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Relationship between bispectral index, auditory evoked potential index and effect-site EC_{50} for propofol at two clinical end-points†

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Background. Many anaesthetists are deterred from using total i.v. anaesthesia because of uncertainty over the concentration of propofol required to prevent awareness. We predicted blood and effect-site concentrations of propofol at two clinical end-points: loss of consciousness and no response to a painful stimulus.

Methods. Forty unpremedicated Caucasian patients were anaesthetized with i.v. propofol delivered by a Diprifusor target-controlled infusion (TCI). Bispectral index (BIS) and auditory evoked potential index (AEPex) were measured and blood and effect-site propofol concentrations were predicted. Logistic regression was used to estimate population values for predicted blood and effect-site propofol concentrations at the clinical end-points and to correlate these with BIS and AEPex.

Results. The effect-site EC_{50} at loss of consciousness was 2.8 μm ml^{-1} with an EC_{05} and an EC_{95} of 1.5 and 4.1 μm ml^{-1}, respectively. The predicted EC_{50} when there was no response to a tetanic stimulus was 5.2 μm ml^{-1} with an EC_{05} and an EC_{95} of 3.1 and 7.2 μm ml^{-1}, respectively.

Conclusions. Unconsciousness and lack of response to a painful stimulus occur within a defined range of effect-site concentrations, predicted by Diprifusor TCI software.

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The concept of a minimum alveolar concentration (MAC) for volatile anaesthetics is well known and widely used clinically to ensure that patients receive sufficient anaesthesia to prevent awareness.[1] A similar concept exists for i.v. anaesthetic agents and is referred to as the effective concentration 50 or EC_{50}.[2] It is defined as the concentration of an i.v. anaesthetic agent at which 50% of patients will not respond to skin incision. This is a clinically useful concept as it is now possible to predict concentrations of propofol in the blood and at the effect-site using a variety of pharmacokinetic models.[3 4] A computer-controlled infusion pump to deliver propofol, which also displays the predicted blood and effect-site propofol concentrations, is commercially available as the Diprifusor (AstraZeneca Pharmaceuticals, Macclesfield, UK).[5]

We predicted blood and effect-site concentrations of propofol when loss of consciousness and lack of purposeful movement to a painful stimulus were noted and recorded the electrophysiological measurements bispectral index (BIS) and auditory evoked potential index (AEPex) at the same time. The results have been presented in preliminary form.[6]

†*Declaration of interest*. Aspect Medical provided hardware and disposables to conduct this study. The hardware and software system used to calculate the AEPex was licensed by Glasgow University to AstraZeneca. Professor Kenny has acted as a consultant to AstraZeneca.

Methods

Forty Caucasian patients undergoing elective day-case surgery were recruited. The study was approved by the hospital ethics committee and all patients gave written informed consent. Exclusion criteria included age <18 yr or >65 yr, recent administration of sedative or opioid drugs, body weight <80% or >120% of ideal weight, and impairment of hepatic, renal, cardiac or respiratory function. Patient characteristics are given in Table 1. No sedative drugs were administered before induction of anaesthesia. Patients had a 20 G venous cannula inserted and monitoring for BIS and AEPex was started. BIS version 3.0 rev. 0.5 was used (Aspect Medical Systems, Cambridge, MA, USA). The AEPex is a mathematical expression of the shape of the auditory evoked potential (AEP) waveform.[7] The AEPex is calculated as the sum of the square root of the absolute difference between every two successive segments of the AEP waveform. Collection of the AEP waveform has been described previously.[8] Clicks 70 dB above the normal hearing threshold were played into both ears at a rate of 6.9 Hz to evoke the AEP. The AEP was recorded using three electrodes placed on the right forehead (+), right mastoid (–) and middle forehead (reference). The final AEP waveform was obtained by averaging 256 epochs of 144 ms duration using a custom-built PC-based system. The awake value of the AEPex is 72.5 (SD 11.2).[7] The AEPex may be better than the BIS at distinguishing the transition from unconsciousness to consciousness.[9 10]

A target-controlled infusion (TCI) of propofol was administered using the Diprifusor (software version 2; AstraZeneca), which contains the Marsh pharmacokinetic model.[11] This system displays both the predicted blood propofol concentration and the effect-site propofol concentration (an estimate of the drug concentration at its site of action based on the response of AEPex to varying propofol concentrations).[12] The model uses an equilibration rate constant, k_{eo}, of 0.2 min^{-1}.

