes any psychologically mediated response which occurs during or after surgery and which can be said to have been elicited by an intraoperative event. Auditory information perceived during anaesthesia may also be remembered implicitly through a ‘dream-like process’ which has been described as a subconscious state of awareness characterized by vivid thoughts and images related to external stimuli. Even though awareness seems to be rare during deep general anaesthesia in non-obstetric and non-cardiac cases (0.2%), it is a complication of anaesthesia which has potential adverse psychological effects. 

Inspection of records of awareness cases for relevant variables such as heart rate, arterial pressure, and anaesthetic technique has not been helpful in explaining retrospectively why awareness occurred. Mid-latency auditory evoked response (MLAERs) monitoring has been proposed as a measure to ascertain the adequacy of the hypnotic state during surgery. The aim of this study was to investigate the presence of subconscious awareness during anaesthesia maintenance—performed with volatile anaesthetics alone or combined with nitrous oxide, which was apparently adequate for suppressing a response to the surgical stimulus, and to examine its relationship to MLAERs.

**Methods**

After obtaining informed consent, 40 patients, aged 18–70 yr, ASA physical status I–II, undergoing elective laparoscopic cholecystectomy, were enrolled in the study. Only patients who were Christians were included in the study; priming in anaesthetized patients is likely to occur when familiar stimuli such as famous Christian religious stories are presented. We used such stories and selected Christian patients so they would not have an adverse reaction to them. Exclusion criteria were a history of neurological or mental disease and hearing impairment. Patients having major haemodynamic changes (mean arterial pressure and cardiac frequency greater than 15% compared with baseline values), and blood loss with acute anaemia as a result of intraoperative surgical complications were also excluded. Patients did not receive any pre-anaesthetic medication. General anaesthesia was induced with thioental sodium 5 mg kg⁻¹, fentanyl 3 µg kg⁻¹, and vecuronium bromide 0.08 mg kg⁻¹. For the maintenance of anaesthesia, patients were assigned, using randomization tables, to one of four anaesthetic regimen groups: Group A, sevoflurane-air (FIO₂ 40%); Group B, sevoflurane+nitrous oxide (60%) in oxygen 40%; Group C, isoflurane-air (FIO₂ 40%); and Group D, isoflurane+nitrous oxide (60%) in oxygen 40%. Boluses of fentanyl 2 µg kg⁻¹ were given according to clinical necessity.

MLAERs were recorded before anaesthesia, at 1 MAC (end-expiratory) of inhaled anaesthetic, and 30 min after awakening. The concentration of anaesthetic, monitored by using an anaesthetic-respiratory gas analyser (Capnomac Ultima; Datex), was maintained at 1 MAC for at least 20 min before the intraoperative recording of MLAERs, 5 min after surgical incision. One of four audiotapes was played immediately after completion of this MLAER recording. Each audiotape contained one of the following stories: (i) The fox and the grapes; (ii) Jesus’s birth; (iii) The prodigal son; and (iv) The miracle of the loaves and fishes. At the end of each of the stories, four key words had been recorded (implicit memory task). The patients were blinded to the method of anaesthesia used and to the contents of the tape (they were not told that there would be a story on the tape). The anaesthesia resident that conducted the post-operative interview did not know which anaesthetic had been used or which story had been played. The stories were played by another anaesthesia resident during each general anaesthetic. The MLAERs were obtained using an Evo Quick EP system (Micromed) from spherical electrodes placed on the vertex (Cz), and earlobes (Ai, Ac), with Fpz as ground. Alternating clicks (105 dBsPL, duration of 0.1 ms) were presented monaurally with a stimulation frequency of 5 Hz using acoustically shielded headphones. The impedance of all electrodes was less than 5.0 kohm. Filters were set at 5–1800 Hz. The number of averaged sweeps for each registration was 1100. Each MLAER registration took about 2 min. The recording procedure was controlled visually on a monitor and an automatic artefact detector rejected signals greater than 50 µV. The monitor interrupts its calculation during sweeps with artefact contamination caused from other electrical devices. When ‘clean’ sweeps are detected again, calculations restart from the point of interruption.

From off-line data, amplitudes and latencies of the Po, Na, Pa, Nb and Pb waves were measured. An interview was conducted in the hospital about 24 h after awakening for assessing explicit and implicit memory which lasted approximately 20 min. Explicit memory was assessed by doing a recall test. Patients were asked about the last thing they remembered before going to sleep; the first thing they remembered when they woke up; and anything which happened in between, including sounds, dreams, and imagination. Implicit memory was tested by letting patients hear a tape in which all 16 key words, from the four stories, had been recorded. Patients were invited to say the first thing that came to mind after listening to each of the words. This story-related free association test was repeated twice during the interview. The test proved to be positive when the patient, after listening to one of the key words, related it to the story he had heard during anaesthesia, and retold something about the story in question (for example, a title or a sentence of the story) without conscious recall of an
intraoperative event. Patients were told at this point that they had listened, intraoperatively, to one of the four stories, and they were asked if talking about the stories brought back any memories of having heard a tape recording during anaesthesia.

