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Psychophysical and electrophysiological responses to experimental pain may be influenced by sedation: comparison of the effects of a hypnotic (propofol) and an analgesic (alfentanil)

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Summary

Sedation may influence the responses of some experimental pain models used to test analgesic efficacy. In this study we compared the effects of a sedative (propofol) and analgesic (alfentanil) on: nociceptive reflex to single and repeated electrical stimulations; mechanical pressure pain; and evoked potentials elicited by nociceptive (electrical and laser) and non-nociceptive (acoustical) stimulation. We studied 12 healthy volunteers with two subanaesthetic concentrations of propofol and two analgesic concentrations of alfentanil. Both propofol and alfentanil increased the threshold for nociceptive reflex to single electrical stimulations, but only alfentanil increased the threshold for nociceptive reflex to repeated electrical stimulations. The pressure pain tolerance thresholds were increased significantly by alfentanil, whereas propofol significantly decreased the thresholds (hyperalgesia). Propofol and alfentanil induced similar reductions in the amplitudes of the evoked potentials elicited by nociceptive (electrical and laser) and non-nociceptive (acoustical) stimulation, whereas only alfentanil reduced the perceived pain to nociceptive stimulations. We have shown that sedation can influence both the psychophysical and electrophysiological responses of some experimental pain tests used to measure analgesic efficacy, and that propofol in subhypnotic doses, has no analgesic effect on painful electrical and heat stimulations, but has a hyperalgesic effect on mechanical pressure pain. (*Br. J. Anaesth*. 1996; **77**: 165–171)

Key words

Anaesthetics i.v., propofol. Analgesics opioid, alfentanil. Pain, experimental.

Testing the sensory aspects of pain is hampered by the subjective and multidimensional nature of pain. This has led to a search for quantitative measures. The nociceptive withdrawal reflex to single electrical stimulations of the sural nerve has been proposed as a technique to assess the excitability of the nociceptive system [1, 2]. The size of the evoked potential elicited by painful stimuli has also been found to correlate with the state of the nociceptive system [3, 4]. For conditions when the subject cannot collaborate, nociceptive reflex and evoked potentials would appear to be adequate tests. Spinal polysynaptic nociceptive reflexes have been used in animals for decades. In a recent study [5], we found that subanaesthetic (0.10–0.26 vol % end-tidal) isoflurane concentrations increased significantly the threshold for nociceptive reflex to single electrical stimulations of the sural nerve, but did not change the reaction to pain elicited by heat, cold or pressure, or the threshold for nociceptive reflex to repetitive stimuli. This indicates that the increase in the threshold of the nociceptive reflex to single electrical stimuli might not reflect analgesia but could be caused by sedation. Furthermore, in another study [6] using similar subanaesthetic isoflurane concentrations, we found that the amplitude of evoked vertex potentials elicited by nociceptive laser and intracutaneous electrical stimulations decreased with increasing isoflurane concentration. But isoflurane caused a similar decrease in amplitudes of evoked vertex potentials elicited by non-nociceptive auditory stimuli, indicating that the decrease in amplitude was not caused by an analgesic effect of isoflurane, but could be a result of general depression of neuronal transmission.

Therefore, it seems possible that sedation could influence the responses of some experimental pain models used to assess analgesic efficacy. In this study we compared the effects of sedation (propofol) and analgesia (alfentanil) on the thresholds of the nociceptive reflex to single and repeated electrical stimulations, the amplitude of evoked vertex potentials elicited by nociceptive and non-nociceptive stimuli and detection and tolerance thresholds to mechanically induced pain.

Several studies [7–12] have been designed to see if hypnotics are hyperalgesic in subhypnotic doses, but results are conflicting. As propofol is one of the most widely used hypnotics in anaesthesia, and is also

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used for sedation in intensive care, it is important to clarify further its influence on nociception in humans.

Subjects and methods

We studied 12 healthy volunteers (eight male), mean age 26 (range 20–42) yr. They were not receiving any medication, had no allergies or earlier adverse reactions to anaesthesia, and for the female volunteers, were not pregnant. Written informed consent according to the Helsinki Declaration was obtained, and the study was approved by the Ethics Committee of the Faculty of Medicine, University of Bern.

