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Multi-level approach to anaesthetic effects produced by sevoflurane or propofol in humans: 2. BIS and tetanic stimulus-induced withdrawal reflex†

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Background. General anaesthesia could be assessed at two sites: cortical structures and the spinal cord. However, the practicalities of measurement at these two sites differ substantially.

Methods. We simultaneously analysed effects of sevoflurane (Group S; $n=16$) or propofol (Group P; $n=17$) on bispectral index (BIS) and the tetanic stimulus-induced withdrawal reflex (TIWR). TIWR was quantified by the area under the curve of the electromyogram of the biceps femoris muscle after electrical stimulation of the sural nerve. After loss of consciousness, TIWR was evoked once per minute. The anaesthetic was increased until TIWR disappeared. After discontinuation of the anaesthetic and reappearance of TIWR, the amount of anaesthetic was increased again. Using a sigmoid E_{max} model and a first-order rate constant k_{e0}, we characterized the dose–response relationships for BIS and TIWR.

Results. Concentration-dependent depression of TIWR was reasonably well modelled for sevoflurane, but poorly for propofol. TIWR was completely suppressed by sevoflurane, but not propofol. Sevoflurane reduced TIWR to 5 mV ms (very weak movement) at 1.68 vol% end-expired concentration [$\approx$ minimum alveolar concentration (MAC value)]. The k_{e0}s for TIWR were smaller than those for BIS: 0.25 (0.16–0.39) *vs* 0.41 (0.33–0.51) min^{-1} for Group S; 0.25 (0.22–0.30) *vs* 0.34 (0.29–0.40) min^{-1} for Group P [geometric mean (95% CI)].

Conclusions. High concentrations of sevoflurane depress TIWR more than propofol. With propofol, we frequently observed a paradoxical behaviour of muscles of the lower leg. TIWR lags behind BIS, indicating different effect sites for two intended anaesthetic effects: unresponsiveness to noxious stimulation and unconsciousness.

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In line with a modern concept of anaesthesia,[1] the state of general anaesthesia assumes the presence of unconsciousness, amnesia, and unresponsiveness to noxious stimulation. Noxious stimuli activate neurones in the dorsal horn of the spinal cord. If the dorsal horn is suppressed adequately, both immobility and autonomic stability in response to noxious stimuli are established. It then follows that the adequacy of general anaesthesia could be assessed at two sites: cortical structures (unconsciousness and amnesia) and the spinal cord (immobility, antinociception, and autonomic stability). However, the practicalities of measurement at these two sites differ substantially.

Spinal cord activity may be assessed by quantifying autonomic responses or motor responses. Indices of autonomic function—heart rate, blood pressure, heart rate variability, and others—have been explored. Motor responses may be investigated by measuring H-reflex, F-waves, or the nociceptive flexion reflex (RIII).[2–8] We used the tetanic stimulus-induced withdrawal reflex (TIWR). Unconsciousness was assessed here with the validated[9] method of the bispectral index (BIS) reflecting the depression of the cerebral cortex.

†This article is accompanied by Editorial I.

In a companion paper,[10] we presented results on forebrain function (BIS) and brainstem function (blink reflex). In the present study, we investigate the relative roles of forebrain (BIS) and spinal cord (TIWR) in the same population. We assess relationships between varying concentrations of sevoflurane or propofol and these two surrogate measures. Pharmacokinetic–pharmacodynamic (PKPD) modelling was used to obtain 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 three specific questions. (1) Is TIWR more sensitive to either sevoflurane or propofol? (2) Does the k_{e0} for the TIWR differ from that for BIS? Different values for k_{e0} may be an argument for distinct anatomical substrates. (3) Is TIWR a good candidate for assessment of immobility?

Methods

Fifty-four patients, aged >18 yr (ASA I or II), undergoing elective plastic and reconstructive surgery participated in this study. The same population participated in the study described in a companion paper.[10] They had no neurological 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 for anaesthesia (i.v. access, ECG, non-invasive blood pressure measurement, and pulse-oximeter). The patient lay in bed with eyes closed.

TIWR was evoked by electrical tetanic stimulation of one of the sural nerves, consisting of a train of 100 stimuli, each with duration of 0.1 ms, during 1 s at 50 mA. Adhesive adult ECG monitoring electrodes (Red dot, 3M, St Paul, MN, USA) were used. The cathode was placed in the lateral retromalleolar sulcus and the anode placed 5 cm cranially. Tetanic stimuli were repeated every 60 s. The stimulator of the electromyography (EMG) system (Medelec Synergy, Oxford Instruments, Abingdon, UK) was used. EMG signals were recorded from the ipsilateral biceps femoris muscle through ECG monitoring electrodes. The active electrode was placed on the belly of the muscle 15 cm above the popliteal fossa. The reference electrode was placed 5 cm cranially. A ground electrode was placed on the lower leg. In approximately half of the patients, we measured muscle activity in the quadriceps femoris, anterior tibial, and gastrocnemius muscles as well. A multi-channel EMG system was used to record, rectify, and store the signals. Band pass filters were set at 20 Hz and 3 kHz, sweep duration at 2 s, and sensitivity 200 μV. Figure 1 shows typical recordings of the raw EMG.

A BIS_{xp} monitor (A-2000; software version 4.0) was used to record BIS with a 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.[11 12] A score of 5 corresponds to 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 mild prodding or shaking, 1 is a response only after eliciting TIWR, and 0 is no response after TIWR. The response was scored positive if there was a verbal reaction or a gross movement. Loss of consciousness (LOC) was defined as reaching an OAAS of 2, and return of consciousness (ROC) was defined as reaching an OAAS of 3.