Statistics

The Shapiro–Francia test was performed to evaluate the distribution of raw data: no data were normally distributed. The physical characteristics of the patients (expressed as mean, 95% interval confidence) were analysed using the Kruskal–Wallis test for non-parametric data. The $\chi^2$ test was used to compare the incidence of awareness between groups. The latency of the Pa waves in patients with or without subconscious awareness before and during anaesthesia was analysed by using the Wilcoxon test for paired data. The Mann–Whitney test was used to compare values of Pa latency before and after anaesthesia. Sensitivity, specificity, and the predictive value were calculated by using a cut off of the 10th percentile of the distribution of the differences between Pa latency during anaesthesia and that from the same patient before anaesthesia. We assigned patients to two groups according to this cut-off. Stata 6.0TM software (College Station, TX) was used for statistical analysis.

Results

There were no statistically significant differences between the groups in age, sex, weight, duration of anaesthesia, and doses of fentanyl received intraoperatively. Patient characteristics are shown in Table 1. No differences were found between the four groups with regard to incidence of subconscious awareness.

In the postoperative interview, none of the patients were able to recollect explicit memories of intraoperative events. One of the male patients from the isoflurane+air group (Group C) showed implicit memory of the intraoperative tape story; typical association was between key word ‘census’ and ‘Jesus’s birth’ during the second free-association test. A dream-like process, related to the story played during anaesthesia, occurred in one of the female patients in the sevoflurane+nitrous oxide group, who had been given a tape of the story of ‘The miracle of the loaves and fishes’. In the postoperative interview, when this patient listened to the key word ‘boat’ during a first free-association test, she said ‘The dream which I had during anaesthesia came to mind. I was surrounded by sounding-depth made of paper-pulp with many fishes and basketfuls of bread. I dreamed I heard your voice which made me feel very relaxed but I don’t remember what you said’. Neither of the patients remembered hearing one of the stories during anaesthesia.

In the awake state, MLAERs show a typical five-wave pattern (Po, Na, Pa, Nb, Pb) (Fig. 1). During deep general anaesthesia in patients without subconscious awareness (Fig. 1B), MLAERs were suppressed or attenuated. In contrast, in patients with subconscious awareness (Fig. 1A), MLAERs showed a wave pattern similar to that of the awake state. The 10th percentile of the distribution of differences between the value of the Pa latency during

---

**Table 1** Patients characteristics. No statistically significant differences were found between groups. The values are mean (range)

<table>
<thead>
<tr>
<th></th>
<th>Group A (sevoflurane) (n=10)</th>
<th>Group B (sevo-N₂O) (n=10)</th>
<th>Group C (isoflurane) (n=10)</th>
<th>Group D (iso-N₂O) (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54 (50–58)</td>
<td>49 (39–59)</td>
<td>52 (47–57)</td>
<td>50 (43–57)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (66–82)</td>
<td>65 (57–73)</td>
<td>74 (66–82)</td>
<td>63 (58–68)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5/5</td>
<td>4/6</td>
<td>4/6</td>
<td>6/4</td>
</tr>
<tr>
<td>ASA physical status I:II (n)</td>
<td>8:2</td>
<td>7:3</td>
<td>7:3</td>
<td>6:4</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>91 (70–112)</td>
<td>90 (65–115)</td>
<td>107 (89–125)</td>
<td>97 (78–116)</td>
</tr>
<tr>
<td>Total dose of fentanyl (μg)</td>
<td>225 (188–262)</td>
<td>243 (209–277)</td>
<td>223 (182–264)</td>
<td>231 (200–262)</td>
</tr>
</tbody>
</table>

---

**Fig 1** Auditory evoked potentials in a patient with (A) and without (B) subconscious awareness.
Table 2  Mean values (±sd) of Pa latency (in milliseconds) and increase of Pa latency (ΔPa latency) in patients with and without subconscious awareness (s.a.).