The propofol infusion was started to provide a blood concentration of 1.5 μm ml^{-1}, and increased by 0.5 μm ml^{-1} every 30 s until patients lost their eyelash reflex and no longer responded to a verbal command. This point was defined as loss of consciousness. BIS, AEPex and predicted blood and effect-site propofol concentrations were recorded at this point. The propofol concentration continued to be increased in 0.5 μm ml^{-1} increments and a tetanic stimulus (50 Hz, 80 mA, 0.25 ms pulses for 4 s) was applied to the wrist using a peripheral nerve stimulator. The patient was observed for gross purposeful movement of the head or extremities. Twisting or jerking the head was considered a purposeful movement, but twitching or grimacing was not. The stimulus was reapplied every 30 s after each increment in propofol concentration until no purposeful movement was observed. This point was defined as no response to a painful stimulus. BIS, AEPex and propofol concentrations were recorded and surgery proceeded as normal.

A quantal response model (probit analysis) was used to calculate EC_{50}, EC_{05} and EC_{95} at each end-point based on predicted blood and effect-site propofol concentrations. Assessment of the linear association between BIS, AEPex or the predicted blood and effect-site propofol concentrations and the probability of consciousness or unconsciousness was performed using logistic regression (software version 8; SAS Institute, Cary, NC, USA). The curves were fitted using the likelihood ratio goodness of fit test.

The standard logistic model for propofol concentrations, BIS and AEPex is:

$$P=C+(1-C)(1/1+e^{-(\beta_0+\beta_1 x_1)})$$

where P is the probability of unconsciousness for predicted blood and effect-site concentrations or the probability of consciousness for BIS and AEPex. C is the initial estimate of the natural response rate, β_0 is the intercept and β_1 is the estimate of the coefficients of the independent variable x_1 (i.e. propofol concentration, BIS or AEPex).

Results

Forty patients were studied. The patients were similar for age, height, weight, gender and ASA distribution (Table 1). The end-points of loss of eyelash reflex and loss of response to verbal command were not distinguishable from each other and were combined as loss of consciousness in the results. Heart rate remained stable during induction of anaesthesia, but mean arterial pressure decreased (Table 2). Pulse oximeter values were stable. Induction of anaesthesia was smooth in all patients, although 12 (30%) reported pain on injection of the propofol.

Predicted blood and effect-site propofol concentrations and values of BIS and AEPex when loss of consciousness was noted are shown in Table 3. No response to a painful tetanic stimulus occurred at the predicted blood and effect-site propofol concentrations, and values of BIS and AEPex shown in Table 4.

Table 1 Patient characteristics. Data are mean (SD) or (range)

n	40
Age (yr)	38.6 (20–64)
Height (cm)	169 (9.0)
Weight (kg)	69.4 (11.7)
Male:female	19:21
ASA I:ASA II	34:6

Table 2 Cardiovascular and respiratory data. Mean (SD). *$P<0.001$ (Student's *t*-test)

	Baseline	Loss of consciousness	No response to tetanic stimulus
Heart rate (beats min^{-1})	78.7 (18.3)	76.0 (10.0)	77.5 (9.1)
Mean arterial pressure (mm Hg)	95.6 (16.0)	84.8 (11.9)*	82.6 (11.0)*
Sa_{O_2} (%)	97.7 (1.4)	97.9 (1.0)	98.2 (0.8)

Table 3 Propofol concentrations and BIS and AEPex values at loss of consciousness. Values in parentheses are 95% confidence intervals

	EC_{05}	EC_{50}	EC_{95}
Predicted blood concentration (μm ml^{-1})	3.1 (2.6–3.5)	5.2 (5.0–5.4)	7.3 (7.0–7.8)
Effect-site concentration (μm ml^{-1})	1.5 (1.3–1.7)	2.8 (2.7–2.9)	4.1 (3.9–4.3)
BIS	88.8 (86.4–92.1)	70.9 (69.0–72.3)	52.9 (47.2–56.9)
AEPex	68.6 (66.6–71.4)	54.3 (52.7–55.6)	40.0 (35.2–43.3)

