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Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials

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Summary

The aim of this study was to see if an analgesic effect of subanaesthetic concentrations of isoflurane could be detected with evoked potentials elicited by nociceptive stimuli. We studied 10 healthy volunteers breathing three steady-state subanaesthetic concentrations of isoflurane (0.08, 0.16 and 0.24 vol% end-tidal). Reaction time, subjective pain intensities and evoked vertex potentials to laser (LEP) and electrical (SEP) stimuli were recorded and compared with auditory evoked potentials (AEP). Compared with baseline, the subanaesthetic concentrations of isoflurane did not change the latencies of the evoked potentials, but caused a significant reduction in the amplitudes of the LEP and SEP at 0.16 and 0.24 vol% and of the AEP at all three concentrations. There were no changes in perceived pain intensity, and isoflurane produced similar reductions in evoked potentials elicited by both nociceptive and non-nociceptive stimuli. The reaction time was increased significantly at 0.24 vol% isoflurane. The results demonstated that subanaesthetic isoflurane concentrations caused similar changes in evoked potentials with both painful and non-painful stimuli, with no effect on perceived pain intensity. (*Br. J. Anaesth*. 1996; **76**: 38–42)

Key words

Anaesthetics volatile, isoflurane. Pain, experimental. Monitoring, evoked potentials.

The analgesic effect of subanaesthetic concentrations of inhalation anaesthetics has been investigated by either clinical assessment [1–3] or pain threshold measurements [4, 5], but with conflicting results. In a recent study we found no analgesic effect of subanaesthetic concentrations of isoflurane on experimental pain tests [6]. These pain tests may, however, not always be able to detect a weak analgesic effect [7]. Laser stimulation may be a more sensitive method, as this has been used to demonstrate the analgesic effect of weak analgesics [8–11]. The purpose of the present study therefore was to see if evoked vertex potentials elicited by nociceptive electrical and laser stimulation could be used to detect weak analgesic effects of subanaesthetic concentrations of isoflurane.

Patients and methods

We studied 10 healthy volunteers (five male, mean age 24 (range 22–30) yr). They were not receiving any medication, had no allergies or adverse reactions to previous anaesthetics and, for the female volunteers, were not pregnant. Written informed consent 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, the volunteers received omeprazole 40 mg (Antra) the evening before testing, and were investigated after a fasting period of at least 6 h. During the tests the volunteers rested comfortably supine. An i.v. infusion of NaCl-glucose was given and Sp_{O_2}, ECG and non-invasive arterial pressure were monitored continuously. The subanaesthetic concentrations of isoflurane were delivered via a face mask. The breathing system and the gas monitors have been described previously [6].

The following tests were applied in a randomized order.

ARGON LASER STIMULATION

The output from an argon laser (Spectra Physics 168) was transmitted via a single 0.2-mm quartz fibre (output controlled with an external power meter). The distance to the skin was adjusted to obtain a laser beam diameter of 3 mm on the skin and a stimulus of 200 ms duration was applied to the dorsum of the right hand (C7 dermatome). The target area was divided into small sectors and, to avoid receptor fatigue, the sectors were stimulated sequentially. Pain threshold, defined as a distinct sharp pinprick, was determined with five ascending and five descending series of stimulation. For

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recording of the laser evoked potentials (LEP), 16 laser stimuli with an intensity of 1.5 times the initial pain threshold and with a random inter-stimulus interval between 10 and 20 s were applied. After the last stimulation, the volunteer was asked to rate the perceived pain intensity on a visual analogue scale (VAS).

ELECTRICAL STIMULATION

An intracutaneous finger electrode applied to the pulp of the third finger was used [12]. A 25-ms single stimulus (in reality train of five, 1-ms, square-wave impulses, but these are perceived as a single stimulus) was delivered from a Digitimer DS 7 (Digitimer Ltd, Hertfordshire, England) constant current stimulator triggered by a Philips Generator PM 5150 (Philips GmbH, Hamburg, Germany). The current was increased from 0 in steps of 0.2 mA until the volunteer rated the perceived pain intensity of the stimulation on the VAS equally with that of laser stimulation. This intensity was then used for recording of the SEP. Application of the 16 stimuli and rating of perceived pain intensity were performed as for the LEP.

ACOUSTICAL STIMULATION

A binaural click with an intensity of 90 dB was provided by a Medelec ST 10 stimulator (Medelec Ltd, Surrey, England) through acoustically shielded headphones. For recording of the AEP, 16 stimuli with a random inter-stimulus interval between 10 and 20 s were applied as described for the laser and electrically evoked vertex potentials.

