

The effect of analgesic state on implicit learning during propofol anesthesia in volunteers

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Abstract : Noxious stimulation may enhance implicit learning during general anesthesia. It is unknown, however, whether analgesic state can influence this memory processing.

Twenty healthy adult volunteers were enrolled our prospective, double-blinded, controlled experiments. Anesthesia was induced with a propofol target controlled infusion (TCI), titrated in step-wise increments to loss of consciousness. In phase A, a 10-word list was played to the subjects while a noxious stimulus was applied (hand immersion in cold water at 2-4°C). In phase B, a remifentanyl TCI infusion was added to the steady-state propofol TCI anesthesia, and titrated to loss of hand movement on cold water immersion. A second 10-word list was then played while maintaining the hand in cold water.

Memory testing, 2 hours post-recovery revealed no evidence of *explicit* memory in any subject during either phase of the study. During phase A, the word stem completion test revealed implicit learning for played words. In contrast, no implicit memory was detected during phase B.

This study indicates that analgesia with remifentanyl TCI (titrated to loss of movement on noxious stimulation), prevented implicit memory processing during stable propofol anesthesia in healthy adult volunteers.

Key words : Anesthesia ; implicit memory ; anesthetics I.V. ; propofol ; remifentanyl.

Studies on implicit memory function during general anesthesia have yielded conflicting results (1-8). Implicit memory represents the unconscious processing of intra-operative events, in the absence of conscious (explicit) recall, and has been investigated in a variety of clinical and experimental settings. In some studies, noxious or surgical stimulation was present when implicit memory was evidenced (1-4). Further investigations, conducted in the absence of such noxious stimulation, have failed to support the phenomenon of implicit memory under general anesthesia (5-8). It seems likely, therefore, that painful stimulation may be a necessary prerequisite for learning during general anesthesia. Indeed, DEEPROSE *et al.* demonstrated

implicit learning during general anesthesia, but only in the presence of surgical stimulation, at comparable anesthetic depth (4). Although memory performance has been shown to decline with increasing depth of hypnosis (9), it remains unclear whether analgesia state plays an important role in implicit memory processing.

In these prospective, double-blinded, randomized experiments, we studied the effect of analgesia on implicit memory function during stable propofol anesthesia in healthy adult volunteers. In a two-stage design, memory function was tested before and after the addition of a target controlled infusion of remifentanyl, titrated to loss of movement on noxious stimulation.

METHODS

This prospective, randomized, double-blinded study was approved by the Ethical Committee of St. Pierre Hospital, Brussels, Belgium. All participants were informed as to the nature of the study

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Table 1
Study design

	Test phase A (Propofol TCI)		Test phase B (Propofol / remifentanil TCI)	
	CD A	CD C	CD B	CD D
Group I (n = 10)	Played	Not played	Played	Not played
Group II (n = 10)	Not played	Played	Not played	Played

TCI : Target controlled infusion.

The different CDs were played during a noxious stimulation (hand maintained in cold water).

and gave their written consent. Twenty healthy adult volunteers, none of whom had memory or hearing impairment, were enrolled. All volunteers were native French speakers, did not take any form of medication and were unaffected by neurological illness. They were randomized into 2 experimental groups (group I and group II). Forty French words, selected from previous experiments (8, 10), were arranged in 4 lists of 10 words, and recorded on 4 separate CDs (A, B, C and D). Word lists were repeated three times, with 1 second pauses between words and were recorded on computer (Fujitsu-Siemens Amilo M-4500, Munich, Germany), using Microsoft Sound Recorder (version 5.1 for Microsoft Windows XP). The investigators were blinded to the contents of each CD. The study protocol was conducted in two phases – Test Phase A followed by Test Phase B (Table 1).

Anesthesia and study protocol

During Phase A, all volunteers were anesthetized with a computer-controlled infusion of propofol (Infusion Toolbox Version 4.11 (11)). This target controlled infusion (TCI) system calculates and targets the blood concentration as well as the effect compartment concentration (C_e) of propofol using the pharmacokinetic model of MARSH (12). Following placement of an intravenous infusion and the placement of standard monitoring (ECG, non invasive blood pressure cuff and arterial oxygen saturation), the volunteers were allowed to breath oxygen for 2 minutes. Anesthesia was then induced by increasing the target blood propofol concentration in steps of 0.5 $\mu\text{g}/\text{mL}$, respecting a maximum blood - C_e gradient of 1 $\mu\text{g}/\text{mL}$, until loss of consciousness (defined as absence of response to a verbal command). During the entire experiment (Phases A and B), the target blood concentration was set and maintained at this C_e associated with loss of consciousness. Following equilibration, heart rate and non-invasive arterial pressure were recorded. Subjects were spontaneously breathing through an oxygen

mask and manually ventilated if deemed necessary. A noxious stimulation was then applied by inserting and maintaining the subject's hand in cold water (2-4°C). Sixty seconds thereafter, a first word list was played through headphones (CD A for group I and CD C for group II) while the noxious stimulus was still present. Heart rate and non-invasive arterial pressure were recorded.

