Available online at www.sciencedirect.com
ScienceDirect
Research in Veterinary Science 81 (2006) 373–381
www.elsevier.com/locate/rvsc

Bispectral index, spectral edge frequency 95% and median frequency recorded at varying desflurane concentrations in pigs

María F. Martín-Cancho [a,*], Juan R. Lima [a], L. Luis [a], Verónica Crisóstomo [a], María A. López [b], Luis J. Ezquerra [b], María S. Carrasco-Jiménez [c], Jesús Usón-Gargallo [a]

[a] *Minimally Invasive Surgery Centre, Avda/Universidad s/n, 10071 Cáceres, Spain*
[b] *Department of Surgery, College of Veterinary Medicine, University of Extremadura, Cáceres, Spain*
[c] *Section of Anaesthesiology and Resuscitation, Department of Surgery, College of Medicine, Cádiz University, Cádiz, Spain*

Accepted 4 January 2006

Abstract

The objective of this study is to evaluate the usefulness of bispectral index (BIS), spectral edge frequency 95% (SEF) and median frequency (MED) in relation to a simple descriptive scale (SDS) as indicators of anaesthetic depth at different desflurane concentrations in swine.

Sixteen pigs were randomly allocated to four groups. Electroencephalograms (EEG) were recorded during desflurane anaesthesia, and BIS, SEF and MED were calculated from the EEG. The agent was administered in pure oxygen at 1, 1.25, 1.5 and 1.7 MAC in randomized order. Anaesthetic depth was evaluated on a SDS.

BIS decreased significantly ($P < 0.001$) at the different anaesthetic dosages used. SEF decreased significantly ($P < 0.001$) from basal to 1 MAC of desflurane. MED decreased significantly ($P < 0.001$) from basal to 1 MAC and from 1 to 1.75 MAC. Good correlation was seen between SDS scores and BIS values and between SDS scores and MED values.

BIS appeared to be useful to predict changes in anaesthetic depth at clinically used dosages of inhalant anaesthesia.

Keywords: Pig; Anaesthesia; Bispectral index; Desflurane and anaesthetic depth

1. Introduction

In a previously reported study (Martín et al., 2003), we evaluated the usefulness of bispectral index (BIS), spectral edge frequency 95% (SEF) and median frequency (MED) as indicators of anaesthetic depth using two different inhalant anaesthetics, sevoflurane and isoflurane at varying concentrations. In that study, BIS was the most accurate EEG indicator of anaesthetic depth in pigs.

BIS, SEF, and MED are variables derived from the EEG. Several studies (Kearse et al., 1994; Vernon et al., 1995; Sebel et al., 1995; Liu et al., 1997; Gan et al., 1997) have reported that these variables have the ability to measure the hypnotic component of the anaesthetic state. The BIS is calculated from an algorithm empirically derived from EEG studies in anaesthetized humans (Sigl and Chamoun, 1994), that takes into account power-spectral variables, burst suppression, and the degree of phase coupling assessed through bispectral analysis, generating a BIS value from 0 to 100, with lower values indicating a higher degree of sedation and hypnosis. SEF is a frequency in the EEG determined by the 95th percentile of the power-spectral density. Low SEF values indicate a high degree of sedation and hypnosis (Schweder et al., 1998). MED is the frequency below which 50% of the total EEG power is located.

Previous results indicated that BIS values were significantly higher during administration of sevoflurane than

* Corresponding author. Tel.: +34 9 27 18 10 32; fax: +34 9 27 18 10 33.
E-mail address: mmartinc@ccmi.es (M.F. Martín-Cancho).

0034-5288/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rvsc.2006.01.003

during administration of isoflurane at the same MAC in pigs. The aforementioned study is lacking data on all the inhalant anaesthetics currently in use in daily practice. In order to complete that work, the present study was undertook to compare the results obtained under desflurane anaesthesia with previously reported sevoflurane and isoflurane data. The ability of these measurements to assess the degree of hypnosis at varying desflurane concentrations was assessed, and these data were compared with BIS values previously obtained in sevoflurane and isoflurane anaesthetized pigs.

In swine, BIS values are able to differentiate lighter planes of anaesthesia approaching consciousness from deeper planes of anaesthesia. It has been reported that BIS does not change in accordance with anaesthetic depth at clinically useful isoflurane concentrations (Haga et al., 1999). Our experience, however, does not support that finding. Another study (Haga, 2001) did not reveal changes in EEG variables in response to nociceptive stimuli in isoflurane anaesthetized swine.