<table>
<thead>
<tr>
<th>Groups, patients n</th>
<th>Before anaesthesia, Pa latency</th>
<th>During anaesthesia, Pa latency</th>
<th>ΔPa latency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pa latency</td>
<td>Pa latency</td>
<td></td>
</tr>
<tr>
<td>All patients with s.a. 2</td>
<td>27.8 (0.1)</td>
<td>33.6 (2.1)</td>
<td>5.8 (2.2)</td>
</tr>
<tr>
<td>All patients without s.a. 38</td>
<td>27.3 (4.1)</td>
<td>52.3 (10.1)*</td>
<td>25.3 (10.6)*</td>
</tr>
<tr>
<td>Group A (sevo¯urane) without s.a. 10</td>
<td>27.8 (3.6)</td>
<td>55.1 (9.5)</td>
<td>27.1 (10.4)</td>
</tr>
<tr>
<td>Group B (sevo-N₂O) with s.a. 1</td>
<td>27.9</td>
<td>32.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Without s.a. 9</td>
<td>27.2 (4.8)</td>
<td>51.6 (4.8)</td>
<td>22.3 (8.2)</td>
</tr>
<tr>
<td>Group C (isoflurane) with s.a. 1</td>
<td>27.7</td>
<td>35.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Without s.a. 9</td>
<td>28.1 (3.7)</td>
<td>53 (12.1)</td>
<td>25.3 (11.40)</td>
</tr>
<tr>
<td>Group D (iso-N₂O) without s.a. 10</td>
<td>28.8 (4.6)</td>
<td>52.3 (11.5)</td>
<td>26.4 (12.6)</td>
</tr>
</tbody>
</table>

anaesthesia and that which the patients had shown before anaesthesia was 8.87. There were four patients in the group with a Pa latency increase less than this value and 36 in the group with a Pa increase greater than 8.87. The two patients with subconscious awareness were in the group with a Pa latency increase less than the 10th percentile. This cut-off showed a sensitivity of 100% and a specificity of 95%, with a positive predictive value of 75% and a negative predictive value of 100% in distinguishing patients with subconscious awareness. These data indicate that in our study a small increase in Pa latency was related to subconscious awareness. When there was a marked increase in Pa latency during anaesthesia, no subconscious awareness was observed.

No difference was found between the mean Pa latency before and after anaesthesia in any patient. As regards the action of different anaesthetics on the MLAER, there were no statistically significant differences in the latency of the Pa, a wave usually present during anaesthesia, among patients without subconscious awareness (Table 2).

Discussion

Our study showed that auditory information may be processed and retained in the form of implicit memory during deep general anaesthesia. Subconscious awareness could be related to cortical processing of auditory stimuli as highlighted by intraoperative tracings of the MLAERs. MLAER recording may help to predict cerebral processing of the auditory input, probably because it reflects activity in the temporal lobe/primary cortex, sites involved in sound registration and in a complex mechanism of implicit (non declarative) memory processing.20 21

Subconscious processing, which suggests the activation of implicit memory mechanisms such as dream-like processes in which patients may remember some intraoperative events, has not been reported often in previous studies, probably because its interpretation is not always easy. There was no absolute proof in our study that the dreaming reported during the postoperative interview actually took place while the patient was anaesthetized; it might, for example, have happened in the recovery room.

Therefore, the main aim of our study was not to demonstrate the presence of dreams during anaesthesia, which would have required a different methodology.1 The important finding is that the auditory information perceived during anaesthesia was incorporated into this form of dream. It was related to the implicit memory system by the clear association with the intraoperative audiotape.

The evidence from our study that intraoperative Pa latency was similar to pre- and postoperative values in patients with subconscious awareness and dissimilar in patients without subconscious awareness strengthened the association found between Pa latency and implicit memory processes happening during anaesthesia. We found a threshold for the Pa latency increase during anaesthesia of 8.87 ms with a positive predictive value of 75%. This means that a Pa latency increase of less than 8.87 was not always sufficient to distinguish a patient with subconscious awareness from one who was not able to recall anything implicitly postoperatively. This observation suggests that the test material used in this study may not have been sufficiently sensitive and that indirect tests of memory probably need further modification in order to show conceptual priming.

Our results are similar to those of Schwender and colleagues whose patients with implicit memory for a tape of the story of ‘Robinson Crusoe’ played during anaesthesia showed preservation of the MLAERs, while in patients without implicit memory the MLAERs were severely attenuated, indicating that auditory stimulus processing was blocked at the level of the primary auditory cortex. Of Schwender’s patients who showed priming, all exhibited a Pa latency increase less than 12 ms during anaesthesia.11

