BJA

*British Journal of Anaesthesia*, 121 (1): 291–302 (2018)

doi: 10.1016/j.bja.2018.03.031

Research Article

# Nociceptive activation in spinal cord and brain persists during deep general anaesthesia

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**Background:** In clinical practice, analgesic drug doses applied during general anaesthesia are considered sufficient when clinical responses (e.g. movement, blood pressure and heart rate elevations) are suppressed during noxious stimulation. We investigated whether absent clinical responses are indicative of suppressed spinal and brain responsiveness to noxious stimulation in anaesthetised subjects.

**Methods:** Ten healthy volunteers were investigated during deep propofol anaesthesia supplemented with increasing doses of remifentanil in a stepwise manner. Noxious electrical stimuli at an intensity comparable with surgical stimulation were repeatedly administered at each targeted remifentanil concentration. During stimulation, we monitored both clinical responses (blood pressure, heart rate, and movement) and neuronal responses. Neuronal responses were assessed using functional magnetic resonance imaging, spinal reflex responses, and somatosensory evoked potentials.

**Results:** This monitoring combination was able to faithfully detect brain and spinal neuronal responses to the noxious stimulation. Although clinical responses were no longer detected at analgesic dosages similar to those used for general anaesthesia in clinical practice, spinal and brain neuronal responses were consistently observed. Opioid doses that are significantly larger than is usually used in clinical practice only reduced neuronal responses to 41% of their maximal response.

**Conclusions:** Nociceptive activation persists during deep general anaesthesia despite abolished clinical responses. Absent clinical responses are therefore not indicative of absent nociception-specific activation. Thus, commonly accepted clinical responses might be inadequate surrogate markers to assess anti-nociception during general anaesthesia. Further research is required to investigate whether persistent nociception causes adverse effects on patient outcome.

**Keywords:** general anaesthesia; magnetic resonance imaging; nociception; propofol; remifentanil

**Editorial decision**: March 14, 2018; **Accepted:** April 11, 2018

**Editor's key points**

- During anaesthesia, analgesic drugs are commonly titrated according to clinical responses to noxious stimuli.
- The authors used functional imaging and spinal neurophysiological monitoring to assess nociception simultaneous with clinical responses during general anaesthesia.
- Opioid doses that prevented clinical responses, attenuated, but did not obliterate, spinal and cortical responses.
- Absence of clinical responses to noxious stimuli does not necessarily imply absence of nociception.

More than 230 million major surgical procedures requiring anaesthesia are conducted worldwide each year.[1] General anaesthesia, the most common form of anaesthesia, is performed by joint administration of a hypnotic drug and a strong analgesic. While an adequate dose of a hypnotic drug is required to induce unconsciousness and prevent memory formation,[2] a sufficient level of suppression of nociception (i.e. antinociception) is required to prevent arousal, body movements, haemodynamic changes,[3,4] neuroendocrine, and metabolic stress responses.[5,6]

In current clinical practice, the general consensus is that a sufficient level of antinociception has been reached when clinical responses such as body movement and heart rate or blood pressure elevations no longer occur during surgical stimulation. In this study, we sought to investigate whether the absence of such clinical responses during deep general anaesthesia indeed indicates the absence of spinal and brain responses to noxious stimuli or to what extent such responses still occur during standard, clinically sufficient, general anaesthesia.

To cover both spinal and brain nociceptive processing, we combined three neurophysiological methods in one setup. Spinal responses to noxious stimulation were assessed via nociception-specific spinal flexion reflex responses using electromyography. Brain responses to noxious stimulation were assessed by monitoring the activity in those brain regions that were found to be activated when contrasting intense noxious *vs* innocuous stimuli using functional magnetic resonance imaging (fMRI), supplemented by simultaneous recording of somatosensory evoked potentials using electroencephalography (EEG).

## Methods

### Participants

We conducted this study with 10 healthy volunteers after approval by the local ethics committee (reference number ZS EK 14 005/10, Ethikkommission des Landes Berlin, Landesamt für Gesundheit und Soziales) and the German federal drug agency (reference number 4038410, Bundesinstitut für Arzneimittel und Medizinprodukte). The study was registered at the German register for clinical trials (Deutsches Register Klinischer Studien, registration number DRKS00000663).

After providing written informed consent, all participants underwent the hospital's standard anaesthesia preparation procedure, which included providing a detailed medical history and undergoing a clinical examination. Additionally, all participants underwent test measurement sessions of the nociceptive flexion reflex and anatomic MRI scans to accustom the participants to the procedures.

### Anaesthetic procedure

Anaesthesia was induced by the infusion of propofol using target-controlled infusion pumps (Injectomat TIVA Agilia; Fresenius Kabi, Bad Homburg, Germany).[7] The propofol effect-site concentration was initially adjusted to 4 μg $ml^{-1}$ for all subjects. Before and during anaesthesia induction a tight-fitting facemask was applied to monitor ventilation and respiratory gases. After the loss of consciousness, defined as a state during which the subjects could not be aroused by strong innocuous stimuli ('shaking and shouting'), a laryngeal mask (LMA Unique; LMA, San Diego, CA, USA) was inserted to facilitate monitoring and assistance of ventilation. Ventilation was assisted using the pressure support ventilation mode of the anaesthesia workstation, which automatically switches to a pressure-controlled ventilation mode during apnoea (Dräger Fabius MRI, Drägerwerk, Lübeck, Germany). Pressure levels in both ventilation modes were continually adapted throughout the course of the study to maintain stable end-tidal $CO_2$ levels at the individual level before induction of anaesthesia. By this method, the individual end-tidal $CO_2$ level varied no more than 0–2.2% (0–0.1 kPa) from the individual means (4.6–5.6 kPa) across all remifentanil concentrations (see supplementary appendix for details). For nine subjects, who did not tolerate the insertion of the laryngeal mask at an effect-site concentration of 4 μg $ml^{-1}$, the effect-site concentration was increased intermittently to 6 μg $ml^{-1}$ (eight subjects) or 8 μg $ml^{-1}$ (one subject) to facilitate insertion. After insertion, the propofol effect-site concentration was decreased back to the lowest individual level that ensured stable unconsciousness without arousal during innocuous ('shaking and shouting') and noxious stimulation (4 and 5 μg $ml^{-1}$ for eight and two subjects, respectively). These individual effect-site concentrations of propofol were then kept stable throughout all measurements. Additional administration of the opioid remifentanil was performed via target-controlled infusion pumps to achieve stable effect-site concentrations of 0, 1, 2, 4, 8 ng $ml^{-1}$ (in ascending order).[8] At each remifentanil concentration, after increasing the targeted effect-site concentration, we waited until the pharmacokinetic/pharmacodynamic (PK/PD) model indicated that the targeted effect-site concentration was reached [time to reach 99% of the target concentration (range): 52–70 s] plus another 5 min (approximately 2–4 equilibration half-life periods of remifentanil[8,9]) to account for individual differences. Sets of measurements to monitor clinical and spinal and brain responsiveness to noxious stimulation were performed at each concentration.

### Monitoring of clinical responsiveness to noxious stimuli

Clinical responsiveness was assessed at each concentration by repeated administration of transcutaneous electrical stimuli to the right ulnar nerve at an intensity comparable with surgical stimulation (30 s tetanic stimulation at 80 mA; NS252, Fisher & Paykel Healthcare Ltd., Auckland, New Zealand).[10] Before, during, and after every stimulus, the heart rate was measured continuously, based on a beat-by-beat analysis of the ECG as integrated in the applied clinical monitoring system (Precess 3160, Invivo, Gainesville, FL, USA). Noxious