We are not aware of any research performed in the field of electroencephalography during desflurane anaesthesia in pigs. Further studies are thus still needed to determine whether BIS can be used to guide anaesthetic management in pigs. The objective of the study reported here was to evaluate BIS, SEF and MED as indicators of anaesthetic depth in pigs anaesthetized using varying desflurane concentrations, and to assess whether BIS recorded during desflurane anaesthesia was any different from data obtained in previous studies using equivalent sevoflurane and isoflurane dosages in swine.

2. Material and methods

Animals – 16 healthy large white X Landrace pigs of both sexes (20.0 ± 3.1 kg) were used for this study. A complete clinical examination, including serum biochemical analyses and thoracic radiography was performed to ensure the animals' good health prior to inclusion in the study. During the study, animals were housed indoors with unlimited access to food and water except during the 24-h period prior to anaesthesia when they were allowed water only. The experimental protocol was approved by the Centre Ethical Committee of Animal Research.

Experimental design – pigs were randomly allocated to four experimental groups (4 pigs/group; 2 female and 2 male). Each group received a specific predetermined sequence of four end-tidal concentrations of desflurane (1, 1.25, 1.5, and 1.75 MAC) in a 4×4 Latin-square design. Reported desflurane MAC in pigs range from 8.28% (Manohar and Parks, 1984) to 10.0% (Eger et al., 1988). For the purposes of this study, the MAC of desflurane was defined as 8.28%. The 16 pigs were anaesthetized in a randomized order. Two days before any animal was anaesthetized in the study, anaesthesia was induced by use of sevoflurane administered via a facemask, to place a 20-gauge catheter in an external iliac artery by use of a femoral approach. This catheter was flushed with heparinized saline (0.9% NaCl) solution and fixed to the skin.

On the study day, anaesthesia was induced administering desflurane in oxygen via a face mask. When anaesthetic depth was deemed adequate, orotracheal intubation was performed with a cuffed endotracheal tube, ensuring correct ventilation in both lungs by auscultation. Pigs were connected to a partial non-rebreathing circular system. Flow rate was 3 L of oxygen/min. Spontaneous ventilation was maintained during the procedure. To maintain body temperature during anaesthesia, pigs were placed in dorsal recumbence on an electric blanket.

EEG monitoring – before induction of anaesthesia, the skin of the head was shaved and defatted using diethyl ether. Gel-coated disposable silver–silver chloride electrodes (Zipprep, Aspect Medical Systems Inc., Natick, MA) were applied to record the EEG. One electrode was placed at each side of the head, 1 cm caudal to the lateral cantus of each eye, a central, or reference, electrode was placed on the midline of the frontal bone equidistant from the two previously applied electrodes, and a ground electrode was placed 2 cm to the left or right edge of the central electrode. This electrode configuration is similar to a technique described for humans (Gan et al., 1997). Before each recording, impedance was checked and maintained at $<10{,}000\ \Omega$ at 128 Hz. The electrodes were connected to an EEG monitor (A-1050TM, version 3.05.05, Aspect Medical Systems Inc., Natick, MA), setting the low-frequency filter at 2 Hz and the high-frequency filter at 70 Hz. Pigs were then placed on a purpose-built stretcher consisting of a wooden frame and nylon straps, and an EEG was recorded during 5-min in the conscious animal.

Pigs were then anaesthetized, maintaining desflurane end-tidal concentration at the specified MAC value for 30 min. The EEG monitor used automatically detected only high-quality signals, as artifact-processing algorithms in the monitor automatically detected and corrected (or rejected) patient-induced artifacts in the EEG (such as those attributable to eye blinking or rolling and head shaking) prior to BIS calculation. BIS values were transferred to a computer for processing on a 5 s basis.