Table 4 Propofol concentrations and BIS, AEPex values when no response to a tetanic stimulus. Values in parentheses are 95% confidence intervals

	EC_{05}	EC_{50}	EC_{95}
Predicted blood concentration (μm ml^{-1})	4.3 (3.6–4.8)	7.9 (7.6–8.1)	11.5 (10.9–12.1)
Effect-site concentration (μm ml^{-1})	3.1 (2.8–3.4)	5.2 (5.1–5.3)	7.2 (7.0–7.5)
BIS	48.2 (46.4–50.8)	36.9 (35.8–37.8)	25.6 (22.0–28.1)
AEPex	53.8 (51.7–56.6)	37.8 (36.4–38.9)	22.7 (20.2–24.7)

The probabilities of loss of consciousness and no response to the stimulus *versus* predicted blood and effect-site propofol concentrations are shown in Figures 1 and 2. The probabilities of loss of consciousness and no response to the tetanic stimulus *vs* BIS and AEPex are shown in Figures 3 and 4.

The estimates of the logistic model for propofol concentrations, BIS and AEPex at loss of consciousness are shown in Table 5. A *P*-value for the test >0.9 indicates that the model is a good fit. The estimates of the logistic model for propofol concentration, BIS and AEPex at no response to tetanic stimulation are shown in Table 6.

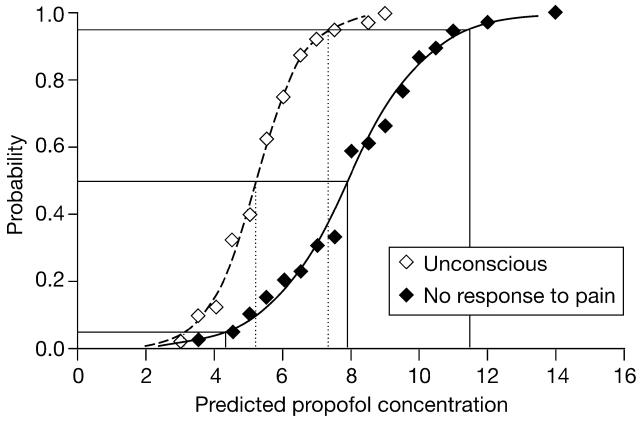

Fig 1 Predicted blood concentration of propofol (μm ml^{-1}) *vs* probability of being unconscious or not responding to a painful stimulus.

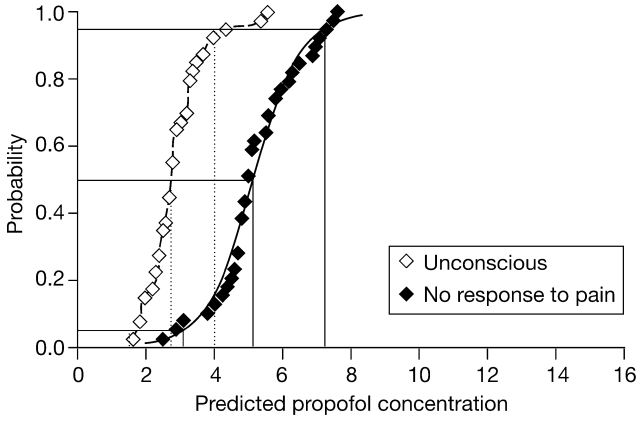

Fig 2 Effect-site concentration of propofol (μm ml^{-1}) *vs* probability of being unconscious or not responding to a painful stimulus.

Discussion

We wished to investigate whether predicted blood and effect-site propofol concentrations and values of AEPex and BIS are useful for predicting whether a patient is unconscious. Awareness is a danger when neuromuscular blocking agents are used and the most important sign of awareness, patient movement, is abolished. Anaesthetists have used the concept of MAC to ensure they are delivering sufficient volatile anaesthetic to patients to ensure they are unconscious. Anaesthetic agent monitors provide a continuous indication that sufficient volatile agent is present in the patient's lungs.