Using a tight-fitting mask, 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 obtained from a calibrated gas analyser (Capnomac Ultima, Datex, Helsinki, Finland) sampling from a nasal catheter introduced 30 mm into the widest nostril. Data from the gas analyser were stored every 15 s on a patient data management system (CompuRecord, Philips, Andover, MA, USA).

Thirty-four consecutive patients received propofol 5 mg kg^{-1} h^{-1}, followed by 10, 15, and 20 mg kg^{-1} h^{-1} each during 3 min, by continuous i.v. infusion (Group P). Oxygen was supplied if the oxygen saturation decreased.

Patients were asked to breathe through their nose. They breathed spontaneously throughout the study. The airway was maintained with chin lift or jaw thrust if needed clinically. In some patients, a laryngeal mask airway (LXM) was inserted during the study (10 in Group S and 6 in Group P). Gas was then sampled from a side stream port of the LXM with the Y-piece.

In a first part of the study,[10] BIS, blink reflexes, and OAAS were recorded during increasing and decreasing concentrations of sevoflurane or propofol. The present study was started when applying the first tetanic stimulus, that is when the patient had lost consciousness for the second time. When TIWR disappeared, anaesthetic administration was stopped until TIWR reappeared. It was then restarted until TIWR disappeared again. If there were haemodynamic or respiratory problems, the study was ended [Figs 1 and 2 (upper row)]. Four patients participated twice in the study, once for sevoflurane and once for propofol, with an interval of several months.

For the TIWR, we measured the area under the curve (AUC) of the rectified EMG from the end of the tetanic

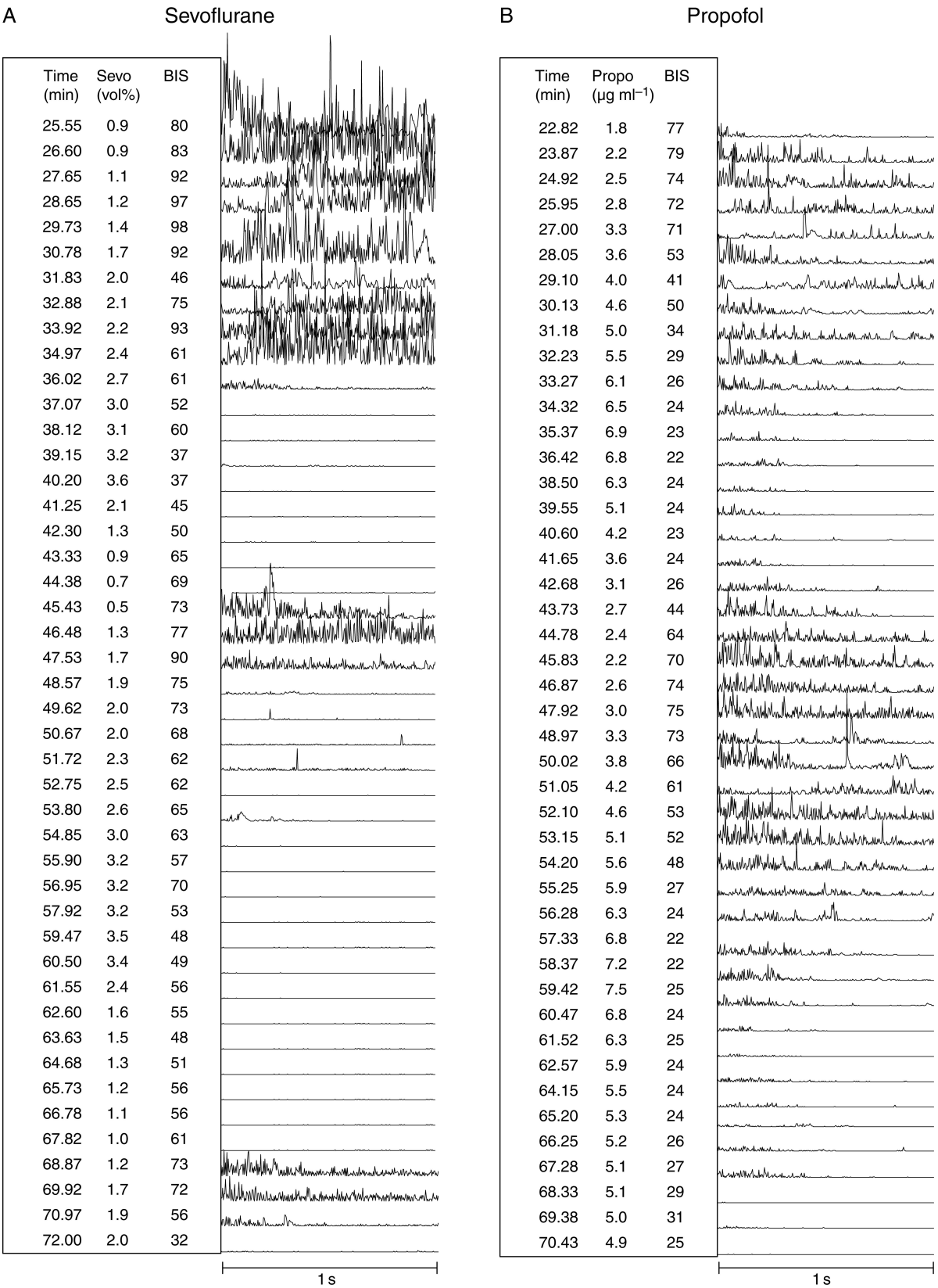

Fig 1 Typical effects of increasing and decreasing concentrations of sevoflurane (A) or propofol (B) on the electromyogram (EMG) recorded from the biceps femoral muscle in a male patient (70 kg, 40 yr) who participated twice in this study. The EMG follows a tetanic electrical stimulus (duration 1 s, 100 Hz, and 50 mA) delivered on the ipsilateral sural nerve every minute. AUC of the rectified EMG signal during 1 s after the stimulus is used as anaesthetic measure. The left margins show time since the start of the experiment, end-expired sevoflurane concentrations (vol%) or calculated arterial propofol concentrations (in μg ml^{-1}), and the BIS values.

