Effect-site half-time for burst suppression is longer than for hypnosis during anaesthesia with sevoflurane†

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Background. The relationship between measures of drug effect such as bispectral index (BIS) and end-tidal (ET) levels of anaesthetic agents is described by the 'effect site equilibrium half-time', \( t_{1/2}(ke0) \). There are limited data available on sevoflurane \( t_{1/2}(ke0) \) during routine anaesthesia and surgery. Preliminary observations suggested \( t_{1/2}(ke0) \) for the degree of hypnosis as estimated by BIS is different from that for burst suppression of the electroencephalograph, occurring at ‘deep’ levels of anaesthesia. This study aimed to determine and compare \( t_{1/2}(ke0) \) for these two 'effects'.

Methods. Large changes in ET sevoflurane were produced in 13 subjects during surgery. ET sevoflurane, BIS, and burst suppression ratio (BSR) were recorded every 10 s. Data were divided into epochs with BIS >30 (BIS) or with BSR >10% (burst suppression). Using a non-parametric modelling technique, \( t_{1/2}(ke0) \) was determined for each epoch.

Results. There were 36 'BIS' and 20 burst suppression zones. Mean (sd) \( t_{1/2}(ke0) \) for BIS was 3.48 (1.12) min and for BSR 9.9 (6.4) min. In all subjects, \( t_{1/2}(ke0) \) BIS > \( t_{1/2}(ke0) \) BSR. These differences were statistically significant \( (P<0.01) \). The pooled mean effect-site sevoflurane concentration producing a BIS of 50 was 1.23 (sd 0.34) vol% and for a BSR of 50% was 3.3 (0.50) vol%. There were considerable intra- and inter-subject variabilities.

Conclusions. The different values of \( t_{1/2}(ke0) \) for these effects suggest different sites or mechanisms of action. These results also establish values of \( t_{1/2}(ke0) \) which can be used to provide the real-time estimates of effect-site sevoflurane concentration in clinical practice.

Br J Anaesth 2008; 100: 72–7

Keywords: anaesthetics volatile, sevoflurane; monitoring, electroencephalography; model, pharmacokinetic

Accepted for publication: September 14, 2007

Traditional delivery of anaesthetic agents has focused on control of the blood or plasma concentrations of various drugs. Delivery of volatile anaesthetics is based on estimation of blood levels using end-tidal (ET) measurement while i.v. control systems such as target-controlled infusion ‘target’ modelled blood levels or, in more recent systems, the effect site. It is recognized that using the effect site as a target should more closely match drug administration and needs. However, the end points for effect-site control (usually achievement of a given effect-site concentration) may differ from traditional clinical end points for control such as lack of movement (described by MAC and derivatives) and haemodynamic stability.

We have previously described a system which guides manual administration of target-controlled sevoflurane anaesthesia and have extended this system to include continuous estimation and prediction of effect-site concentration \( (Ce) \). Calculation of \( Ce \) is dependent on using the appropriate rate of transfer between the plasma and effect-site compartments, described by the effect-site equilibrium half-time \( [t_{1/2}(ke0)] \). The availability of measures of anaesthetic effect such as the bispectral index (BIS) allows estimation of these parameters for the effects measured by BIS.

†This project was presented in part at the Euroanaesthesia Meeting, Vienna, Austria, May 2005.
Limited data are available on $t_{1/2}(ke0)$ for volatile anaesthetics. Almost all of these data have been collected under laboratory conditions and may not reflect conditions occurring during routine anaesthesia when the influence of other drugs, such as opioids, and surgery needs to be considered. In addition, the collection of pilot data for the present study suggested that the $t_{1/2}(ke0)$ for the effect of burst suppression was different from that of the ‘hypnotic’ component of the BIS. Burst suppression is known to be a component of the BIS algorithm and becomes the sole determinant of BIS once the burst suppression ratio (BSR) exceeds a threshold of around 40%.