To minimize the risk of acid aspiration, volunteers were tested after a fasting period of at least 6 h. During testing volunteers rested comfortably in the supine position. An i.v. infusion of NaCl-glucose was started and haemoglobin oxygen saturation by pulse oximetry, ECG and non-invasive arterial pressure were monitored continuously during the study.

NOCICEPTIVE REFLEX THRESHOLD TO SINGLE STIMULI

The sural nerve was stimulated behind the lateral malleolus via surface electrodes filled with electrode gel (inter-electrode distance approximately 2 cm). A 25-ms, train-of-five, 1-ms, square-wave impulse (perceived as a single stimulus) was delivered from a computer-controlled constant current stimulator (University of Aalborg, Denmark). Electromyographic reflex responses were recorded from the middle of the biceps femoris and the rectus femoris muscles (surface silver–silver chloride electrodes). The EMG signal was amplified and filtered (1.5–150 Hz) by a Hellige (PPG Hellige GmbH, Germany) single channel EMG–EEG amplifier, recorded and analysed with NFRsys software (University of Aalborg, Denmark). The stimulation current was increased from 1 mA in steps of 1–2 mA until an ipsilateral reflex with an amplitude exceeding 20 μV for at least 10 ms was detected by the computer program. If a reflex was recorded three times at the same current intensity, this intensity was defined as the nociceptive reflex threshold to single stimulation. Maximal stimulation intensity was 80 mA. Eight reflexes, elicited with a stimulation intensity of 1.4 times the threshold intensity, were recorded, averaged and the root mean square (RMS) value in the 80–180-ms interval after the stimulus was calculated with EPsys software (University of Aalborg, Denmark). The volunteer then rated the perceived pain of the eight stimulations on a 10-cm visual analogue scale (VAS).

NOCICEPTIVE REFLEX THRESHOLD TO REPEATED STIMULI

The sural nerve was stimulated as described above, but the single stimulus was repeated five times with a frequency of 2 Hz, as described by Arendt-Nielsen and colleagues [13, 14]. Current intensity was increased from 1 mA in steps of 1–2 mA until a psychophysical or electrophysiological summation was detected by the computer program. The summation thresholds were defined as an increase in pain during the five stimulations (psychophysical summation threshold) or an increase in amplitude of the last one or two reflexes above a fixed limit of 20 μV for at least 10 ms (electrophysiological summation threshold). Maximal stimulation intensity was 80 mA.

MECHANICAL PRESSURE PAIN DETECTION AND PAIN TOLERANCE THRESHOLDS

Pressure pain detection and pain tolerance thresholds were measured on the centre of the pulp of the second (pain detection) and third (pain tolerance) finger of the right hand with an electronic pressure algometer (Somedic AB, Stockholm, Sweden) [15–17]. A probe with a surface area of 0.28 cm^2 was used, and the pressure increase was 30 kPa s^{-1}. Pain detection was defined as the point when pressure turned into pain, and pain tolerance as the point when the volunteer did not want the pressure to be increased further. For determination of both thresholds, the mean of two consecutive measurements was used.

REACTION TIME

A 1000-Hz tone was delivered from a computer with randomized intervals of 3–8 s, and a timer was started simultaneously. The volunteer was told to press a button as fast as possible after each tone. Reaction time was defined as the time from the tone until the volunteer pressed the button. The mean of three consecutive measurements was used.

EVOKED POTENTIALS

Argon laser stimulation

A 200-ms stimulus and a 3-mm laser beam diameter were used. Laser stimuli were applied to the dorsum of the hand (C7 dermatome). Repeated stimulation in the same area was avoided. The pain threshold was defined as a distinct sharp pinprick, and was calculated as the mean of five ascending and five descending series of stimulations. A laser stimulus of 1.4 times the initial pain threshold was used as stimulation for recording of the evoked potentials.