But, Schwender and colleagues studied patients undergoing cardiac surgery and interviewed them 3–5 days postoperatively, whereas we studied patients undergoing laparoscopic cholecystectomy as this enabled us to conduct an earlier postoperative interview (24 h after wakening). An early interview conducted when patients have recovered sufficiently from the detrimental effects of anaesthesia on cognitive functions and before any priming effects have dissipated, seems to be more appropriate to assess memory.19 Merikle and Daneman observed that there
seemed to be no memory when testing was delayed more than 36 h after the end of surgery.22,23

Moerman and colleagues found that 65% of patients who experienced awareness during general anaesthesia did not inform their anaesthetist about what had happened.3 Patients might not voluntarily report their experiences without being asked directly. For this reason, we interviewed patients postoperatively for 20 min in a detailed and extensive manner to ‘jog’ their memories of intraoperative experiences. Furthermore, we did not find any explicit recall of the story played during anaesthesia, which would have suggested a lighter level of anaesthesia. One of our patients showed conceptual priming during the second free association test. We gave our patients a story-related free association test twice in the same way as Ghoneim and colleagues. These authors found most of the priming effects during the second test, and explained this with the hypothesis that repeated elicitation of association produced sufficient activation of unconscious traces in memory to demonstrate priming.10 Another fact to be considered is that subjects may have exhausted their strongest, most immediate associations during the first association test; then, during the second test, they had weaker, less dominant association.

Our results are in keeping with those of other studies which show that different anaesthetics cause similar changes in the features of the MLAER waveform.23 We also did not find any differences in the incidence of subconscious awareness during nitrous oxide-free anaesthesia and anaesthesia with nitrous oxide and volatile agents. As a sole agent (with oxygen), nitrous oxide does not reliably prevent conscious memory.24 Tolerance may occur to the analgesic effects of nitrous oxide, although there is conflicting evidence as to whether tolerance may occur to its amnesic effect.25 Nitrous oxide is capable of stimulating as well as depressing the central nervous system and might thereby antagonize the depressant effects of volatile anaesthetics.26 Possibly, nitrous oxide does not improve the ability of volatile anaesthetics to prevent memory. We chose the four anaesthetic regimen groups according to guidelines which have been suggested to prevent conscious awareness.27 These guidelines recommend supplementing nitrous oxide and opioids with halogenated anaesthetic agents at end-tidal concentration of 0.6 MAC. When halogenated anaesthetics are used alone, at least 1 MAC should be administered, bearing in mind that the end-tidal, not the inspired concentration of volatile agents should be monitored. Our incidence of subconscious awareness in this study of 5% suggests that these recommendations do not help the anaesthetist prevent this form of awareness, which probably is due to an increased anaesthetic requirement in some patients. It should be noted that our patients were being surgically stimulated when MLAERs were recorded and when they were listening to the audiotape, to investigate what happens under clinical conditions. We sought as much as possible to record during similar noxious stimuli by standardizing the timing of the study (5 min after skin incision) and the type of surgical procedure (laparoscopic cholecystectomy), which was always carried out using the same surgical equipment.

The literature suggests that priming may occur under relatively high end-expiratory concentrations (1.0 (SD 0.5)% of isoflurane.28 If a surgical stimulus is lacking, lower concentrations (up to 0.8%) seem to be sufficient to suppress implicit memory.29 As yet, we do not know which concentration of the commonly used anaesthetics is required to reliably suppress subconscious processing of auditory stimuli in any single patient.19

In conclusion, MLAER monitoring could help in distinguishing patients with subconscious awareness, although this finding remains to be proven in a large number of patients. The precise state under which events happening during anaesthesia can be processed and retained in the form of implicit memory outside of conscious awareness, remains to be determined. Future studies about dreams during anaesthesia, which will focus on their content, are necessary to study their cognitive aspect, and to ascertain the precise moment in which these episodes occurred during anaesthesia.

References

4 Sebel PS. Memory during anaesthesia. Gone but not forgotten? Anesth Analg 1993; 81: 668–70
6 Ghoneim MM, Block RI. Learning and consciousness during general anaesthesia. Anesthesiology 1992; 76: 279–305
7 Bailey AR, Jones JG. Patient’s memories of events during general anaesthesia. Anesthesia 1997; 52: 460–76
8 Bower GH. Reactivating a reactivation theory of implicit memory. Conscious Cogn 1996; 5: 27–72
16 Drummond JC. Monitoring depth of anesthesia. Anesthesiology 2000; 93: 876–82
19 Ghoneim MM, Block R. Learning and memory during general anesthesia. Anesthesiology 1997; 87: 387–410
20 Manns JR, Squire LR. Perceptual learning, awareness and the hippocampus. Hippocampus 2001; 11: 776–82
26 Pellegrino DA, Miletich DJ, Hoffman WE, Albrecht RF. Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. Anesthesiology 1984; 60: 405–12