The aims of this study were, therefore, to characterize the range of values for $t_{1/2}(ke0)$ occurring during routine anaesthesia and surgery with sevoflurane and to compare the values for $t_{1/2}(ke0)$ determined for BIS values in the hypnotic range (40–60) [$t_{1/2}(ke0)_{BIS}$] with $t_{1/2}(ke0)$ for the effect of burst suppression [$t_{1/2}(ke0)_{BS}$].

Methods

This study was approved by the Canterbury Regional Ethics Committee. Written informed consent was obtained from each subject. Eighteen patients, ASA I–III, undergoing elective surgery at Christchurch Hospital were enrolled between November 2002 and June 2004. After induction with propofol, anaesthesia was maintained with sevoflurane in air/O₂ mix without N₂O. In those patients in whom an epidural was used, this was sited before operation, and initiated and maintained with local anaesthetic, typically bupivacaine 0.5%, to provide the major analgesic component of the anaesthetic. All patients were intubated and ventilated with ET CO₂ maintained within the range 30–40 mm Hg. Muscle relaxation was provided as required to facilitate surgery. Other details of anaesthesia management were left to the anaesthetist in charge of the case. No study interventions occurred until at least 30 min after propofol induction.

Standard monitoring was used, including inhalation agent analysis (Datex S/5) and BIS monitoring, with additional monitoring such as invasive pressure monitoring used as appropriate for each case. For monitoring of BIS, an Aspect A2000 BIS (software version 2.10) monitor was used with the averaging time set to 15 s. Data were collected from the Datex S/5 monitor every 10 s using locally developed software which allowed later transfer to a spreadsheet. The A2000 monitor outputs data every 5 s and BIS, BSR, and signal quality data were collected from this device to a separate computer file. Consecutive pairs of data from the A2000 were averaged to produce 10 s samples and these data were incorporated into the spreadsheet with the rest of the monitored data. Data associated with a signal quality index (SQI) <20 were ignored as per the Aspect guidelines.

Once at least 30 min had elapsed after induction of anaesthesia, a series of increases and decreases in ET sevoflurane were produced by altering the vaporizer dial between 0 and 5–8%. Each increase or decrease aimed to produce a gradual change from baseline BIS value followed by a return to the initial values. BIS values were allowed to increase towards 60 or decrease towards zero. A locally developed display which incorporates an estimate of current effect-site sevoflurane concentration, based on a $t_{1/2}(ke0)$ of 3.0 min, and predictions of future ET and effect-site values was used in all cases to allow adjustments in vaporizer settings to be made in anticipation of the maximum or minimum BIS values.

Hypotension associated with high sevoflurane concentration was managed with 0.5 mg increments of metaraminol. If more than one dose was required within a 5 min period, the sevoflurane vaporizer was turned off and sevoflurane concentrations allowed to decrease.

Data analysis

Data were imported into a spreadsheet (Microsoft Excel) and expired sevoflurane, BIS, and BSR values plotted against time. From these plots, epochs for detailed analysis were identified. Epochs with a decrease then an increase in ET-sevoflurane accompanied by an increase then a decrease in BIS, with BIS in the range 30–60, were analysed for the effect of ‘BIS’, whereas an increase then a decrease in ET-sevoflurane accompanied by an increase and a decrease in BSR while BIS<30 was analysed for the effect of burst suppression. Examples of these patterns are shown in Figure 1. The first 30 min of the case was excluded from the analysis to minimize the effects of the induction dose of propofol on the electro-encephalographic parameters.