Electrical stimulation

An intracutaneous electrode, as described by Bromm and Meier [4], was used. The finger pulp of the third or fourth finger was stimulated with a blunt 1-mm steel pin electrode, with a digital ring finger electrode placed proximal as reference. A 25-ms, train-of-five, 1-ms, square-wave impulse (perceived as a single stimulus) delivered from a Digitimer DS7 constant current stimulator (Digitimer Ltd, UK) triggered by

a Phillips PM5150 Generator (Phillips GmbH, Germany) was used as stimulus. The horn layer of the epidermis was scraped carefully in a 2 × 2-mm area. Intracutaneous placement was accepted when a stimulation current of less than 0.5 mA was felt as a distinct pinprick. The current was increased from 0 in steps of 0.2 mA until the volunteer scored the stimulus (VAS) as painful as the laser stimulus of 1.4 times the initial laser pain threshold. This intensity was used for recording of the electrical evoked potentials.

Auditory stimulation

Auditory evoked potentials were elicited by click stimulation (Medelec ST 10, Medelec Ltd, UK) with 90 dB applied binaural through acoustically shielded headphones.

Recording

The evoked vertex potentials were recorded from a needle electrode (scalp electrode, 0.3 × 10 mm, Dantec, Denmark), inserted at Cz′ *vs* a surface silver–silver chloride electrode on the right mastoid. The signal, in the interval of 0.5 s before the stimulus until 2 s after the stimulus, was amplified and filtered (0.1–30 Hz) with a Hellige (Hellige AG, Germany) single-channel EEG amplifier and recorded, averaged and analysed with EPsys software (University of Aalborg, Denmark). Evoked potentials from 16 stimulations were averaged.

Perceived pain from laser and electrical stimulations

After each series of 16 laser or electrical stimulations, volunteers rated perceived pain on a 10 cm VAS.

MEDICATION

Volunteers were tested on two different days, at least 1 week apart. They received, in randomized order, alfentanil on one day and propofol on the other. The medication was prepared by an anaesthetist who monitored the volunteer and study but did not take part in the measurements. The volunteer and other investigators were blinded as to the medication.

The first concentration of alfentanil (low dose) was attained by a loading dose of 7.5 $\mu g\,kg^{-1}$ i.v. followed by an infusion of 0.1 $\mu g\,kg^{-1}\,min^{-1}$ and the second (high dose) by a loading dose of 15 $\mu g\,kg^{-1}$ i.v. followed by an infusion of 0.3 $\mu g\,kg^{-1}\,min^{-1}$. The first propofol concentration (low dose) was attained by a loading dose of 0.5 $mg\,kg^{-1}$ i.v. followed by an infusion of 10 $\mu g\,kg^{-1}\,min^{-1}$ and the second (high dose) by a loading dose of 1 $mg\,kg^{-1}$ i.v. followed by an infusion of 30 $\mu g\,kg^{-1}\,min^{-1}$.

EXPERIMENTAL DESIGN

The tests were explained to the volunteer and a trial testing was performed in order to familiarize the volunteer with the procedure. Thereafter a baseline test series was performed. Further test series were performed 20 min after each loading dose during the infusion.

STATISTICAL ANALYSIS

The Friedman test for repeated measures analysis of variance on ranks, and the Student–Newman–Keuls test for multiple comparisons were used for statistical analysis. $P < 0.05$ was considered significant.

Results

NOCICEPTIVE REFLEX (TABLE 1)

The threshold for nociceptive reflex to single stimulations was increased significantly by propofol and alfentanil compared with baseline, but there was no difference in the increase caused by propofol or alfentanil. The RMS of the recorded reflex was decreased significantly by propofol and alfentanil compared with baseline, but the high dose of propofol decreased the RMS significantly more than the high dose of alfentanil. The perceived pain to stimulations with a current intensity of 1.4 times the baseline threshold intensity was not decreased by propofol, whereas alfentanil produced a significant decrease in pain intensity compared with baseline. Propofol did not change the psychophysical or electrophysiological threshold for summation of the nociceptive reflex, but both thresholds were increased significantly by alfentanil compared with baseline and the difference between high-dose propofol and high-dose alfentanil was significant.

MECHANICAL PRESSURE (TABLE 1)

The pressure pain detection thresholds tended to be decreased by propofol and increased by alfentanil, but differences from baseline were not significant. However, the difference between high-dose propofol and high-dose alfentanil was significant. The pressure pain tolerance thresholds were decreased significantly by propofol at the high dose, whereas alfentanil increased significantly the threshold at the high dose compared with baseline. The difference between high-dose propofol and high-dose alfentanil was significant.