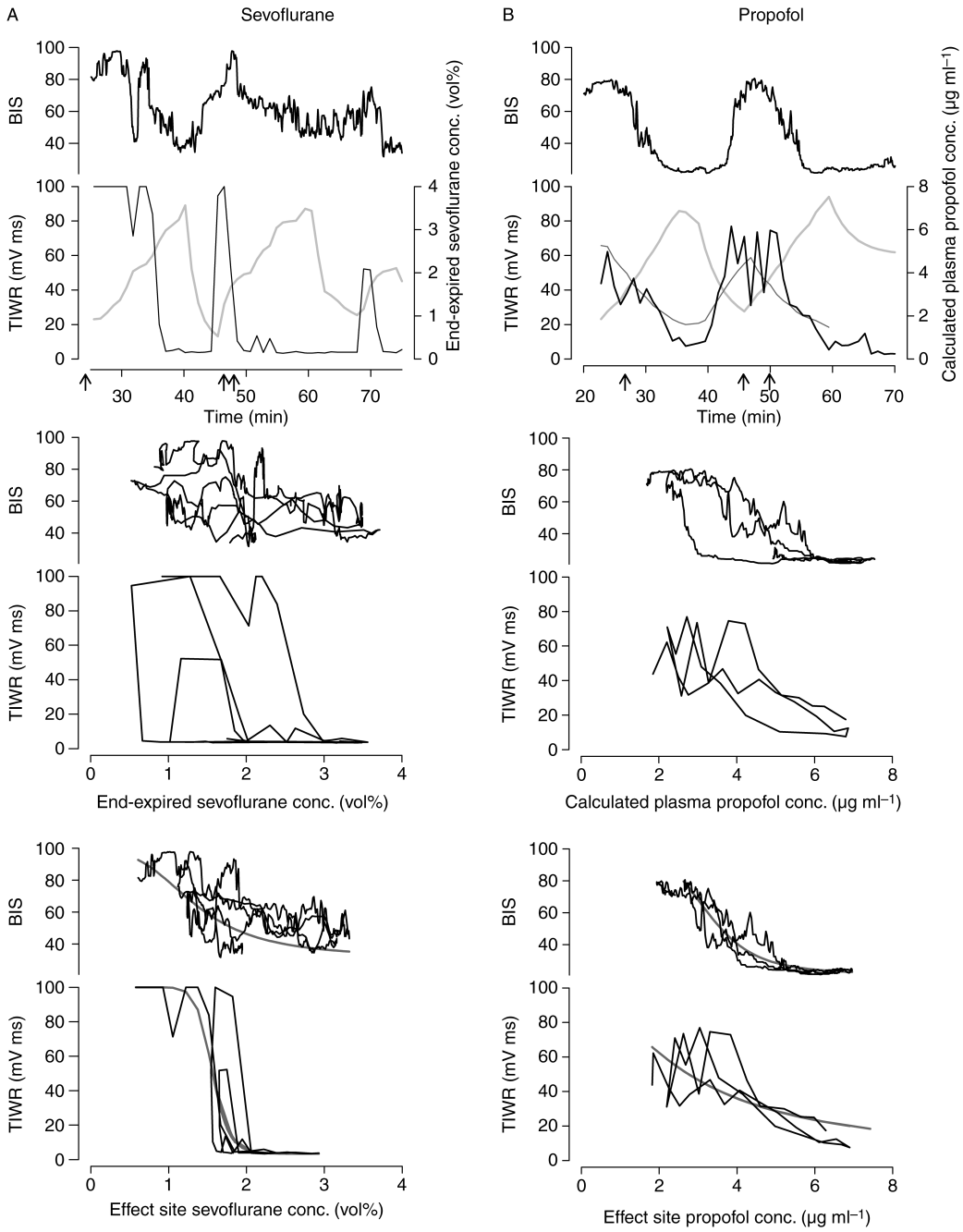

Fig 2 PKPD modelling of the raw data obtained in the same patient as in Figure 1 for sevoflurane (A) and propofol (B). Upper row: raw data showing time courses of concentrations (grey line), BIS, and TIWR (black line), with arrows on the abscissa indicating, from left to right, LOC, ROC, and next LOC. Middle row: raw data showing hysteresis loops when effects are plotted against end-expired or plasma concentrations. Lower row: collapsed loops are obtained when effects are plotted against apparent effect-site concentrations obtained in the PKPD modelling process. Grey lines represent effect *vs* concentration curves calculated for this patient with equations (1) and (2).

stimulus for 1 s, using the marker tool of the EMG system. AUC calculation was performed by the EMG system. As violent movements of the leg caused electrode or cable displacement resulting in baseline shift, a cut off value of 100 mV ms was used.

EMG, burst suppression (BS) ratio, and signal quality index data were obtained from the BIS_{XP} monitor. BIS data obtained during periods of excitation (simultaneous occurrence of EMG >40 dB, OAAS <3, and increasing BIS) and periods of BS (BS ratio >50%) were excluded from analysis.

Artifacts in the end-expired sevoflurane data, as a result of interruption of nasal breathing and during placement of the LXM, or as a result of technical difficulties, were deleted. Linear interpolation between remaining data yielded one data point per second.

Propofol plasma concentrations in arterial blood, one data point per second, were calculated for each patient using Simulink and Matlab software (version. 6.5.1, Mathworks, Natick, MA, USA). The pharmacokinetic parameter set of Marsh and colleagues[13] was used.