Some anaesthetists do not use i.v. techniques because they are unsure whether they are providing sufficient anaesthetic agent.[13] The EC_{50} is a concept analogous to MAC and can indicate how much i.v. drug needs to be administered. Unfortunately, unlike volatile agents, drug concentration cannot be measured in real time and instead we have to predict blood concentration.

We chose to study the Diprifusor system for TCI administration of propofol because it is widely available. The predicted blood and effect-site concentrations displayed

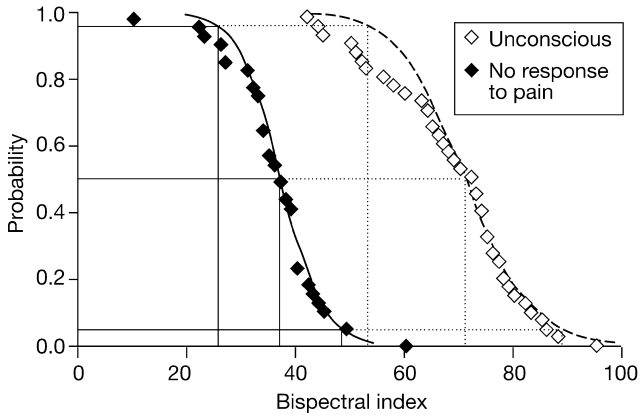

Fig 3 Bispectral index *vs* probability of being unconscious or not responding to a painful stimulus.

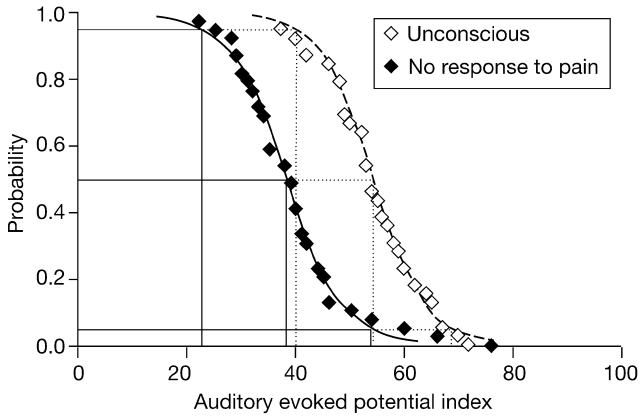

Fig 4 Auditory evoked potential index *vs* probability of being unconscious or not responding to a painful stimulus.

by the Diprifusor are used by many anaesthetists who do not have access to other pharmacokinetic models to guide the administration of propofol. The popularity of the system made our results, based on a study of the values displayed, applicable to all physicians using this infusion system.

In this study, we increased the predicted blood concentration of propofol by small increments every 30 s. Despite this slow increase in predicted blood propofol concentration, there was insufficient time for the propofol to equilibrate with the brain. Equilibration of the effect-site with the blood concentration takes four to five times the k_{eo} half-life [$T_{1/2}$ (k_{eo})], where $T_{1/2}$ (k_{eo})=0.693/k_{eo}. The Diprifusor uses a k_{eo} of 0.2 min^{-1}. Therefore, it will take approximately 15 min for blood and effect-site concentrations to equilibrate. Because of this there was considerable discrepancy between the predicted blood and effect-site concentrations, emphasizing that during induction and recovery the effect-site concentration is a more useful clinical correlate than the predicted blood concentration. We believe that the ability to clearly display effect-site concentration should be an integral part of any TCI system.[14]

Tetanic stimulation of the ulnar nerve is easy to perform and has the advantage over skin incision as a stimulus in that it is repeatable. One study has shown no significant difference between EC_{50} tetanic stimulus and EC_{50} skin incision in somatic response, but significant differences in haemodynamic response using this technique.[15] As we were looking for patient movement in response to the stimulus, it was useful in this study to have a reproducible and repeatable stimulus to apply at different propofol concentrations.

Ninety per cent of patients will lose consciousness and have no response to a tetanic stimulus at propofol concentrations between the EC_{05} and the EC_{95} for these responses.

