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CLINICAL PRACTICE

Multi-level approach to anaesthetic effects produced by sevoflurane or propofol in humans: 1. BIS and blink reflex†

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Background. The relative roles of forebrain and brainstem in producing adequate anaesthesia are unclear.

Methods. We simultaneously analysed the effects of sevoflurane (Group S; $n=18$) or propofol (Group P; $n=29$) on the bispectral index (BIS) and the first component of the blink reflex (R1). The dose of anaesthetic agent was increased until loss of blink reflex. After discontinuation and reappearance of blink reflex activity, the amount was increased again. The area under curve R1 (area-R1) of the electromyogram of the orbicularis oculi muscle after electrical stimulation of the supraorbital nerve was measured. Using a sigmoid E_{max} model and a first-order rate constant k_{e0}, we characterized the dose–response relationships for BIS and area-R1.

Results. Concentration-dependent depression of BIS and area-R1 was adequately modelled. The concentration that causes an effect midway between minimum and maximum (EC_{50}) for area-R1 was smaller than EC_{50} for BIS in both groups [0.34 (0.19) *vs* 1.29 (0.19) vol% and 1.78 (0.65) *vs* 2.69 (0.67) $\mu g\ ml^{-1}$; mean (SD)]. At doses of sevoflurane and propofol with equivalent depression of BIS, sevoflurane depressed area-R1 more than propofol. The k_{e0} for area-R1 was about half that for BIS in both groups: 0.24 (0.19–0.29) *vs* 0.48 (0.38–0.60) min^{-1} for Group S; 0.28 (0.23–0.34) *vs* 0.46 (0.40–0.54) min^{-1} for Group P, geometric mean (95% CI).

Conclusions. The blink reflex (brainstem function) is more sensitive to sevoflurane or propofol than BIS (forebrain function). Sevoflurane suppresses the blink reflex more than propofol. Different k_{e0}s for blink reflex *vs* BIS indicate different effect sites.

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Hypnosis and immobility after noxious stimulation may be separate components of general anaesthesia. Hypnotic effects of anaesthetics occur in the forebrain, whereas immobilizing effects occur mainly at the level of the spinal cord.[1] Therefore, adequacy of anaesthesia must be measured at least at both sites. Our aim is to assess simultaneously the relative roles of forebrain and brainstem in humans. The brainstem is the source for all cranial nerves that deal with sensory and motor function in the head and neck. The bispectral index (BIS) was used in the present study as an indicator of the level of hypnosis.

An electrically evoked blink reflex was used to assess brainstem function. The traditional eyelash reflex, commonly used as a clinical endpoint of anaesthesia induction, is initiated by a non-standardized stimulus and is evaluated by subjective observation. With the use of electrical stimulation and electromyography (EMG), the stimulus is standardized, the response is objectively recorded, and additional information is obtained. We used the early ipsilateral reflex component (R1), which is less depressed

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by sedatives and anaesthetics than the late bilateral components R2 and R3.[2–4]

We have assessed the relationships between varying concentrations of sevoflurane or propofol and two surrogate anaesthetic measures, BIS and blink reflex, using pharmacokinetic–pharmacodynamic (PKPD) modelling, yielding two important measures: the concentration that causes an effect midway between minimum and maximum (EC_{50}) and the rate constant of equilibration between end-expired (or plasma) and effect-site concentrations (k_{e0}).

We focused on answering four specific questions. (1) Which of the two anaesthetic measures, the blink reflex or BIS, is more sensitive? (2) Is the blink reflex more sensitive to either sevoflurane or propofol? (3) Does the k_{e0} for the blink reflex differ from that for BIS? Different values for k_{e0} may be an argument for distinct anatomical substrates, and thus different effect sites, for the two measures of anaesthetic effect. (4) Is the blink reflex a good candidate to detect awareness or to assess immobility?

Methods

Fifty-four patients, aged >18 yr, ASA I or II, undergoing elective plastic and reconstructive surgery, participated in this study. They had no neurological or ophthalmic disease, and did not use analgesics, psychotropic agents, or excessive amounts of alcohol. The Hospital Ethical Committee approved the study, and all subjects gave informed, written consent. No premedication was given. The study took place in a quiet, warm anaesthesia induction room. Before the start of the study, the patient was prepared as usual for anaesthesia (i.v. access, ECG, non-invasive blood pressure measurement, pulse-oximeter). The patient lay in bed with eyes closed.