In test phase B, a TCI of remifentanil was started (Infusion Toolbox Version 4.11) using the pharmacokinetic model of MINTO (13) while the propofol TCI was still running. The target blood concentration was increased in steps of 0.5 ng/mL until no withdrawal movement was observed following cold water immersion of a hand during 60 seconds. At equilibration, heart rate and non-invasive arterial pressure were recorded. A second word list was played through headphones (CD B for group I and CD D for group II) while maintaining the hand in cold water.

Following completion of the study protocol, the volunteers were allowed to emerge from the anesthesia and their memory function tested 2 hours later.

Memory function testing

Two tests, as previously described (8, 10), were adapted to French and used to study implicit and explicit memory function under anesthesia.

Explicit memory was tested using free recall : the volunteers were asked to cite any words they remembered having heard whilst anesthetized. General memory performance (implicit and explicit memory) was tested using the word stem completion test. The subjects were presented with a written list of 3 letter stems for each of the 40 words used in the study. They were asked to complete these stems with the first word they could think of. Thus, each volunteer was presented with 20 stems for words already played during anesthesia as well as stems for the 20 words played to the reciprocal group. The two study groups therefore acted as controls for each other.

Table 2
Subject characteristics

	Group I (n = 10)	Group II (n = 10)
Age (yr)	28 ± 9	24 ± 4
Sex (M/F) (n)	3/7	4/6
Effect-site concentration of propofol at LOC (µg/ml)	3.0 ± 0.4	2.8 ± 1.0
Effect-site concentration of remifentanil at no ROW (ng/ml)	2.2 ± 0.8	1.9 ± 0.3

Values are mean ± SD or number (n).
LOC = Loss of consciousness ; ROW = Reaction of withdraw.

Table 3
Haemodynamic results

	LOC	Test Phase A	Test Phase B
Blood pressure of all subjects (n = 20) (mmHg)	109 ± 11	123 ± 10 *	106 ± 9
Blood pressure of unconscious subjects (n = 3) (mmHg)	115 ± 12	123 ± 11 *	113 ± 7
Heart rate of all subjects (n = 20) (min-1)	66 ± 11	77 ± 11 *	59 ± 10 *
Heart rate of unconscious subjects (n = 3) (min-1)	63 ± 17	67 ± 21 *	59 ± 14 *

Values are mean ± SD.
LOC : loss of consciousness. Unconscious subjects are volunteers not woken up by the noxious stimulation during the Test Phase A.
*p < 0.05 compared LOC values.

Statistical analysis

Data were expressed as mean ± SD. Inter-group comparisons were made using an unpaired Student's *t* test and Mann-Whitney *U*-test for parametric and non-parametric variables respectively. Hemodynamic data were analyzed with a one-way ANOVA on time. Memory function tests were analyzed with the Mann-Whitney *U*-test. Probability values < 0.05 were considered to be significant. Statistical analyses were performed using SPSS 13.0 for Windows (SPSS Science Inc., Chicago, IL).

RESULTS

There were no statistical differences between groups I and II regarding age, sex, effect-site concentration of propofol at loss of consciousness and effect-site concentration of remifentanil at loss of movement (Table 2).

During Test Phase A, the calculated effect site concentration for propofol was 3.0 ± 0.4 µg/mL and 2.8 ± 1 µg/mL for groups I and II respectively. 17 of the 20 volunteers woke up during noxious stimulation (eye opening and response to verbal commands) while the 3 other volunteers remained unconscious. Systolic arterial pressure and heart rate significantly increased during noxious stimula-

tion, compared with baseline values obtained at loss of consciousness (P < 0.05).

During Test Phase B, the calculated effect site concentration of remifentanil was 2.2 ± 0.8 ng/mL and 1.9 ± 0.3 ng/mL for groups I and II respectively. No volunteer awakened during this phase of the experiments. Compared with those values obtained at loss of consciousness, systolic arterial pressure remained unchanged, whereas heart rate significantly decreased (P < 0.05) (Table 3).

In the free recall test, no patient remembered any word from the lists presented during the Test Phases A and B (Table 4). Statistically, during Test Phase A (propofol TCI only) the 20 subjects completed more correct words in the word stem completion test for the played versus unplayed word lists (P < 0.05). No differences in the test were observed between played and unplayed word lists during Test Phase B.