Monitoring of other variables – all pigs were monitored during anaesthesia. Monitoring included lead-II ECG (Hewlett–Packard model 86S, Hewlett–Packard, Geneva, Switzerland) with the electrodes placed in the interdigital spaces of all four limbs, pulse oxymetry recorded by use of a probe (Clip Tip sensor, Oximeter Sensor, Datex-Ohmeda, Louisville CO, USA) placed on the tongue, rectal temperature (digital thermometer), tidal volume, end-tidal concentration of desflurane, end-tidal CO_2 ($ETCO_2$) concentration, and respiratory rate (Ohmeda RGM 5250, Ohmeda, Madrid, Spain). The probe used to sample exhaled gases was placed at the facemask in conscious pigs and at the oral end of the endotracheal tube in anaesthetized pigs. Arterial blood pressure and heart rate were also measured by a blood pressure module

(Hewlett–Packard Press M 1006B, Hewlett–Packard, Geneva, Switzerland) connected to a system for monitoring hemodynamic variables (Hewlett–Packard model 86S, Hewlett–Packard, Geneva, Switzerland). Cardiovascular recordings were obtained by connecting the catheter that had been previously inserted in an external iliac artery to the monitoring system via a transducer (Ohmeda transducer DT-XX, Ohmeda, Madrid, Spain). Heart rate was also measured by examination of the ECG. Although the variables were continuously monitored during the experiment, cardiovascular values were recorded only at 5-min intervals.

After the EEG was recorded for 5 min, an anaesthesiologist (JRL) who was blinded to both EEG results and desflurane concentration assessed each pig to determine the type and strength of reflexes present. This information was assessed, along with physiologic variables and used to create a subjective judgement of the depth of anaesthesia, which was scored on a 150-mm-long simple descriptive scale (SDS). The SDS was divided into five categories on the basis of the reflexes that would be expected at each plane of anaesthesia (Martín et al., 2003) (Appendix). This scale was prepared based on our clinical experience (Martín et al., 2003) and the description of the expected characteristics of each anaesthetic plane provided elsewhere (Thurmon et al., 1996) based on Guedel's classification (Guedel, 1936). Nociceptive response was evaluated by clamping a Pean forceps on the vestigial remnant of the second or fifth digit (i.e., dewclaw) of a hind limb for up to 15 s. This was used to establish anaesthetic depth as determined on the SDS.

Statistical analysis – one-way ANOVA for repeated measures followed by the Tukey test to examine intra-group deviations were used to analyze changes in EEG, hemodynamic, and ventilatory variables related to each concentration of inhalant anaesthetic. A Bonferroni procedure for multiple comparisons was conducted to minimize the possibility of finding significant results by chance. Stepwise multiple-regression analysis was performed to evaluate the relationship between SDS as the dependent variable and BIS, SEF, and MED. For all analyses, values of $P < 0.05$ were considered significant. Statistical analysis of data were performed with a statistical software package (SPSS 10.0 statistical package for Windows, SPSS Inc., Chicago, IL).

3. Results

Results are expressed as mean ± SD and range. Age, weight, and baseline values were similar for all groups. All pigs completed the study without evidence of adverse effects. Anaesthetic induction was smooth in all animals, without any excitatory movements observed in any case. Recovery from anaesthesia was similarly uneventful.

BIS decreased significantly with increasing desflurane concentrations. Significant ($P < 0.001$) changes in SEF and MED were also detected at the different anaesthetic concentrations.

BIS decreased significantly ($P < 0.001$) at the following desflurane concentration intervals: from basal to 1, 1–1.25, 1.25–1.5, and 1.5–1.75 MAC (Table 1 and Fig. 1). SEF values decreased significantly ($P < 0.001$) from basal to 1 MAC, but no further significant changes in SEF were detected at any other studied interval. As to SEF, recorded MED values decreased significantly ($P < 0.001$) from basal to 1 MAC and from 1 to 1.75 MAC. There was no significant change in MED between 1 and 1.25, 1.25–1.5, or 1.5–1.75 MAC (Table 1).

No significant changes in SDS could be seen between 1.5 and 1.75 MAC, but a significant variation was detected in SDS between basal and 1, 1–1.25, and 1.25–1.5 MAC (Table 1 and Fig. 2).

Despite the significant decrease in mean BIS values observed with increasing MAC concentrations, the examination of the evolution of BIS values with changes in desflurane concentrations in each individual pig revealed an increase in BIS in one animal when passing from 1.25 to 1.5 MAC and in another pig at the change from 1 to 1.25 MAC (Fig. 1).