Table 5 Estimates of the logistic models for propofol concentrations, BIS and AEPex values at loss of consciousness. SE=standard error

Independent variables	*C*	β_0 (SE)	β_1 (SE)	*P*-value for linear regression goodness-of-fit test
Target blood concentration	0	–7.24 (0.65)	1.39 (0.12)	0.9843
Effect-site concentration	0	–6.44 (0.48)	2.31 (0.17)	0.9802
BIS	0.077	–11.64 (1.24)	0.16 (0.02)	0.9986
AEP	0.031	–11.18 (1.24)	0.21 (0.02)	0.9995

Table 6 Estimates of the logistic models for propofol concentrations, BIS and AEPex values at response to tetanic stimulation. SE=standard error

Independent variables	*C*	β_0 (SE)	β_1 (SE)	*P*-value for linear regression goodness-of-fit test
Target blood concentration	0	–6.50 (0.49)	0.82 (0.06)	0.9966
Effect-site concentration	0	–7.44 (0.46)	1.44 (0.09)	0.9383
BIS	0.04	–9.64 (1.08)	0.26 (0.03)	0.9998
AEP	0	–7.25 (0.51)	0.19 (0.01)	0.9935

For loss of consciousness, the range of effect-site concentrations to include 90% of patients was 1.5–4.1 μm ml^{-1} and for no response to the tetanic stimulus it was 3.1–7.2 μm ml^{-1}. The predicted effect-site concentration range is smaller than the predicted blood concentration range and is therefore more useful in guiding propofol administration. Although the range of predicted propofol concentrations is useful in the assessment of whether a patient will be unconscious, neither the predicted concentration range nor the MAC guarantees lack of awareness.

Comparison of the results of this study performed on a Caucasian population with the results of another study performed on Chinese patients revealed similar results for predicted effect-site concentrations.[16] The EC_{50} for effect-site propofol concentration at loss of consciousness was 2.8 μm ml^{-1} in the Caucasian and 2.7 μm ml^{-1} in the Chinese populations. The EC_{95} was 4.1 μm ml^{-1} in Caucasians compared with 3.8 μm ml^{-1} in Chinese. The EC_{50} at no response to the tetanic stimulus was 5.2 and 4.5 μm ml^{-1} and the EC_{95} 7.2 and 6.4 μm ml^{-1} in the Caucasian and Chinese populations respectively. Despite the similarity in predicted effect-site concentrations between the two populations, there are large differences in the predicted blood concentrations, the concentration in the Caucasian population being consistently higher. This is explained by a difference in the rate at which the blood concentration of propofol was increased in the two studies. The propofol concentration was increased more quickly in the Caucasian patients and so the predicted blood concentration was greater at loss of consciousness and lack of response to the painful stimulus. As the site of action is the brain and not the blood, the predicted effect-site values are similar between the populations. We believe this reinforces the value of the effect-site rather than the predicted blood concentration in determining the pharmacodynamic effects of propofol on the individual patient.

In this study, 90% of patients lost consciousness at a BIS value between 88.8 and 52.9 and an AEPex between 68.6 and 40. The range for AEPex is smaller than for BIS, and this would suggest that AEPex is more useful in predicting loss of consciousness. Loss of response to a tetanic stimulus occurred between BIS values of 48.2 and 25.6 and AEPex values of 53.8 and 22.7 for 90% of patients. The range for BIS is smaller and so possibly BIS is more useful in predicting lack of response to painful stimuli.

The BIS values are also very similar between the Caucasian and Chinese populations when there is no response to a tetanic stimulus, with EC_{50} values of 36.9 and 40.1 and EC_{95} values of 25.6 and 27.3 in the Caucasian and Chinese populations, respectively. The BIS values at loss of consciousness differ slightly, possibly because loss of consciousness is a more subjective end-point than loss of response to a painful stimulus.

We believe that the predicted effect-site concentration of propofol is a more useful and reproducible indicator than the predicted blood propofol concentration. Prediction of the effect-site EC_{05}, EC_{50} and EC_{95} at which patients become unconscious and when they no longer respond to a painful stimulus will guide physicians in the administration of propofol using the Diprifusor in a manner analogous to the MAC when using volatile agents.

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