Data were analysed using the non-parametric method described by Verotta and Sheiner. This was implemented as a Visual Basic function for Microsoft Excel (the numerical convolution and loop collapsing objective function are available as part of the library of functions contained in the ‘PKPD Tools for Excel’ dynamic link library for excel for Windows available at http://www.pkpdtools.com). We used a numerical convolution to obtain a set of predicted values for Cₑ as a function of time for the range of observations of ET values with a given value of $t_{1/2}(ke0)$. This algorithm first determines the boundary of the Ce interval over which there is hysteresis. It next locates a number of points spaced equally along the Ce axis over this interval and calculates effect predictions for each of these points. The result of the objective function is the average of all the squared distances between distinct pairwise combinations of these predictions which is an index of the degree of hysteresis. An initial estimate of the best $t_{1/2}(ke0)$ was obtained by trialling $t_{1/2}(ke0)$ values to find values that appeared to collapse the hysteresis loop graphically. After obtaining this starting estimate, Excel’s optimizer (Solver) was used to obtain the $t_{1/2}(ke0)$ value that minimized the objective function.
For each data segment, the effect-site concentration corresponding to a BIS of 50 (BIS50) or a BSR of 50% (BSR50) was determined by determining the line of best fit for the relationship between Ce and BIS or BSR as appropriate using the optimum $t_{1/2}(k_{e0})$ for that data segment.

Statistics
Data were analysed using the values for $t_{1/2}(k_{e0})_{BIS}$, $t_{1/2}(k_{e0})_{BS}$, BIS50, and BSR50 determined for each data epoch. These data were combined using the arithmetic mean value for each subject. The distribution of these means was assessed using the D’Agostino and Pearson omnibus normality test. These values were then used to calculate pooled means and standard deviations (SD) for each effect.

Two statistical approaches were used. For those subjects in whom data for both BIS and BSR were available, the values for $t_{1/2}(k_{e0})_{BIS}$ and $t_{1/2}(k_{e0})_{BS}$ and for BIS50 and BSR50 were compared using a paired two-tailed t-test.

The second approach was to use generalized linear modelling (PROC GLM, SAS/STAT 8.02) to allow for variable numbers of data points (including none) in each subject while allowing all data points to be used. In the model, individual subjects were set as a random factor and the type of effect as a fixed factor, with a subject by type interaction included. Because variance appeared to increase with the mean, a log transformation was carried out. Values of $t_{1/2}(k_{e0})_{BIS}$ and $t_{1/2}(k_{e0})_{BS}$ were compared using this method.

Results
Data were available for 13 of the 18 subjects enrolled in the study. In three subjects, there were problems with data capture; in one case, the planned surgical procedure was considerably shortened and in another, no significant changes in BIS were produced. Of the 13 sets of data contributing to the results, the surgery was open anterior resection of the rectum in eight, and general anaesthesia was supplemented with an epidural in three of these (Subjects G, K, and M). Other operations were closure of stoma (Subjects E and F), laparoscopic cholecystectomy (L), radical neck dissection (C and D), and lumbar laminectomy (A). Total fresh gas flows between 0.8 and 1.8 litre min$^{-1}$ were used. Opioid use was variable. The five subjects undergoing anterior resection without use of an epidural received between 500 and 1500 mg of fentanyl, the remaining received no more than 500 mg. Morphine up to 0.15 mg kg$^{-1}$ was used in a small number of subjects. The mean duration of anaesthesia was 164 min (range 50–300 min), and the mean age of the subjects was 56 yr (31–89). The frequency distribution of systolic arterial pressure determinations is shown in Figure 2. Direct invasive measurement of arterial pressure was used in four subjects, in the remaining, automated non-invasive arterial pressure measurement was used.

There were 36 epochs with data for the effect of BIS from 12 subjects (maximum five per subject) and 20 epochs of burst suppression in 10 subjects (maximum four). The individual data points for each subject are shown in Figure 3. The subject means for $t_{1/2}(k_{e0})$, BIS50, and BSR50 were normally distributed (D’Agostino and Pearson omnibus normality test). The pooled mean $t_{1/2}(k_{e0})$ for hypnosis as measured by BIS was 3.48 (1.13) min and for burst suppression was 9.9 (6.4) min. Using a two-tailed paired t-test, these values were significantly different, $P=0.009$. Analysing the data using generalized linear modelling (PROC GLM, SAS 8.02, SAS Institute Inc, Cary, NC, USA) allowed all data points to be analysed, giving $F(12,34)=3.13, P=0.0004$.