REACTION TIME

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

RECORDING OF THE EVOKED POTENTIALS

All evoked potentials were recorded from a needle electrode (Dantec, Denmark), inserted at Cz′ (according to the international 10–20 system) against a surface Ag-AgCl electrode on the right mastoid. The signal was filtered (bypass 0.1–30 Hz), amplified, recorded and averaged on a personal computer (PC) with the EPsys software (Aalborg University, Denmark) in the interval from 0.5 s before the stimulus until 2 s after the stimulus.

In order to familiarize the volunteer with the procedure, all experiments were explained before trial testing was performed. The mask was then fitted and the volunteer breathed air for 5 min, or until he felt comfortable, and there were no leaks from the mask. A baseline test series of the above

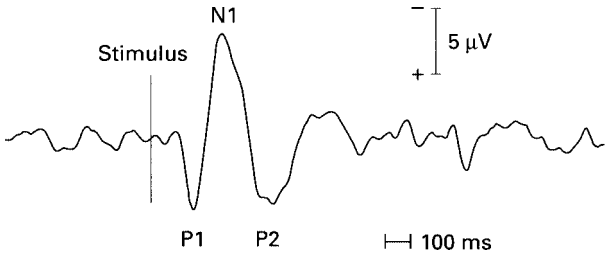

Figure 1 An LEP, which is the average of 16 evoked potentials elicited by short laser stimulations of 200 ms duration.

described tests was then performed. Thereafter, isoflurane was introduced slowly into the breathing system and adjusted to the desired end-tidal concentration. This was chosen randomly from one of the three concentrations, 0.08, 0.16 and 0.24 vol%. We did not use concentrations higher than 0.24 vol% (about 0.2 MAC isoflurane), as volunteers at higher concentrations tend to be too sedated to co-operate [13]. After 15 min of equilibration at a constant end-tidal concentration, a test series was performed. This procedure was repeated with the two other isoflurane concentrations. The delivered isoflurane concentration was known only to the anaesthetist performing "anaesthesia". After testing had been performed at all three isoflurane concentrations, isoflurane was discontinued.

Latencies and peak-to-peak amplitudes of the first three major peaks, P1, N1 and P2 of the late LEP, SEP and AEP were measured (fig. 1). Statistical analysis was performed independently for each class of the evoked vertex potentials and the reaction time with the software SigmaStat v1.01 (Jandel Scientific GmbH, Erkrath, Germany). Median values and quartiles were calculated for the three isoflurane concentrations. The numerical values of all measurements were expressed as a percentage of baseline values. The values at the different isoflurane concentrations were compared with baseline using Friedman's test for repeated measures analysis of variance on ranks, and the Student–Newman–Keuls test for multiple comparison. $P < 0.05$ was considered statistically significant.

Results

Evoked vertex potentials were recorded in all subjects. There were no statistically significant changes in the latencies of the LEP and SEP compared with baseline (table 1) or with the AEP. The results in the peak-to-peak amplitudes are summarized in table 2. Statistically significant reductions compared with baseline were observed for P1–N1 amplitudes of the SEP at 0.16 and 0.24 vol% and for AEP at 0.08, 0.16 and 0.24 vol% isoflurane. N1–P2 amplitudes were reduced significantly for the LEP and SEP at 0.16 and 0.24 vol% and for AEP at 0.08, 0.16 and 0.24 vol% isoflurane. Furthermore, N1–P2 amplitude of the SEP at 0.08 vol% was reduced significantly less compared with those of the SEP and AEP at 0.16 and 0.24 vol%. There were no

Table 1 Change in latencies (median (25–75 percentiles)) of evoked vertex potentials to laser, electrical and auditory stimulation. Values are percentage of baseline values