REACTION TIME (TABLE 1)

Both propofol and alfentanil increased the reaction time compared with baseline, but a significantly larger increase was found with high-dose propofol compared with high-dose alfentanil.

EVOKED VERTEX POTENTIAL LATENCIES (TABLE 2)

A typical evoked vertex potential (laser) is shown in figure 1. Neither propofol nor alfentanil changed the latencies of the vertex evoked potentials, except for N1 latency at the high propofol concentration (increase of 10 % compared with baseline and 16 % compared with high-dose alfentanil).

Table 1 Numerical results from experimental pain tests and reaction time. All values are median (5–95 percentiles), and are expressed as percentage change from baseline (baseline = 100%). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, L = low concentration, H = high concentration

Test	Propofol		Comparison P–A	Alfentanil	
	Low concn	High concn		Low concn	High concn
Nociceptive reflex threshold	125.0 (85.7–162.5) *B, *H	200.0 (79.3–270.5) *B, *L	ns (PL–AL) ns (PH–AH)	115.4 (93.5–161.2) *B, *H	140.0 (73.9–235.4) *B, *L
Nociceptive reflex RMS	63.2 (34.6–151.9) *B, *H	25.3 (10.7–136.6) *B, *H	ns (PL–AL) *(PH–AH)	81.0 (26.3–105.6) *B	56.1 (15.0–150.8) *B
Nociceptive reflex VAS	100.0 (63.7–117.5) ns	85.4 (60.2–126.6) ns	ns (PL–AL) *(PH–AH)	94.6 (61.5–102.9) *H	78.4 (49.3–101.1) *B, *H
Nociceptive reflex summation psychophysical threshold	104.5 (82.2–131.7) ns	104.5 (87.8–142.6) ns	ns (PL–AL) *(PH–AH)	100.0 (100.0–158.7) *H	127.3 (100.0–215.8) *B, *L
Nociceptive reflex summation electrophysiological threshold	100.0 (84.0–123.9) ns	109.7 (76.4–142.3) ns	ns (PL–AL) *(PH–AH)	109.1 (100.0–128.5) *H	133.3 (100.4–214.2) *B, *L
Pressure pain threshold	90.8 (69.9–115.2) ns	81.8 (73.0–116.6) ns	ns (PL–AL) *(PH–AH)	100.6 (69.8–140.6) ns	115.6 (84.1–163.5) ns
Pressure pain tolerance	97.3 (84.9–110.0) *H	87.2 (70.2–100.8) *B, *L	ns (PL–AL) *(PH–AH)	109.0 (85.0–121.3) *H	117.4 (85.5–136.3) *B, *L
Reaction time	120.1 (77.0–156.2) *H	123.8 (108.5–235.5) *B, *L	ns (PL–AL) *(PH–AH)	109.5 (101.1–134.6) *B	112.7 (98.1–192.1) *B

Table 2 Numerical results from latencies of the evoked potentials (EP). All values (ms) are median (5–95 percentiles). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, B = baseline, L = low concentration, H = high concentration

