SUBHYPNOTIC DOSES OF THIOPENTONE AND PROPOFOL CAUSE ANALGESIA TO EXPERIMENTALLY INDUCED ACUTE PAIN

E. ANKER-MØLLER, N. SPANGSBERG, L. ARENDT-NIELSEN, P. SCHULTZ, M. S. KRISTENSEN AND P. BJERRING

SUMMARY

Subhypnotic doses of thiopentone are considered to have a hyperalgesic effect, while propofol has a hypoalgesic effect. We investigated the effect of these drugs on the nociceptive system by measuring the pain threshold to laser stimulation and the pain evoked potential (power and latency). Nineteen patients (ASA group I) participated. Twelve patients received thiopentone 0.5 mg kg\(^{-1}\) and propofol 0.25 mg kg\(^{-1}\) in random order separated by an interval of 14 h, and seven patients received saline. Immediately after the injection of both agents, the pain threshold was increased significantly (P < 0.001) and the amplitude of the evoked potential was reduced significantly (P < 0.05), while the latency of the evoked potential remained constant. It is concluded that, in subhypnotic doses, both thiopentone and propofol decrease the acute pain evoked by argon laser stimulation.

KEY WORDS


PATIENTS AND METHODS

Twelve non-premedicated, ASA I patients (eight female) participated in the investigation. Median age was 33 (range 21–49) yr and median weight 64 (44–86) kg. Seven non-premedicated patients (one female) participated as controls; their median age was 33 (29–35) yr and median weight 80 (52–85) kg. Informed consent was obtained in agreement with the Helsinki II declaration, and the investigation was approved by the local Ethics Committee. During the experiment the patients rested comfortably and wore goggles to protect against the laser light.
Laser stimulation

The output from an argon laser (Spectra Physics, 168) was transmitted to the skin via a quartz fibre. Output power could be adjusted from 50 mW to 3.5 W. The argon light wavelengths were 488 nm (blue) and 515 nm (green); the beam was composed of both wavelengths, and the energy distribution was 33% and 66%, respectively. This distribution remained constant for laser intensities greater than 50 mW. An external laser power meter (Ophir, Israel) was used to measure the power dissipated from the fibre. A continuous, low energy beam (50 mW) from the argon laser was used to visualize the stimulation site. To keep the energy density of the beam low, a 200-ms stimulus duration and a 3-mm laser beam diameter were used; these stimulus parameters have been found adequate to elicit distinct pain without causing superficial burn lesions [5]. The greatest laser intensity applied to the skin was 3 W, because intensities greater than this may cause minor, superficial burns. The laser stimulus was applied to the dorsal part of the right hand within a target area of $1 \times 3$ cm$^2$. The target area was encircled by ink to ensure that the same area was used for consecutive stimulations. Repeated stimulations at identical points within this area were avoided by dividing the area into small sectors which were stimulated sequentially.

Pain thresholds to laser stimuli

The pain threshold to laser stimulation was defined as the lowest energy eliciting a distinct, sharp pinprick sensation. The thresholds were calculated as a mean of three ascending and three descending series of stimulation [5]. Initially the threshold was determined five times.

Recording of pain related potentials

The pain threshold is defined as a change in modality, but the intensity of the pain perceived cannot be evaluated by the threshold alone. Pain evoked potentials include this dimension, because the amplitude or power of the potential reflects the intensity of the pain perceived.

The potentials were recorded with a platinum needle electrode (Disa 25C04) inserted over the vertex of the scalp with reference to the linked earlobes. The EEG was amplified, filtered by a second order filter (0.5–12 Hz) and sampled by a computer. Pain evoked potentials recorded over the vertex are large, and 16–24 potentials were averaged in order to obtain a sufficient signal-to-noise ratio. The major complex of the evoked potentials had a latency of approximately 300 ms (fig. 1). This potential is often characterized as a vertex potential. The amplitude or power of this complex is within a range of intensities found to correlate with the intensity of the pain stimulus, and is thus a quantitative technique for assessment of experimentally induced pain [9]. The latency of the complex provides information on velocity of conduction along the peripheral and central pain pathways.

The laser intensity used for stimulation corresponded to strong pain. This stimulus intensity was maintained constant throughout the experiment. The intervals between stimuli were randomized with a mean of 15 s (10–20 s). To avoid visual and auditory interference, volunteers wore protective goggles and earphones. The power (0.5–7.5 Hz) of the pain-evoked response 200–700 ms after stimulation was calculated and used for quantification [9]. This measurement has been shown previously to be sensitive to changes in the intensity of pain perceived [9].