	Isoflurane		
Latencies	0.08 %	0.16 %	0.24 %
Laser evoked potentials P1	102.9 (100.0–108.8)	99.0 (95.9–103.1)	103.3 (98.1–115.1)
Laser evoked potentials N1	99.3 (96.1–102.5)	99.2 (97.4–102.5)	101.0 (95.1–114.5)
Laser evoked potentials P2	97.6 (94.8–100.0)	98.3 (95.8–101.4)	94.4 (85.3–101.9)
Somatosensory evoked potentials P1	106.3 (76.5–109.3)	102.0 (94.9–116.0)	113.6 (100.0–122.9)
Somatosensory evoked potentials N1	97.6 (93.2–100.0)	102.2 (100.0–107.1)	98.6 (91.4–109.3)
Somatosensory evoked potentials P2	102.7 (96.1–104.7)	99.7 (90.7–105.4)	101.4 (95.9–104.7)
Auditory evoked potentials P1	100.0 (95.6–100.0)	100.0 (100.0–105.1)	106.9 (100.0–110.3)
Auditory evoked potentials N1	101.5 (100.0–106.0)	100.0 (95.3–108.0)	108.4 (103.2–114.3)
Auditory evoked potentials P2	95.4 (93.1–101.9)	102.3 (93.1–107.6)	96.7 (90.7–107.6)

Table 2 Change in amplitudes (median (25–75 percentiles)) of evoked vertex potentials to laser, electrical and auditory stimulation. Values are percentage of baseline values. *$P < 0.05$ compared with baseline; †$P < 0.05$ compared with baseline and the SEP at 0.08 vol% isoflurane

	Isoflurane		
Amplitudes	0.08 %	0.16 %	0.24 %
Laser evoked potentials Pl–N1	98.5 (51.6–126.9)	64.7 (54.4–86.6)	51.8 (30.4–107.1)
Laser evoked potentials N1–P2	76.2 (51.7–100.0)	68.9 (23.6–83.8)*	47.2 (37.5–55.8)*
Laser evoked potentials VAS	97.4 (89.7–100.0)	98.5 (90.0–105.3)	103.7 (92.0–108.7)
Somatosensory evoked potentials P1–N1	49.6 (42.0–86.0)	50.9 (28.9–61.9)*	18.3 (6.8–42.1)*
Somatosensory evoked potentials N1–P2	76.5 (59.5–102.7)	51.5 (35.8–59.4)†	40.9 (17.9–60.7)†
Somatosensory evoked potentials VAS	90.0 (66.7–100.0)	88.6 (71.2–111.1)	87.0 (65.9–111.1)
Auditory evoked potentials P1–N1	53.8 (37.7–65.7)*	48.0 (39.7–54.6)*	45.8 (36.1–70.7)*
Auditory evoked potentials N1–P2	56.1 (40.8–67.5)*	39.0 (37.1–51.6)†	42.3 (25.0–58.9)†

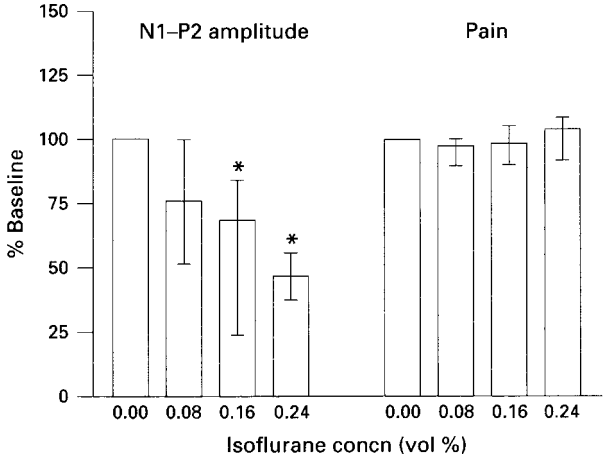

Figure 2 Argon laser stimulation. Comparison between the decrease in N1–P2 amplitude (expressed as percentage of baseline values) with increasing isoflurane concentrations of the long latency vertex potential to laser stimuli, and the perceived pain rated on a visual analogue scale. *Significantly different from baseline.

significant differences between the reductions in the amplitudes of the LEP and SEP compared with the AEP at each of the three isoflurane concentrations (figs 2–4).

There was no significant reduction in perceived pain intensity for either laser or electrical stimulation. Compared with baseline, median reaction time was 97.7 % (25–75 percentiles 79.7–127.9 %) at 0.08 vol%, 116.5 % (94.2–128.7 %) at 0.16 vol% and 161.1 % (131.6–238.7 %) at 0.24 vol%. Reaction time was increased significantly at 0.24 vol% compared with baseline, 0.08 and 0.16 vol%.