Test	Propofol			Comparison P–A	Alfentanil		
	Baseline	Low concn	High concn		Baseline	Low concn	High concn
Laser EP latencies P1	320 (258–382) ns	305 (259–343) ns	324 (222–366) ns	ns (PL–AL) ns (PH–AH)	313 (242–382) ns	320 (228–373) ns	320 (252–352) ns
Laser EP latencies N1	445 (414–492) *H	442 (376–525) *H	488 (387–565) *B, *L	ns (PL–AL) *(PH–AH)	438 (376–514) ns	430 (375–461) ns	422 (360–477) ns
Laser EP latencies P2	641 (492–740) ns	633 (511–763) ns	648 (572–876) ns	ns (PL–AL) ns (PH–AH)	594 (541–664) ns	633 (563–717) ns	641 (532–777) ns
Electrical EP latencies P1	152 (126–179) ns	156 (148–179) ns	148 (103–186) ns	ns (PL–AL) ns (PH–AH)	156 (141–180) ns	156 (133–194) ns	148 (141–202) ns
Electrical EP latencies N1	273 (207–318) ns	254 (228–358) ns	273 (213–397) ns	ns (PL–AL) ns (PH–AH)	281 (227–351) ns	266 (219–379) ns	266 (219–433) ns
Electrical EP latencies P2	434 (338–518) ns	450 (358–569) ns	445 (422–582) ns	ns (PL–AL) ns (PH–AH)	445 (423–634) ns	445 (438–614) ns	477 (319–659) ns
Auditory EP latencies P1	141 (118–155) ns	148 (117–156) ns	148 (126–163) ns	ns (PL–AL) ns (PH–AH)	141 (125–156) ns	148 (133–145) ns	155 (133–164) ns
Auditory EP latencies N1	231 (201–258) ns	227 (204–307) ns	219 (204–335) ns	ns (PL–AL) ns (PH–AH)	234 (203–304) ns	219 (203–326) ns	227 (211–320) ns
Auditory EP latencies P2	403 (368–518) ns	426 (275–459) ns	449 (322–498) ns	ns (PL–AL) ns (PH–AH)	422 (354–497) ns	453 (344–492) ns	453 (300–484) ns

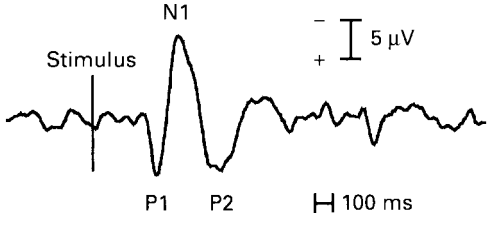

Figure 1 Laser evoked potential, which is the average of 16 evoked potentials elicited by short argon laser stimuli of 200 ms duration.

EVOKED VERTEX POTENTIAL AMPLITUDES (TABLE 3)

Neither propofol nor alfentanil changed the P1/N1 amplitudes of the laser evoked potentials. For the N1/P2 amplitudes of the laser evoked potentials and for the P1/N1 and N1/P2 amplitudes of the electrical and the auditory evoked potentials, both propofol and alfentanil reduced the amplitudes. In several cases (see table 3) propofol produced a significantly larger reduction than alfentanil. High-dose propofol and high-dose alfentanil induced the same amplitude reductions in the evoked potentials elicited by nociceptive stimuli (laser and electrical) as in the evoked potentials elicited by non-nociceptive stimuli (auditory) ($P = 0.12$ for P1/N1 amplitudes and $P = 0.21$ for N1/P2 amplitudes).

PERCEIVED PAIN TO LASER AND ELECTRICAL STIMULATIONS (TABLE 4)

Propofol did not reduce perceived pain (VAS scores) to laser and electrical stimulations, whereas high-dose alfentanil reduced significantly VAS scores

Table 3 Numerical results from amplitudes of the evoked potentials (EP). All values are median (5–95 percentiles), and are expressed as percentage change from baseline (baseline = 100%). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, L = low concentration, H = high concentration

	Propofol		Comparison	Alfentanil	
Test	Low concn	High concn	P–A	Low concn	High concn
Laser EP amplitudes P1/N1	97.8 (59.3–108.8) ns	81.2 (28.6–115.3) ns	ns (PL–AL) ns (PH–AH)	96.0 (44.4–133.0) ns	91.3 (44.6–141.7) ns
Laser EP amplitudes N1/P2	73.2 (27.1–110.7) *B, *H	43.1 (22.3–71.5) *B, *L	NS (PL–AL) *(PH–AH)	78.8 (58.1–125.7) *B	70.8 (41.2–132.1) *B
Electrical EP amplitudes P1/N1	54.7 (43.7–134.9) *B, *H	45.5 (15.9–77.0) *B, *L	*(PL–AL) *(PH–AH)	84.2 (67.4–148.6) *H	71.7 (23.6–132.1) *B, *L
Electrical EP amplitudes N1/P2	58.7 (30.0–76.9) *B	42.1 (32.7–67.8) *B	*(PL–AL) ns (PH–AH)	92.0 (75.3–126.0) *B, *H	78.6 (31.1–133.6) *B, *L
Auditory EP amplitudes P1/N1	70.7 (30.8–198.1) *B	46.1 (19.2–96.5) *B	*(PL–AL) ns (PH–AH)	86.4 (66.6–103.4) *B, *H	77.5 (52.3–85.7) *B, *L
Auditory EP amplitudes N1/P2	73.2 (27.1–110.7) *B, *H	43.1 (22.3–71.5) *B, *L	ns (PL–AL) *(PH–AH)	78.7 (58.1–125.7) *B	70.8 (41.2–132.1) *B