Procedure

I.v. subhypnotic doses of propofol (0.25 mg kg$^{-1}$, 10 mg ml$^{-1}$) or thiopentone (0.5 mg kg$^{-1}$, 2.5 mg ml$^{-1}$) were injected in random order. The patients and investigator were blinded to the injections, the duration of which was 10–15 s, whatever the volume. The intervals between injections were 13–15 h. The pain threshold was measured before and every 1 min after injection for 10 min. In eight of the patients the evoked potentials were registered before and 15 min after the injections. The group of seven controls were given i.v. saline 10 ml and pain thresholds were determined at the same times as in the thiopentone and propofol groups. Evoked potentials were measured before and 15 min after injection.

The patients were asked to report any side effects.

Statistical analysis

Wilcoxon’s test (signed rank sum) and Student’s $t$ test were used for statistical evaluation of the results. Statistical significance was accepted at a 5% level.

Side effects

No side effects were noted, but the patients generally felt more drowsy after thiopentone than
after propofol. Drowsiness occurred 0.5–1 min after injection.

**Pain threshold**

In the control group no significant changes were observed (fig. 2). The coefficient of variance was 4.2%.

After injection of thiopentone 0.5 mg kg⁻¹ the pain threshold increased rapidly ($P < 0.001$) to approximately 1.5 times the initial value (fig. 2). The peak value was reached 2 min after injection. The pain threshold declined slowly for the next 10 min, but was still increased significantly ($P < 0.001$) after 10 min.

The pain threshold increased gradually up to 10 min after injection of propofol 0.25 mg kg⁻¹. After 10 min the pain threshold was increased significantly ($P < 0.001$), to 1.35 times the initial value.

**Evoked potentials**

The power of the evoked potentials measured from the control group decreased ($P < 0.05$) by 11 (SEM 5)%.

Fifteen minutes after thiopentone, the pain-related evoked potential was decreased ($P < 0.05$) by 15 (4)% compared with the initial value and with the placebo group. The power of the evoked potential after propofol was reduced ($P < 0.001$) by 17 (5)% compared with baseline and placebo.

The latency of the major negative complex remained constant under all conditions (mean 364 (SEM 40) ms), indicating no effect of the drugs on velocity of conduction along the pain pathways.
DISCUSSION

One of the main problems in pain research is measurement of pain. One method used to elicit pain is the algesimeter, with which a metal disc (9.2 mm) is pressed against the anterior part of the tibia with increasing pressure from 454 to 7264 g. This method was introduced by Clutton-Brock [4] and was used by Dundee [2] to show that subhypnotic doses of thiopentone have a hyperalgesic effect. Briggs and co-workers [3] compared the effects of subhypnotic doses of thiopentone and propofol and found the latter to have a hypoalgesic action. Robson, Davenport and Sugiyama [10] showed that, although thiopentone decreased the pain threshold as measured by tibial pressure, it increased the pain threshold as measured by thermal stimulation from a heated platinum wire pressed on the thenar eminence. This is in agreement with our results indicating that the pain from tibial pressure differs from pain elicited by heat stimulation. The obvious explanation is that the algesimeter stimulates not only nociceptive receptors, but also those for touch and pressure. The argon laser pulses stimulate predominantly the Aδ innervated nociceptors [5, 9] and facilitate the study of the hypo/hyperalgesic effects of different substances.

While the assessment of the pain threshold reflects mainly changes in sensitivity to the stimulus, the pain-evoked potential also encompasses perception of the stimulus and changes in velocity of conduction along pain pathways.

Clutton-Brock [11] explained the hyperalgesic effect of thiopentone (and several other anaesthetics) by the inhibition of an ascending, reticulo-cortical inhibitory system facilitating the perception or transmission of pain. The evoked potentials showed a decrease in amplitude after both thiopentone and propofol, but no changes in velocity of conduction along the pain pathway.

The decrease in amplitude of the pain-evoked potential for the control group is a general feature for this class of brain potentials [9]. The potential evoked by pain is not fundamentally different from the so called vertex potentials evoked by auditory and visual stimuli. These potentials also decrease by 10–20% between subsequent recordings, probably because of changes in attention. Attention and distraction are known to augmentate and reduce, respectively, the amplitude of the vertex potential. As attention is difficult to control, the potential inevitable decreases for repetitive recordings.

In conclusion, both thiopentone and propofol increased the pain threshold and reduced the amplitude of the evoked potential to acute laser induced pain. The latency of the potential remained constant. We cannot confirm the previous findings of a hyperalgesic effect of thiopentone.

ACKNOWLEDGEMENT

This work was supported by the Danish Cancer Society (Grant No. 87-006).

REFERENCES