A two-stage approach was used for PKPD modelling. Individual concentration–response functions were fitted to the data (Solver Tool in Excel, Microsoft, Redmond, WA, USA) using a sigmoid model defining the relationship between the apparent effect-site concentration of a drug (C_E) and a measure for its anaesthetic effect (E) as:

$$E = E_0 - (E_0 - E_{max})\left(\frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50}^{\gamma}}\right) \quad (1)$$

where E_0 is the baseline effect, E_{max} the maximum effect value, and γ is a coefficient, determining shape and slope of the curve. $E_{0\ BIS}$ is the average BIS during the control period, and $E_{max\ BIS}$ is the average BIS during the plateau phase,[14] which is easily recognized visually either in the first cycle or in the next cycle. A real E_0 for TIWR could not be obtained, because it is not ethical to use an extremely painful stimulus in an awake individual. Vigorous movement in response to a tetanic stimulus during consciousness would result in an AUC for the EMG far larger than the cut off value of 100 mV ms. Thus, we used this cut off value as substitute for E_0 for TIWR. E_{max} was derived from the data of the individual patient.

The time delay between changes in concentration and observed effect was modelled by an effect compartment and a first-order rate constant, k_{e0}:

$$\frac{dC_E}{dt} = (C_x - C_E)k_{e0} \quad (2)$$

where C_x is the calculated propofol concentration in arterial blood or the measured end-expired sevoflurane concentration. The variable to be minimized was the sum of the squared differences between observed and modelled effects. The coefficient of determination was used to judge the goodness of fit:

$$\rho^2 = 1 - \frac{\sum_{i=1}^{i=n}(E_{measured_i} - E_{calculated_i})^2}{\sum_{i=1}^{i=n}(E_{measured_i} - \overline{E}_{measured})^2} \quad (3)$$

where $\bar{E}_{measured}$ is the average measured effect and n is the number of data points. The individual parameters were averaged to obtain population parameters.

As patients were already unconscious, PKPD modelling for TIWR was performed without the usual initial conditions of a known effect at zero effect-site concentration. Therefore, we estimated the initial C_E to be the same as the coinciding C_E of the previous investigation period.[10] We tested the validity of this procedure with simulated data and found only a small deviation of the estimated parameters (0.5% maximum). As we had no C_E for TIWR, we used the corresponding C_E of the blink reflex, assuming that spinal cord and brainstem have roughly the same PKPD properties. Using simulated data, we demonstrated that maximal deviation of k_{e0} and EC_{50} was 1% if the initial C_E chosen was 10% too high or low.

The ratio of EC_{50} for TIWR and BIS ($EC_{50\ TIWR}/EC_{50\ BIS}$) was used to compare the potency of sevoflurane or propofol to suppress TIWR with respect to their potency to suppress BIS. Therefore, it was necessary to demonstrate that BIS values at different clinical endpoints (LOC and ROC) for sevoflurane or propofol were comparable.

Power calculation was performed for the preceding study period.[10] It showed that a minimum of 16 patients in each group was required. Sample size was justified, because the *post hoc* measured variability of the ratio $EC_{50\ TIWR}/EC_{50\ BIS}$ was smaller in the present study. To compensate for dropouts, the number of patients in each group was adjusted upwards.

Graphical analysis of data preceded formal statistical analysis. Lilliefor's test was used to test whether data were normally distributed. Either non-parametric tests (Wilcoxon signed ranks test or Mann–Whitney U test) or parametric tests (paired or unpaired two-sided t-test) were used as appropriate. Data skewed to the right were analysed using parametric tests on log-transformed data. For categorical data, Fisher's exact test was used. Data are presented as mean (SD), unless stated otherwise. $P<0.05$ was considered statistically significant. The Statistical Package for Social Sciences was used (SPSS version 11.0 IL, USA).

Results

Data from 16 and 17 patients were finally analysed in Group S and P, respectively. In Group S, four patients did not complete the study: two patients became agitated and were given propofol; and one patient did not show reflex activity; one patient showed prolonged paradoxical BIS elevation. In Group P, data from 17 patients were discarded: technical difficulties delivering the stimulus in 1 patient and background noise in 6 patients; in 4 patients, 2 of whom were obese, no reflex activity could be recorded; and 6 patients showed no, or only weak, reflex activity of the biceps femoris muscle, although they moved in response to the stimulus and the EMG of other muscles could be recorded. Failure to evoke EMG responses in the biceps femoris muscle was higher in the propofol group ($P<0.01$).

The groups were similar with respect to gender (9 and 12 females), age 40 (15) and 42 (15) yr, weight 76 (8) and 76 (14) kg, and height 176 (11) and 170 (8) cm in Groups S and P, respectively.

The coefficient of determination for the PKPD model (Table 1) indicates that TIWR for propofol was poorly modelled with the sigmoid E_{max} model. EC_{50} for the TIWR was smaller than EC_{50} for BIS for each of the two

Table 1 Pharmacodynamic parameters of the sigmoid E_{max} models for BIS and the AUC of the EMG during 1 s after a TIWR. E_0 (baseline effect value) and E_{max} (maximal effect value) were derived from the data of individual patients. Calculated parameters were γ (shape), EC_{50} (concentration that causes an effect midway between baseline and maximum), and k_{e0} (first-order rate constant determining the efflux from the effect compartment). ρ^2 is the coefficient of determination. Data are given as arithmetic or geometric means ($E_{max\ TIWR}$, γ, and k_{e0}) and 95% CI. *Different from propofol with $P<0.001$, **different from propofol with $P<0.05$, and †different from TIWR with $P<0.001$