Table 4 Numerical results of perceived pain scores (VAS) from the laser and electrical evoked potentials (EP). All values are median (5–95 percentiles), and are expressed as percentage change from baseline (baseline = 100%). *$P < 0.05$ compared with baseline, ns = not significant compared with baseline, P = propofol, A = alfentanil, L = low concentration, H = high concentration

	Propofol		Comparison	Alfentanil	
Test	Low concn	High concn	P–A	Low concn	High concn
Laser EP VAS	94.9 (50.5–133.3) ns	100.8 (73.8–161.8) ns	ns (PL–AL) ns (PH–AH)	95.2 (62.9–131.1) *H	83.8 (45.2–109.4) *B, *L
Electrical EP VAS	97.2 (56.5–133.1) ns	94.1 (45.2–122.2) ns	ns (PL–AL) *(PH–AH)	95.9 (35.2–120.1) *H	75.5 (23.9–122.9) *B, *L

compared with baseline and low-dose alfentanil. VAS scores were also significantly smaller for high-dose alfentanil compared with high-dose propofol.

Discussion

We have shown that sedation can influence both the psychophysical and electrophysiological responses of some experimental pain tests used to measure analgesic efficacy. Propofol increased the threshold of the nociceptive reflex to single stimulations and decreased the amplitude of the evoked potentials elicited by nociceptive laser and electrical stimulations. This indicates that these may not, under all circumstances, assess the excitability of the nociceptive system. Propofol, in subhypnotic doses, had no analgesic effect on painful electrical and heat stimulations, but had a hyperalgesic effect on pressure pain.

NOCICEPTIVE REFLEX

Willer [18] investigated the relation between nociceptive reflex and perceived pain. The occurrence of the reflex was related closely to the pain threshold, and a linear relation was found between perceived pain and amplitude of the nociceptive reflex. This finding was confirmed later by Chan and Dallaire [19]. The reflex threshold to single stimuli has been found to increase with i.v. morphine [20], extradural morphine [21], i.m. alfentanil [22], but also with the weaker, non-opioid analgesics ketoprofen [23] and acetylsalicylic acid [24]. This indicates that the nociceptive reflex to single electrical stimulations of the sural nerve can be used to demonstrate analgesia produced by pure analgesic drugs. However, sub-anaesthetic (0.10–0.26 vol % end-tidal) isoflurane concentrations significantly increase the threshold for nociceptive reflex to single stimuli, but do not change the reaction to pain elicited by heat, cold or pressure, or the threshold of the nociceptive reflex to repetitive stimuli [5]. Training and attention has been shown to influence the pain threshold and the threshold for the nociceptive reflex [2], and distraction has been shown to decrease the nociceptive reflex [25]. In this study, propofol, in sedative doses, produced the same increase in the nociceptive reflex threshold to single stimulations as alfentanil, but showed hyperalgesic effects for tolerance to mechanical pressure. This indicates that the increase in threshold of the nociceptive reflex could be caused by sedation and not analgesia. The nociceptive reflex to single electrical stimulations may therefore not be a measure of analgesia when the drug tested also has sedative effects. As the nociceptive reflex has a sensory afferent and motor efferent component, the difference between propofol and alfentanil could be explained by stronger depression of the motor component by propofol. However, this would influence reflexes elicited by single and repeated stimulations in the same manner. Propofol did not change the threshold for temporal summation of the nociceptive reflex to repeated stimulations, indicating that the muscle component is not influenced significantly by propofol.