Heart rate did not change significantly during administration of desflurane anaesthesia at any concentration. The agent caused a significant ($P < 0.001$) decrease in arterial blood pressure when 1 MAC was administered, that remained significantly lower at 1.25, 1.5 and 1.75 MAC. Statistical analysis of ventilatory variables revealed a significant decrease in breathing rate between 1.5 and 1.75 MAC. $ETCO_2$ measured during the study increased significantly ($P < 0.05$) with increasing desflurane concentrations. Rectal temperature decreased significantly ($P < 0.001$) as desflurane concentration increased (Table 2).

Table 1
Mean ± SD (range) values for a simple descriptive scale (SDS), bispectral index (BIS), spectral edge frequency 95% (SEF), and median frequency (MED) determined in pigs anaesthetized by use of various desflurane concentrations

Desflurane concentration		SDS[a]	BIS	SEF	MED
%	MAC				
0	Basal	0.00 ± 0.00 (0.00–0.00)	97.55 ± 1.13 (93.45–98.00)	24.61 ± 3.51 (17.45–28.74)	9.01 ± 1.95 (5.44–11.65)
8.3	1	49.94 ± 15.98 (27.00–79.00)	57.16 ± 13.86 (34.81–78.96)	14.65 ± 3.83 (10.53–22.88)	4.84 ± 1.38 (3.06–8.30)
10.4	1.25	72.94 ± 25.02 (33.00–125.00)	41.37 ± 12.51 (23.86–65.92)	13.38 ± 4.01 (6.39–23.44)	4.35 ± 1.56 (1.54–7.53)
12.4	1.5	114.12 ± 11.39 (98.00–139.00)	31.26 ± 9.10 (20.08–55.96)	15.35 ± 4.19 (10.10–27.23)	4.17 ± 1.31 (2.11–5.98)
14.5	1.75	123.94 ± 16.58 (94.00–142.00)	19.41 ± 5.40 (13.00–27.60)	12.77 ± 2.93 (8.33–19.25)	3.34 ± 0.83 (1.92–5.42)

MAC, minimum alveolar concentration.
[a] Scored on a scale of 0–150.

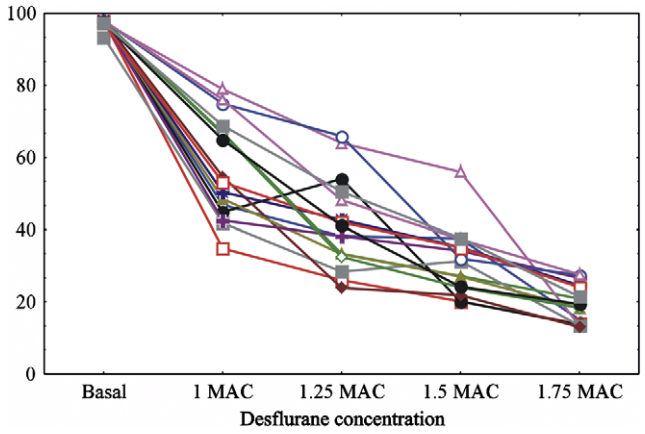

Fig. 1. Bispectral index (BIS) obtained for all 16 pigs at each concentration of desflurane. Each pig is indicated by a unique symbol. MAC, minimum alveolar concentration.

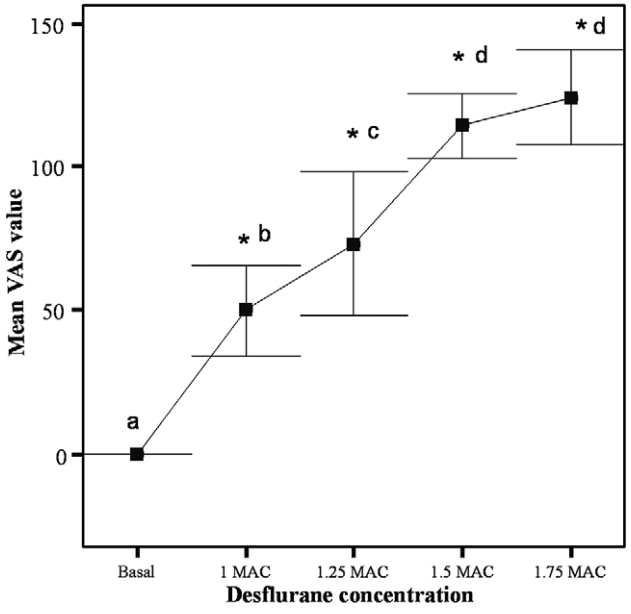

Fig. 2. Mean SDS values at different MAC concentration of desflurane in pig. *, significant changes from baseline ($P < 0.05$). Different letters mean statistically significant changes between means.