	E_0 (BIS-units or mV ms)	E_{max} (BIS-units or mV ms)	γ	EC_{50} (vol% or μg ml^{-1})	k_{e0} (min^{-1})	ρ^2
Sevoflurane						
BIS	95.1 (93.6-96.7)	25.9 (24.3-27.5)**	2.83 (2.28-3.52)* †	1.28 (1.15-1.41)†	0.41 (0.33-0.51)†	0.83 (0.77–0.89)
TIWR	100	2.78 (2.52–3.06)*	6.66 (4.39–10.11)	0.90 (0.73–1.06)	0.25 (0.16–0.39)	0.69 (0.58–0.81)
Propofol						
BIS	96.4 (95.6–97.3)	24.0 (23.0–25.0)	4.67 (3.98–5.47)	3.10 (2.82–3.38)†	0.34 (0.29–0.40)	0.88 (0.86–0.91)†
TIWR	100	4.12 (3.73–4.54)	4.60 (4.07–5.21)	1.98 (1.83–2.12)	0.25 (0.22–0.30)	0.62 (0.57–0.66)

anaesthetics (Fig. 3). The γ value was smaller for TIWR than for BIS, for sevoflurane but not for propofol.

The individual model fits for the relation between TIWR and effect-site concentrations (Fig. 4), and the relationship of the two measures against effect-site concentrations of sevoflurane and propofol (Fig. 5) have an extra ordinate to score the movement of the leg after tetanic stimulation. Careful observation brought us to the following scale: background noise (<3 mV ms); visible twitch (3–5 mV ms); weak (5–10 mV ms), moderate (10–50 mV ms), and strong (50–100 mV ms) movements. The effect at $EC_{50\ TIWR}$ corresponds to the transition from moderate to strong movement. To give a better representation of the observed movements, the left *y*-axis is presented as a decimal logarithm. There was no difference in $EC_{50\ TIWR}/EC_{50\ BIS}$ between Groups S and P: 0.70 (0.23) and 0.65 (0.20), respectively.

Suppression of TIWR by propofol started at lower concentrations, expressed in $EC_{50\ BIS}$ units, compared with sevoflurane (Fig. 5). However, TIWR did not disappear at high propofol concentrations as there was still a visible twitch with $E_{max\ TIWR}$ of 4.1 (3.7–4.5) mV ms [geometric mean (95% CI)]. At high concentrations of sevoflurane, the corresponding $E_{max\ TIWR}$ of 2.8 (2.5–3.1) mV ms was smaller ($P<0.05$) and indicated only noise (Fig. 1). The apparently steeper slope for TIWR in Group S is not statistically different from Group P.

BIS values at LOC (just before the first tetanic stimulus) were higher with sevoflurane: 80 (9) compared with 63 (8) ($P<0.0001$). TIWR at LOC did not differ: 27 (30)

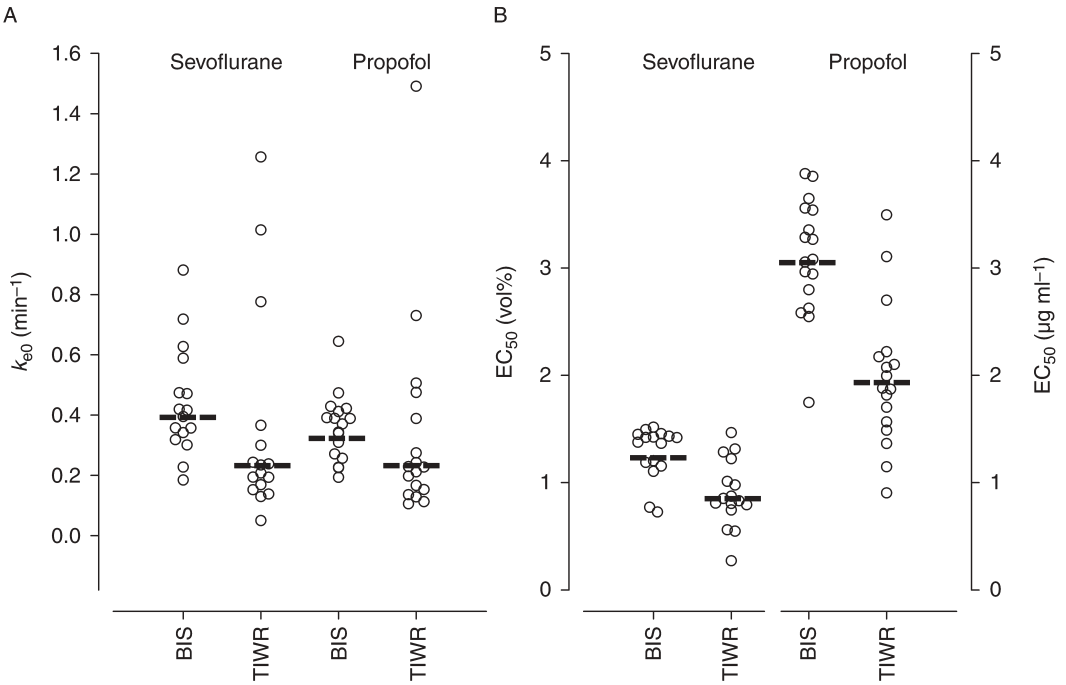

Fig 3 Individual values for k_{e0} (A) and EC_{50} (B) obtained with PKPD modelling for two measures of anaesthetic effect, the BIS and the TIWR, in patients receiving either sevoflurane or propofol. Horizontal bars represent the geometric mean of the individual k_{e0}s (A) and the arithmetic mean of the individual EC_{50}s (B).