MECHANICAL PRESSURE

Early studies by Clutton-Brock [8, 26] and Dundee [9], using a relatively simple mechanical pressure pain model showed that small doses of thiopentone had a hyperalgesic effect. Our study showed that

propofol, in subhypnotic doses, had a similar hyperalgesic effect on pressure pain. *In vitro* studies in single neurones [27] and isolated spinal cord models [10] showed that propofol and thiopentone depressed spinal nociceptive transmission, but they may have a different effect, through GABA inhibitory neurones, in the intact animal or human [28].

EVOKED VERTEX POTENTIALS

Arendt-Nielsen [3] correlated the amplitude or power of the long latency evoked vertex potential to an argon laser nociceptive thermal stimulation with the intensity of the perceived pain. With this method an analgesic effect of alfentanil [29], ibuprofen [30], paracetamol [31], codeine [32] and extradural morphine [33] has been demonstrated. A recent study failed to show an effect on laser evoked potentials of i.v. morphine [34]. In a recent review on nociceptive laser evoked vertex potentials by Arendt-Nielsen [35], it was suggested that sedation might influence the evoked potential. Evoked potentials to non-nociceptive stimuli should therefore be recorded as a control for sedation. We have shown recently that subanaesthetic isoflurane concentrations (0.10–0.26 vol % end-tidal) also decreased the amplitude of the evoked vertex potentials to painful laser and electrical stimuli [6]. But isoflurane produced a similar reduction in the amplitude of non-pain related auditory evoked vertex potentials recorded with the same paradigm, and did not reduce the perceived pain. In our study, propofol reduced the amplitude of evoked vertex potentials, but showed a hyperalgesic effect in the pain tolerance threshold to mechanical. This indicates that the reduction in amplitude of evoked vertex potentials by propofol and isoflurane is not caused by an analgesic effect. Anker-Møller and co-workers [7] also found a decrease in laser evoked vertex potentials with subhypnotic doses of thiopentone and propofol, but they did not measure the effect on non-pain-related potentials.

DRUG CONCENTRATIONS

The concentrations of propofol and alfentanil used in this study were chosen on empirical grounds, so that the low doses produced slight sedation (propofol) and slight analgesia (alfentanil), and the high doses distinct sedation and analgesia. The reaction time for low-dose propofol was slightly but not statistically increased compared with baseline, but for the high dose a significant increase was found compared with baseline and low-dose propofol. Low-dose alfentanil produced a slight but not significant increase in pain tolerance to mechanical pressure, but for the high dose of alfentanil a significant increase was found compared with baseline and the low dose. Furthermore, the threshold for the nociceptive reflex to single stimulations, and the decrease in the amplitude of the vertex potentials were not different for high-dose propofol and high-dose alfentanil. This indicates that the chosen doses were relevant according to the initial criteria, and that an effect of sedation on the nociceptive reflex and the amplitude of the vertex potentials could be investigated at these concentrations.

SHORT *VS* REPEATED OR LONGER LASTING STIMULATIONS

Arendt-Nielsen and co-workers [36, 37] and Brennum and co-workers [17, 38] have shown that brief localized nociceptive stimuli can be attenuated to a greater extent by extradural lignocaine or morphine than noxious stimulations of longer duration or involving larger areas. That central temporal and spatial summation of nociceptive stimuli are important for determination of anaesthetic efficacy is supported by our study. The responses to experimental pain tests involving short or single stimulations were influenced by the sedative effect of propofol, whereas tests involving longer lasting or repeated stimulations were not. Alfentanil showed the expected analgesia on both the short or single stimulations, and the longer lasting or repeated stimulations used in this study (these results are in accordance with previous studies [22, 29]).

PAIN DETECTION *VS* PAIN TOLERANCE THRESHOLDS

Measuring pain tolerance thresholds and not just pain detection was also important in this study. If we had only measured pain detection thresholds to mechanical pressure, we would not have detected the hyperalgesic effect of propofol on mechanical pain.

This study showed that when experimental pain models were used to measure an analgesic effect, the effects of sedation on both psychophysical and electrophysiological responses must be controlled. It is important to combine threshold measurements and electrophysiological responses with psychophysical pain ratings. Furthermore, models eliciting temporal or spatial summation, or both, of nociceptive stimuli appear to be less influenced by sedation.

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