During administration of desflurane, good correlation was found between SDS scores and BIS values and between SDS scores and MED values but not between SDS scores and SEF values. MED and BIS accounted for 62.7% of SDS variability, whereas SEF did not influence SDS variability (Table 3).

Table 3
Results from multiple-regression analysis of SDS score with values of BIS, SEF, and MED

Anaesthetic agent desflurane			
Variable	Coefficient	SE	*P* value
Intercept	138.195	10.457	<0.001
BIS	−0.919	0.177	<0.001
SEF	0.459	1.039	0.662
MED	−5.574	2.539	0.031

4. Discussion

The usefulness of BIS monitoring has been evaluated in several human studies (Kearse et al., 1994; Sebel et al., 1995; Liu et al., 1996, 1997; Billard et al., 1997; Glass et al., 1997; Flaishon et al., 1997; Gajraj et al., 1999), as well as in other species anaesthesia (Haga et al., 1999; Antognini et al., 2000; Haga and Dolvik, 2002; Greene et al., 2002; Martín et al., 2004). A direct measure of anaesthetic effects on the brain that could be applied at clinically used ranges of anaesthetics and spans all agents is still lacking. Anaesthetic dosages are generally based on a number of clinical signs. It is accepted that, as the brain is the target site of action of general anaesthetics, it would be reasonable to expect a neurophysiologic measure of anaesthetic effect to exist. Such a measurement should be sufficiently sensitive to detect an inadequate plane of anaesthesia and be useful in predicting recovery from anaesthesia. It should also be independent of the anaesthetic agent used and should correlate with anaesthetic concentration at the site of action.

The SDS used in this study, was based both on objective measurements, such as heart rate and mean arterial blood pressure, and on subjective measurements, such as the degree of response to stimuli. The scale was created based on our clinical experience and on the expected characteristics of each plane of anaesthesia provided elsewhere (Thurmon et al., 1996). Our findings are similar to those of another study (Glass et al., 1997) conducted on linear correlations between isoflurane concentrations or BIS values

Table 2
Mean ± SD (range) values for heart rate, mean arterial blood pressure (MABP), breathing rate, end-tidal CO_2 ($ETCO_2$) concentration, and rectal temperature determined in pigs anaesthetized by use of various desflurane concentrations

Desflurane concentration		Heart rate (beats/min)	MABP (mmHg)	Breathing rate (breaths/min)	$ETCO_2$ (mm Hg)	Rectal temperature (°C)
%	MAC					
0	Basal	111.9 ± 8.1 (104.0–160.0)	78.8 ± 13.3 (62.0–107.0)	21.2 ± 5.1 (14.0–31.0)	34.1 ± 2.1 (30.0–37.0)	38.6 ± 0.4 (38.1–39.4)
8.3	1	112.1 ± 18.4 (85.0–150.0)	64.7 ± 10.6 (53.0–86.0)	22.4 ± 7.0 (9.0–34.0)	37.2 ± 5.2 (29.0–47.0)	38.1 ± 0.3 (38.6–37.3)
10.4	1.25	117.9 ± 27.8 (86.0–146.0)	59.1 ± 13.1 (46.0–90.0)	19.6 ± 7.1 (10.0–32.0)	37.4 ± 5.6 (28.0–49.0)	37.9 ± 0.3 (38.9–37.4)
12.4	1.5	119.7 ± 34.7 (82.0–179.0)	48.3 ± 9.0 (37.0–71.0)	13.1 ± 2.6 (10.0–20.0)	37.1 ± 5.8 (30.0–56.0)	37.8 ± 0.2 (37.5–38.5)
14.5	1.75	116.1 ± 23.7 (88.0–165.0)	45.9 ± 6.9 (33.0–60.0)	13.6 ± 2.1 (10.0–20.0)	40.2 ± 5.5 (34.0–48.0)	37.8 ± 0.3 (37.3–38.2)

and an observer's assessment of the alertness-sedation score in human. This study, however, was performed in lightly anaesthetized patients whereas in our swine protocol we assess much deeper levels of anaesthesia.