Figure 4 shows the distribution of mean effect-site sevoflurane concentrations that produced a BIS of 50 (BIS50) and a BSR of 50% (BSR50). The pooled mean value for BIS50 was 1.23 (0.34) vol% whereas that for BSR50 was
3.3 (0.50) vol%. The difference between these values was also statistically significant (P<0.0001). The maximum individual value for BIS50 was 1.9 vol%.

**Discussion**

The two findings of this study are that the mean value for $t_{1/2}(ke0)_{BIS}$ for the ‘hypnotic’ effect of sevoflurane was 3.48 (1.12) min, which is similar to previous reports and that, in contrast, $t_{1/2}(ke0)_{BS}$, for the effect of burst suppression was significantly greater at 9.9 (6.4) min.

The value determined in this study for $t_{1/2}(ke0)_{BS}$ of 3.48 min is similar to that reported in settings where sevoflurane was the only drug used or there was no surgery taking place. This value is also in the range of that for the ‘brain’ compartment of a physiological model, although a similarity in values for $t_{1/2}(ke0)$ does not necessarily imply similarities in the site of effect. In addition to the cascade of factors enumerated elsewhere, we might have expected that many factors associated with this type of surgery and anaesthesia would impact on $t_{1/2}(ke0)$. These factors include those with the potential to change cardiac output and regional blood flow distribution such as changes in CO₂, arterial pressure changes and the use of vasopressors, surgical positioning, and retraction, and also other factors such as the diverse range of drugs, anaesthetic techniques, and surgical influences. Although we did see considerable variability in $t_{1/2}(ke0)$ both between and within subjects, this variability is well within the range reported previously in studies without the confounding effects of surgery and associated manipulations and drugs. It is not possible within the design of this study to assess the influence of these factors. Previous studies have shown that adjunct drugs such as remifentanil can affect $t_{1/2}(ke0)$. It has also been reported that low to moderate levels of fentanyl or morphine have little effect on MAC-awake, whereas higher fentanyl levels may influence MAC-awake. It may be that there is a parallel and similar threshold for synergy between adjunct drugs and sevoflurane effect-site half-times.
is significantly greater than $t_{1/2}(\text{ke}0)_{\text{BIS}}$ for hypnosis both for the pooled data and in each individual for which both values for $t_{1/2}(\text{ke}0)$ could be determined. This result has not been reported previously, although it has been demonstrated that a simple sigmoid Emax model does not adequately describe the relationship between Ce and BIS over the full range of BIS values.\textsuperscript{13} This difference in values for $t_{1/2}(\text{ke}0)$ and the complexity of the full BIS:Ce relationship suggests that the effect of burst suppression occurs at a different site from the other components of the BIS algorithm.\textsuperscript{6}

The variability of $t_{1/2}(\text{ke}0)_{\text{HS}}$ is larger than that for $t_{1/2}(\text{ke}0)_{\text{BIS}}$. The reasons for this increase are not clear to us but could be due to a genuine increased variability, some function of the analysis method used which is effectively calculating the slope of the best fit line with minimum hysteresis, or the relatively small number of data points. There are little comparative data available to help determine either the typical distribution of possible reasons for the variability seen. What is important is that not only are the pooled mean values for $t_{1/2}(\text{ke}0)_{\text{HS}}$ larger than that for $t_{1/2}(\text{ke}0)_{\text{BIS}}$ but that in any subject all the individual estimates of $t_{1/2}(\text{ke}0)_{\text{HS}}$ are greater than any estimates of $t_{1/2}(\text{ke}0)_{\text{BIS}}$ in that subject.

The difference between the effect-site concentration required to produce a BIS of 50 or a BSR of 50% (1.2 and 3.2 vol%, respectively) represents a right shift of the concentration effect curve and is consistent with previous observations that burst suppression occurs at ‘deeper’ levels of anaesthesia.\textsuperscript{14,15} Although it will necessarily take longer to reach these levels, it does not automatically follow that the effect-site time constant will be different. Our results suggest that the occurrence of burst suppression during routine anaesthesia is a function of both a high rate of sevoflurane delivery and prolonged delivery at these levels. The longer $t_{1/2}(\text{ke}0)_{\text{HS}}$ also implies that once burst suppression occurs it may be sometime after the rate of sevoflurane delivery is decreased before burst suppression ceases. It is of interest that the highest Ce required to give a BIS of 50 in any individual data set was 1.9 vol% and the upper bound of the 99% confidence interval for BIS50 $(d=0.99, df=10)$ was 1.6 vol%. These results suggest that sevoflurane Ce values in the range 0.7–0.9 MAC are sufficient to keep BIS below a value 50, a common target value for BIS-guided control algorithms, and well below the levels at which burst suppression occurs.