The 17 volunteers who awoke during noxious stimulation in Test Phase A completed statistically more correct words of the played list than the 3 patients who remained unconscious.

DISCUSSION

In these prospective, double-blinded, randomized experiments, we investigated the effect of analgesic state on implicit memory function during

Table 4
Results of memory tests

Test Phase	Memory test	Subjects	Played list	Unplayed list
A	WSCT (words)	All subjects (n = 20)	1.9 ± 1.2*	0.9 ± 0.7
	WSCT (words)	Awake subjects (n = 17)	2.1 ± 1.0*	
	WSCT (words)	Unconscious subjects (n = 3)	0.3 ± 0.6°	
	FRT (words)	All subjects (n = 20)	0	0
B	WSCT (words)	All subjects (n = 20)	1.0 ± 0.8	1.1 ± 0.9
	FRT (words)	All subjects (n = 20)	0	0

Values are mean ± SD.

Test Phase A = Propofol TCI. Test Phase B = Propofol / remifentanil TCI.

WSCT = Word Stem Completion Test (implicit memory test) ; FRT = Free Recall Test (explicit memory test).

* p < 0.05 (compared to the list not played) ; ° p < 0.05 (compared to awake subjects).

light propofol anesthesia, in healthy adult volunteers.

Implicit memory, which refers to the unconscious recall of intraoperative events, can lead to psychological sequelae for patients and medico-legal concerns for the anesthesiologist (14). Previous studies on implicit memory during general anesthesia have yielded contradictory results. Whereas some investigations have supported the notion of implicit learning (1-4), other studies using similar methodology have failed to concur (5-8). The discordance of these findings may be explained by the presence or absence of noxious/surgical stimulation during the experiments. At a comparable depth of general anesthesia, Deepröse *et al.* (4) demonstrated implicit learning only in the presence of surgical stimulation, suggesting that a noxious stimulus may facilitate implicit memory processing. In their study however, the analgesia protocol may have been insufficient during surgery, allowing widespread fluctuations in the observed BIS values (range 25 to 75) possibly associated with some period of consciousness. In a further study, this group replicated their experiments by investigating patients randomized to either receive or not receive fentanyl (1.5 µg/kg) at induction of anesthesia (15). Evidence for implicit learning still occurred, in the presence of mean BIS values of 37.9 (No fentanyl group) and 41.8 (Fentanyl group). The mean percentage of BIS readings > 60 was 11.9% and the wide variability in BIS values (range 22-88) suggests insufficient analgesia responsible for hypnotic state fluctuations that could be responsible for memory activation during anesthesia (16). Following exclusion of patients with a maximum BIS value > 60, implicit learning was still apparent however.

The present study was designed to investigate the influence of analgesia on implicit learning enhanced by noxious stimulation, during anesthesia

in experimental conditions. A reproducible and constant noxious stimulus, originally described by VINIK *et al.* (17) was used in volunteers anesthetized by propofol TCI, titrated to loss of consciousness.

No explicit memory was observed during our experiments. Evidence of implicit memory was seen only during light propofol anesthesia, before remifentanil was infused to prevent movement during stimulation. However, our study design cannot distinguish whether this learning occurred due to awakening during stimulation (17 out of the 20 volunteers awoke) or because of the sympathetic reaction caused by the stimulation (both heart rate and blood pressure significantly increased during application of the stimulus in Test Phase A). Indeed, catecholamines released in response to a psychological stress or a noxious stimulus may facilitate implicit learning during general anesthesia by activating the amygdala complex, a cerebral structure modulating long-term memory consolidation during emotionally arousing experiences (18). When clinically adequate analgesia was achieved (absence of movement on noxious stimulation in Test Phase B), the subjects remained unconscious, did not show any sympathetic reaction and did not show evidence of implicit learning. Interestingly, 3 subjects did not wake up when stimulated during the propofol TCI (Test Phase A). They showed a statistically significant increase in both heart rate and blood pressure, but did not exhibit evidence of implicit memory processing. This might suggest that the most important factor for implicit learning during general anesthesia is awakening, rather than a sympatho-adrenal discharge activating the amygdala complex. The findings in these 3 volunteers merit further investigation by future studies enrolling larger numbers of subjects. Moreover, the mechanisms by which implicit learning occurs during general anesthesia require further study.

In conclusion, during light propofol TCI anesthesia in healthy adult volunteers, implicit learning, in the presence of noxious stimulation, is prevented by adequate remifentanyl TCI analgesia (titration of analgesia to loss of movement on stimulation).

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