Discussion

We have shown that subanaesthetic concentrations of isoflurane did not change the latencies of the evoked vertex potentials, but caused a significant reduction in the amplitudes of the LEP and SEP at 0.16 and 0.24 vol% and of the AEP at all three concentrations. There was no change in perceived pain intensity, and isoflurane produced similar

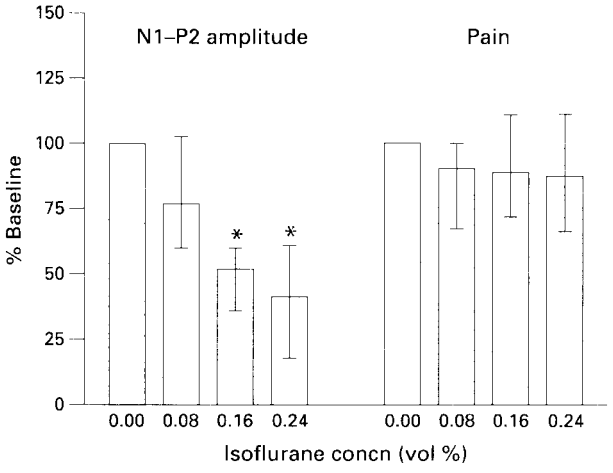

Figure 3 Electrical stimulation. Comparison between the decrease in N1-P2 amplitude (expressed as percentage of baseline values) with increasing isoflurance concentrations of the long latency vertex potential to electrical stimuli, and the perceived pain rated on a visual analogue scale. * Significantly different from baseline.

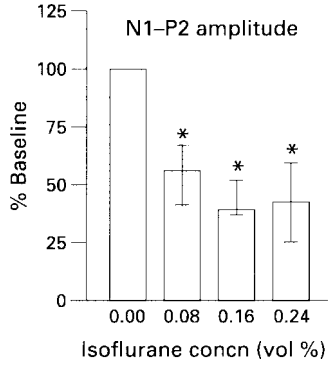

Figure 4 Auditory stimulation. Decrease in N1–P2 amplitude (expressed as percentage of baseline values) with increasing isoflurane concentrations of the long latency vertex potential to auditory stimuli. * Significantly different from baseline.

reductions in amplitudes of the evoked potentials elicited by both nociceptive and non-nociceptive stimuli. The reaction time was increased significantly at 0.24 vol% isoflurane. We conclude that subanaesthetic concentrations of isoflurane have a sedative but no or only a minimal analgesic effect which the present techniques could not detect.

Several studies have shown that potentials, evoked by noxious laser stimuli, correlate with perceived pain intensity [10, 11, 14, 15]. In contrast, there is a lack of correlation between the amplitude of the vertex potential evoked by nociceptive electrical stimulation on the surface of the skin and subjective pain rating [16, 17]. This suggests that transcutaneous electrically evoked vertex potentials are not a reliable measure or correlate for changes within the nociceptive system.

In the present study electrical stimulation was applied using the intractaneous technique [12]. This procedure ensured a high current density at the superficial nociceptors. As a consequence, pain thresholds were up to 10 times lower compared with transcutaneous stimulation. The sensation is described as a distinct pricking pain, very similar to that elicited by laser stimulation. This perception is attributed to the activity in the Aδ nociceptive afferents [18]. Kochs and colleagues [19] used the same technique for eliciting latè SEP. They found that the recorded SEP were sensitive to opioid treatment during inhalation anaesthesia.

We did not find any correlation between the decrease in amplitudes of the LEP and SEP, and subjective pain rating. There was a reduction in the peak-to-peak amplitudes for the evoked vertex potentials elicited by nociceptive electrical and laser stimulation at the two higher isoflurane concentrations (see table 2), which could be interpreted as an analgesic effect [16, 20–22]. But the same decrease in the peak-to-peak amplitudes was observed also for the non-nociceptive AEP, and furthermore the perceived pain intensity did not differ significantly from baseline. These results suggest that the reduction in peak-to-peak amplitudes of the LEP and SEP are caused by a non-specific effect of isoflurane on the vertex potentials (sedation ?) rather than by a specific analgesic effect on the nociceptive system.

We have shown that when evoked vertex potentials are used to investigate the analgesic effect of a drug, it is important not only to evaluate the effects of nociceptive stimuli, but also to control for a non-analgesic general effect on the evoked vertex potentials elicited by non-nociceptive stimuli. Furthermore, the electrophysiological responses should (when possible) be compared with subjective pain ratings. If we had measured only the effect of subanaesthetic concentrations of isoflurane on the amplitude of the evoked vertex potentials to painful laser and electrical stimulation, we would have presumed this to result from an analgesic effect, which in reality was not present.

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