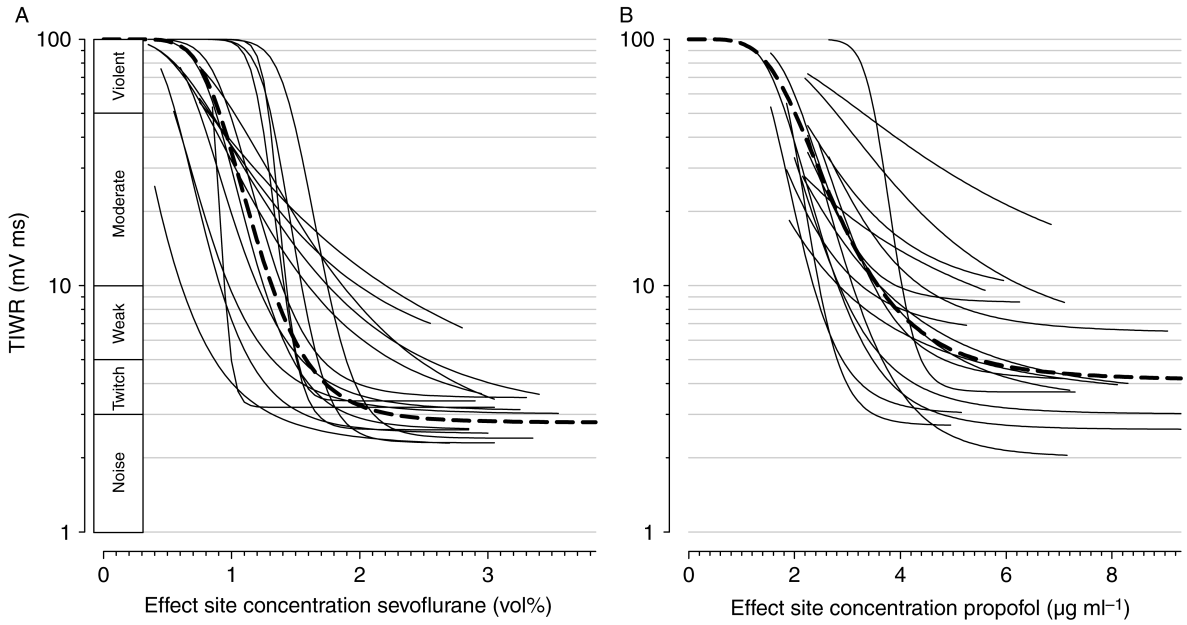

Fig 4 Individual concentration–response curves for suppression of the TIWR by either sevoflurane (A) or propofol (B). Population curves (dashed lines) were generated from the data given in the table. The vertical bar near the left *y*-axis shows a scale based on clinical observation of the strength of movements of the leg after the tetanic stimulus (see text for details).

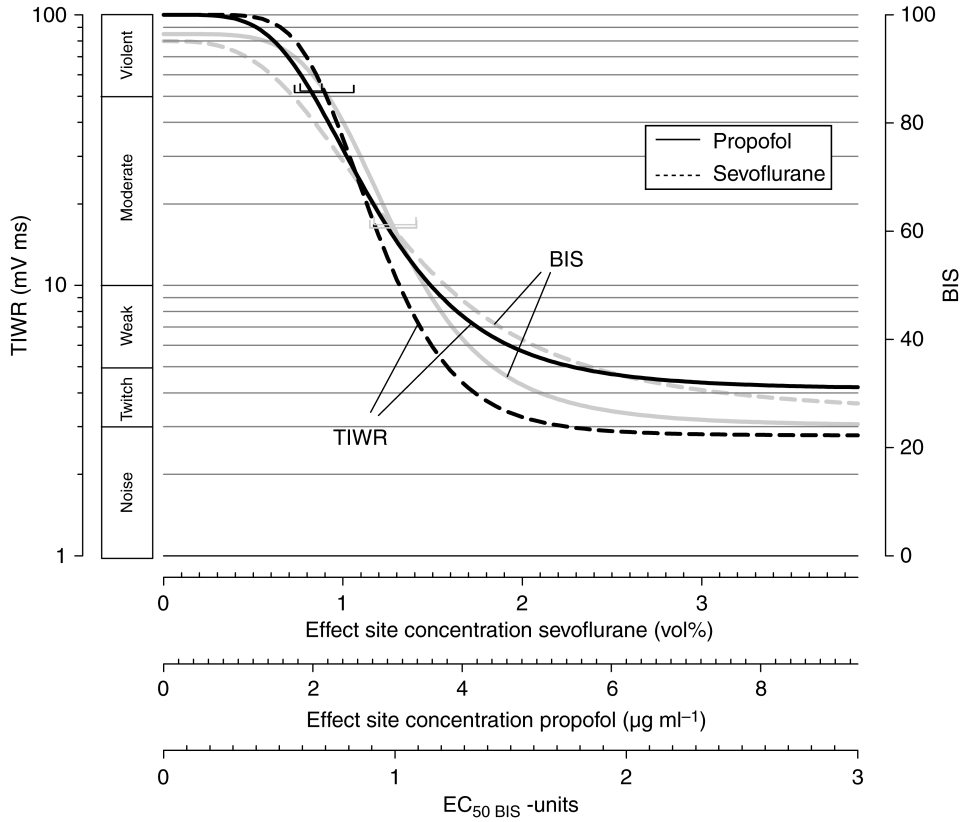

Fig 5 Concentration–response curves for suppression of the BIS (grey line) and the TIWR (black line) by sevoflurane (dashed line) or propofol (solid line). As concentrations of the two drugs have different units, two *x*-axes are needed. Each abscissa has a length of three times the EC_{50} for BIS ($EC_{50\ BIS}$): 3.84 vol% and 9.30 μg ml^{-1}. The two concentration–response curves for BIS intersect at $EC_{50\ BIS}$. The third *x*-axis uses $EC_{50\ BIS}$ as the unit; the axis length is necessarily three times the $EC_{50\ BIS}$. Horizontal error bars are the 95% CI for the EC_{50}s. The vertical bar near the left *y*-axis shows a scale based on the clinical observation of the movements of the leg after the tetanic stimulus.