This study has a number of other potential limitations. We decided to not use a standardized anaesthetic to allow us to observe the range of results that might be seen in clinical practice; however, this makes interpretation of the differences between subjects and differences within subjects at different points in time difficult. These differences may be due to subject variability, changing levels of other drugs, surgical factors, the duration of the anaesthetic or factors potentially influencing the uptake, and distribution of sevoflurane such as arterial pressure changes. This study was not designed to explore these factors. However, these results suggest that $t_{1/2}(\text{ke}0)$ for sevoflurane remains within a reasonably narrow band as these other factors vary. For example, there is no obvious difference in those subjects receiving a combined epidural and general anaesthetic. In addition, our previous results suggest that variability of this magnitude has little effect on predictions of effect-site concentration.\textsuperscript{2} We used a non-parametric approach to estimation of $t_{1/2}(\text{ke}0)$. All such techniques are based on removing hysteresis between the concentration and the effect.\textsuperscript{16} The disadvantage of our technique is that we are not able to determine other parameters of the pharmacokinetic/pharmacodynamic (PK/PD) relationship, but that was not our primary interest and to do so requires producing a full range of effects. Our results for the effect of hypnosis are similar to those determined using a formal parametric approach and at the optimum value for the $t_{1/2}(\text{ke}0)$ of burst suppression the relationship between Ce and BSR was consistently close to a straight line, suggesting that this approach provides reasonable estimates of $t_{1/2}(\text{ke}0)$. Because the value for BIS is averaged over a series of epochs and then subject to a processing delay, any BIS value is at least 15 s old. This means that the ‘true’ value of $t_{1/2}(\text{ke}0)$ will be slightly less than that determined taking BIS as the measure of effect. However, most studies have not corrected for this difference which may explain the shorter $t_{1/2}(\text{ke}0)$ seen when other EEG measures such as spectral edge frequency are used as the ‘effect’.\textsuperscript{3,4} Processing of data for burst suppression follows a similar pattern to that for BIS so that the offset between values for BIS and burst suppression should be minimal.

Most PK/PD studies with inhaled anaesthetics use ET levels as an indication of central compartment concentration. Although it is accepted that there may be differences between ET and arterial concentrations\textsuperscript{17} the gradient generally remains constant in an individual and ET concentrations have the advantage over blood samples of providing a nearly instantaneous and continuous measure. The influence of the rate of change of volatile concentration on this gradient has not been studied. In our subjects, the typical maximum rate of change in ET sevoflurane was 1.5% over 5 min. If the change in arterial concentration did lag behind the ET concentration, this would lead to a shorter value for $t_{1/2}(\text{ke}0)$.

This study has demonstrated that the $t_{1/2}(\text{ke}0)$ for sevoflurane for the effect of hypnosis as measured by the bispectral index during routine surgery is similar to the values found in a laboratory setting and to those derived from the parameters of the brain compartment of physiological models of anaesthetic uptake and distribution. This result supports the use of values for $t_{1/2}(\text{ke}0)$ in the range 3.0–3.5 min in a system to provide the real-time estimates of sevoflurane effect-site concentration. This study has also demonstrated that the $t_{1/2}(\text{ke}0)$ for the effect of burst suppression is much larger than for hypnosis.
Acknowledgements
Statistical and methodological advice was provided by Assoc. Prof. Elisabeth Wells, and Prof. Jamie Sleigh.

Funding
Canterbury Medical Research Foundation; Australian and New Zealand College of Anaesthetists.

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