One of the supraorbital nerves was stimulated transcutaneously to obtain blink reflexes. Paediatric ECG monitoring electrodes were cut to an ellipse to fit above (anode) and beneath (cathode) the eyebrow (Red Dot, 3M, St Paul, MN, USA). Only adhesive material was removed. The cathode was placed over the supraorbital notch (Supplementary Figure).

The supraorbital nerve was stimulated every 15 s throughout the study, using a pair of constant-current, square-wave pulses of 0.1 ms duration and 5 ms interstimulus interval. The stimulus was delivered by a multichannel EMG system (Medelec Synergy, Oxford Instruments, Abingdon, UK).

The resulting EMG signals were recorded from the orbicularis oculi muscles of both eyes through surface electrodes (silver disc diameter 9 mm). The active electrode was placed in the middle of the inferior rim of the orbit and the reference electrode was placed halfway on the eye–ear line. A ground electrode was placed under the chin. Before the application of electrodes, all skin surfaces were cleaned with alcohol, and electrodes were coated with conductive paste (Mingograf, Siemens-Elema AB, Sweden) (electrode impedance <8 kΩ).

The EMG recording of an electrically evoked blink reflex shows three components, namely R1, R2, and R3 (Fig. 1). The anatomy and neurophysiology of the blink reflex are reasonably well known.[2–4] The first or early response (R1) is brief and occurs after a latency of about 10 ms on the side of the stimulation. Clinically, this response is not visible.[5] The second response (R2) has a latency of about 30 ms, which is more prolonged and bilateral.[6] The R2 response causes contraction of the orbicularis oculi muscle.[5] A third response (R3), produced bilaterally, occurs after strong stimulation,[7] has a latency of around 75–90 ms, and is more related to a startle reaction. Neurophysiological studies report that the R1 component of the blink reflex is stable in the awake, normal human[2] and in subjects receiving nitrous oxide for at least 30 min.[8]

We first sought for the optimal stimulus intensity by gradually increasing the current until visual observation of the EMG showed that, in the presence of a clearly visible R3 component, the R2 component ceased to increase. This stimulus intensity was then maintained throughout the study. The multi-channel EMG system recorded and stored EMG signals from both orbicularis oculi muscles. Band pass filters were used (20 Hz–3 kHz). Sweep duration was 200 ms and sensitivity 200 μV.

A BIS_{XP} monitor (A-2000; software version 4.0) calculated the BIS with 15 s smoothing rate. Electrodes (BIS_{XP} sensor, type standard) were applied according to the instructions of the manufacturer. BIS data were stored every 5 s using AK2logger (Aspect Medical Systems, Newton, MA, USA).

The level of sedation and anaesthesia was assessed clinically using an observer's assessment of anaesthesia and sedation scale (OAAS), which is a modification of the observer's assessment of alertness/sedation scale (OAA/S) score.[3 9] A score of 5 corresponds with readily responding to name spoken in normal tone, 4 with a lethargic response, 3 is a response only after name is called loudly or repeatedly, 2 is a response only after prodding or shaking, and 1 is no response after prodding or shaking. Loss of consciousness (LOC) was defined as reaching an OAAS of 2, and return of consciousness (ROC) as reaching—in the reversed direction—an OAAS of 3.

Control blink reflexes, BIS, and OAAS were recorded during 3 min before administration of sevoflurane or propofol.

Using a tight-fitting facemask, 20 consecutive patients inhaled sevoflurane (Group S) delivered by a vaporizer (Tec 5, Ohmeda, Madison, WI, USA) into a circle system (Cicero, Dräger AG, Lubeck, Germany) with a fresh-gas flow of 5 litre min^{-1} oxygen. The vaporizer setting was increased by 1 vol% every 3 min. End-expired sevoflurane and carbon dioxide (CO_2) concentrations were measured with a calibrated gas analyser (Capnomac Ultima, Datex, Helsinki, Finland) connected to a nasal catheter introduced

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