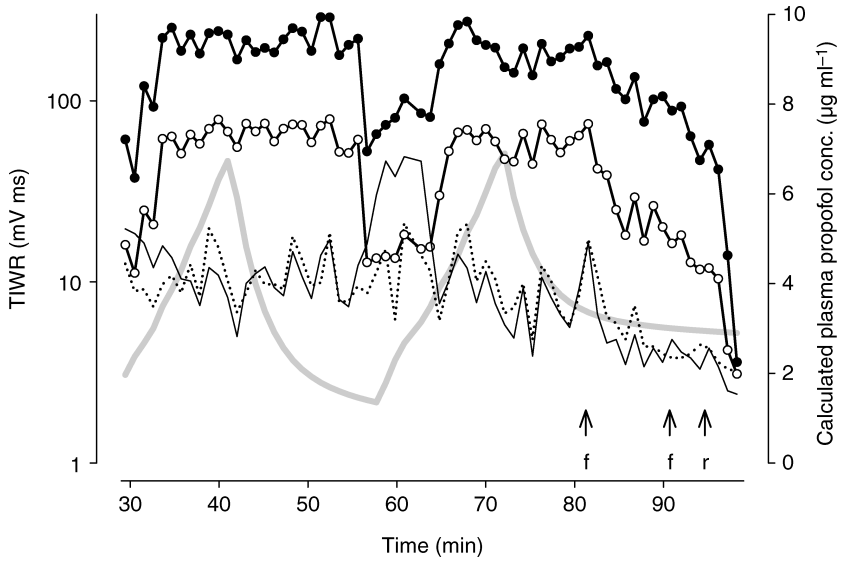

Fig 6 Example of a paradoxical reaction of the TIWR in a patient (male, 73 kg, 27 yr) receiving propofol. Calculated arterial propofol concentrations are represented with a thick grey line. TIWR was recorded from the biceps femoris muscle (dotted line), quadriceps femoris muscle (hair line), gastrocnemius muscle (open circle), and tibialis muscle (filled circle). Reflexes in muscles of the lower leg were more forceful at high propofol concentrations. Arrows on the abscissa indicate administration of 1 μg kg^{-1} fentanyl (f) and 0.5 mg kg^{-1} rocuronium (r).

and 25 (20) mV ms for Groups S and P, respectively. The maximum TIWR was larger with sevoflurane: 69 (31) compared with 45 (29) mV ms ($P<0.05$) (after introducing the cut off value). In four and two patients in Groups S and P, respectively, the cut off value was exceeded ($P=0.4$). For both anaesthetics, the rate constants for TIWR were substantially smaller than for BIS. The difference was only statistically significant for sevoflurane.

Paradoxical reactions were observed with propofol, but not with sevoflurane. EMG activity was relatively low at low concentrations of propofol and increased with increasing propofol concentrations in a number of patients. Properties of three other muscles were investigated in 12 patients in Group S and 21 patients in Group P, with 11 and 15 patient data sets, respectively, useful for further analysis. TIWR derived from the quadriceps muscle behaved similarly to that from the biceps femoris muscle. PKPD analysis of the TIWR of the gastrocnemius and the tibialis muscles yielded negative shape parameters in six and eight patients, respectively. In these patients, paradoxical reactions were observed. In the example (Fig. 6), all reflex activity diminished after fentanyl administration and only noise remained after rocuronium was given to facilitate intubation required for the intended surgery. TIWR derived from the biceps femoris muscle was weaker and could not be modelled.

Discussion

The relationship between end-expired sevoflurane concentrations and the TIWR was reasonably well described by a sigmoid E_{max} model and a first-order rate constant. The depression of TIWR by propofol was poorly modelled. Concentration-dependent depression of BIS was well modelled for both agents.

TIWR is a novel variable to study the anaesthetic effects on the spinal cord. Variants of the method have been described.[6 8 15] A drawback of TIWR is that the stimulus is too painful to be used in awake subjects. Obvious advantages are that TIWR can be measured repeatedly and recorded objectively without causing injury. Until now, PKPD studies of analgesics have focused on EEG changes,[16] but assessing the spinal cord by TIWR may be a better option. However, the method requires testing for longer periods at steady state.

The first of our three questions was whether TIWR was more sensitive to sevoflurane or propofol. Major differences exist between the actions of sevoflurane and propofol on the TIWR. Sevoflurane at high concentrations suppresses the TIWR more than propofol, but periods of hyper-reflexia are observed at low sevoflurane concentrations. The TIWR values for sevoflurane are higher at low concentrations, but lower at high concentrations, compared with propofol. The E_{max} values for TIWR also differed and, although the difference seems to be small, the $E_{max\ TIWR}$ for sevoflurane only represents noise, whereas the $E_{max\ TIWR}$ for propofol corresponds to a visible twitch (Fig. 5). It is interesting that in a number of patients, the administration of fentanyl or rocuronium reduced TIWR to the level where only noise was present (Fig. 6). The sevoflurane curve accords more with an on–off phenomenon (Fig. 4). It appears that high concentrations of sevoflurane depress TIWR more than high concentrations of propofol. This is corroborated by our clinical observations that most patients moved after tetanic stimulation despite high concentrations of propofol.

However, the ratio $EC_{50\ TIWR}/EC_{50\ BIS}$ for sevoflurane is similar to that for propofol, and the curves for TIWR intersect near $EC_{50\ TIWR}$ values.

Other methods of investigating anaesthetic effects on the spinal cord in humans under dynamic conditions, such as the H-reflex and the F-wave, have reported conflicting results. Propofol suppresses the H-reflex at concentrations where LOC is achieved,[4] whereas the H-reflex is preserved until 1 minimum alveolar concentration (MAC) of sevoflurane.[7] The F-wave was also suppressed at comparable low concentrations of both propofol[2] and sevoflurane.[3] Supraspinal influences of propofol on these reflexes play a more important role compared with sevoflurane.[5] In contrast, we found that sevoflurane depressed the TIWR and blink reflex[10] more than propofol. Our findings are more in line with clinical experience with these anaesthetics. During inhalation of sevoflurane, a stage of excitation characterized by increased reflex activity is to be passed through, followed by a stage with increasing muscle relaxation and finally disappearing reflex activity. Using propofol, the stage of excitation is less pronounced, but at higher concentrations spontaneous movements and remaining reflexes can be observed.

There is some experimental evidence for why sevoflurane might depress TIWR more than propofol. In mice with a mutation of the $GABA_A$ receptor, propofol failed to suppress withdrawal reflexes, which indicates that propofol causes immobility predominantly by $GABA_A$ receptors.[17] Picrotoxin, a $GABA_A$ receptor blocker, increased the ED_{50} immobility dramatically for propofol in rats, whereas the increase was small for isoflurane.[18] *In vitro* experiments on rat cultured spinal cord showed that propofol acts exclusively by $GABA_A$ receptors, whereas inhaled anaesthetics act on multiple molecular targets, including glycine, $GABA_A$, and, probably, glutamate receptors.[19 20] The less depressant effect of propofol found in spinal cord slices could explain why immobility is not achieved so well with propofol. In humans, propofol produces surgical immobility at concentrations three times those needed to suppress consciousness, whereas this difference is much smaller for inhaled anaesthetics.[21] In comparison with inhaled anaesthetics, the smaller spinal-suppressive effects of propofol also appear from better preservation of transcranially elicited motor-evoked potentials[22] and cortical somatosensory evoked potentials.[23]

Our second question was whether there was a difference in the k_{e0} for TIWR and for BIS. The k_{e0}s for TIWR (spinal cord function) are smaller than those for BIS (cortical function), suggesting that different effect sites are involved. In agreement with previous research using H-reflex, F-wave, or blink reflex, we found a much smaller k_{e0} for TIWR than for BIS in Group S. The difference in rate constants between forebrain and spinal cord may originate either from differences in the wash-in and wash-out of two different effect compartments or from different neuronal effects at the same sites. The former explanation is supported by studies in rats that showed reduced blood flow to the spinal cord.[24]

As addressed in the accompanying paper,[10] the k_{e0} we found for BIS is substantially larger than that found by others, and we excluded periods of excitation and BS from the analysis. As we are interested in relative differences between k_{e0} for TIWR and for BIS, absolute values are not critical to our findings.[10]

The final question was the value of TIWR for assessing immobility. To be a candidate for predicting immobility after a noxious surgical stimulus, TIWR must be preserved up to an end-expired sevoflurane concentration of 1 MAC (1.8 vol%)[25] or propofol C_{50} for skin incision (10 $\mu g\ ml^{-1}$).[21] Although $EC_{50\ TIWR}$ is the effect halfway between minimal and maximal effect, it has no direct relation with the effect represented by 1 MAC and any similarity would be coincidental. The effect at $EC_{50\ TIWR}$ corresponds to the transition of strong to moderate movement, and this effect occurs at concentrations <1 MAC.

The minimal effect-site concentration that prevents a weak movement (TIWR <5 mV ms) in 50% of our patients was 1.68 vol% sevoflurane, which is near the MAC value of 1.71 vol% reported by Katoh and Ikeda.[26] MAC is useful to compare potencies of anaesthetics, but the anaesthetic dose that prevents 95% of patients (AD_{95}) from moving has greater clinical utility. Katoh and Ikeda[26] reported the AD_{95} to be 2.07 vol%. At this concentration, 5 of 16 patients still show a response of >5 mV ms. The AD_{95} in our study seems to be higher. Despite the hazards associated with extrapolation, we calculated from the individual fits an AD_{95} of 3.46 vol%. Kimura and colleagues[27] have also reported higher values for AD_{95}, a measure with a larger confidence interval than that for MAC. Further investigation of TIWR as a surrogate measure for MAC and AD_{95} is needed.

An unexpected finding was, in half of the patients in Group P, the tibialis muscles behaved paradoxically (i.e. TIWR increased with increasing propofol concentrations). This may be related to the observed involuntary movements in all extremities at high propofol concentrations and the low potency to suppress TIWR. As this was not seen in Group S, we assume that this is an effect of propofol. The mechanism is unclear, but may be an expression of the inhibition by propofol of a supraspinally mediated inhibition of spinal reflexes.

TIWR had a high between-patient variability. The coefficients of variation of the PKPD measures for TIWR were twice those for BIS. TIWR at LOC had a much larger variability than BIS, suggesting that it is not a good measure for LOC compared with BIS. Within-patient variability of the TIWR could not be investigated because of the dynamic study design.

In conclusion, TIWR may be a good candidate for monitoring immobility. The method may be useful in experimental studies, but high between-patient variability is a considerable problem. We showed that spinal cord reflexes are more depressed with high concentrations of sevoflurane than with propofol. In addition, we frequently

observed a paradoxical behaviour of muscles of the lower leg when propofol was administered. Effects measured by TIWR lag behind effects measured by BIS, suggesting that different effect sites exist for two intended anaesthetic effects: unresponsiveness to noxious stimulation and unconsciousness.

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