The use of SDS as a criterion-referenced standard has been considered questionable, because the scale itself is not used in a clinical setting (Martín et al., 2003). However, we have routinely used this same scale with good results in our daily practice. Moreover, the reflexes and functions used to calculate this scale represent the only way that most practitioners can use to monitor anaesthetic depth in their daily practice (Thurmon et al., 1996). A potential limitation of this study is that the variables included in the SDS represent primarily subcortical reflexes and functions, whereas BIS measures cortical activity, but, as explained above, we studied the relationship between anaesthetic depth as monitored by BIS or by SDS, because this last monitoring is normally the only one available to the clinician. The only true indicators of the consciousness level would be neurophysiological measurements of brain cortex activity, namely EEG and auditory evoked potentials.

SDS results obtained in this study in desflurane anaesthetized swine were higher than previously reported values for sevoflurane and isoflurane anaesthetized pigs (Martín et al., 2003) at 1.50 and 1.75 MAC. This suggests that, when administered at equivalent concentrations, a higher anaesthetic depth is achieved with desflurane. This could be explained by the MAC values chosen for each anaesthetic agent. Different investigators report varied MAC ranges for each agent in the different species. Moreover, individual variability to MAC has been recently reported (Barter et al., 2004; Pypendop and Ilkiw, 2005), and this may have had also an import in the SDS results. In pigs, reported sevoflurane MAC ranges between 1.97% (Steffey, 1996) and 2.66% (Manohar and Parks, 1984) and desflurane MAC is reported to be within 8.28% (Manohar and Parks, 1984) and 10.0% (Eger et al., 1988). For each species, MAC is determined by administering increasing agent concentrations while applying a supramaximum stimulus. In our studies, the highest sevoflurane MAC reported was chosen, because 1.97% was reported for newborn piglets, and the lowest desflurane MAC was used, because we considered 10.0% too high a concentration, based on our own experience, including previous studies and daily practice. Nonetheless, SDS values indicated that a higher anaesthetic depth was achieved with desflurane was higher. In our opinion, these results suggest that no differences can be seen between SDS values at low concentrations (1 or 1.25 MAC), but at higher concentrations, desflurane has a higher hypnotic capacity in pigs.

The main finding of this study was that, in pigs, the EEG-BIS correlated with anaesthetic depth as determined by SDS during desflurane-maintained anaesthesia. A significant correlation was demonstrated between BIS values and anaesthetic score and between MED values and anaesthetic score but not between SDS score and SEF values. However, this correlation was stronger between BIS value and anaesthetic score than between MED value and anaesthetic score for desflurane. Still, given that the BIS is a hypnotic index, this correlation between BIS and SDS may have been only a coincidence and further studies are probably needed to better define the components of this correlation. The poor correlation with MED and lack of correlation with SEF was consistent with results of other studies (Martín et al., 2003; Schweder et al., 1998; Liu et al., 1996). It has been reported (Dwyer et al., 1994; Drummond et al., 1991; Chen et al., 1994) that SEF is not a useful guide for determining depth of anaesthesia. Our results suggest that SEF and MED values alone cannot be used to correctly estimate anaesthetic depth or to determine clinically useful concentrations of anaesthetic agents in pigs. Although there was a mild correlation between MED value and SDS score obtained from desflurane anaesthetized pigs, analysis of the results by use of an ANOVA revealed significant differences only between values determined for baseline and 1 and 1–1.75 MAC. SEF values only changed significantly from baseline to 1 MAC without additional significant changes detected at any other concentration of the anaesthetic agent. Some researchers have reported (Werry et al., 1996; Schwilden et al., 1987) that MED monitoring provides information about depth of anaesthesia, whereas others (Katoh et al., 1998; Dwyer et al., 1994; Drummond et al., 1991; Chen et al., 1994) have claimed that MED values do not correlate with depth of anaesthesia. Additional studies are required to evaluate, the use of SEF and MED values for assessing anaesthetic depth because a correlation existed between SEF value and anaesthetic score but not between SDS score and MED value in sevoflurane and isoflurane anaesthetized pigs (Martín et al., 2003), whereas in desflurane anaesthetized swine the opposite results were found. Taking into account all the reported results, it can be stated that SEF and MED cannot be used as reliable means to guide anaesthetic management in swine, because the results obtained with these variables are related to the anaesthetic used.

In human studies, desflurane caused a dose-dependant decrease in SEF, with sudden suppression at 1.24 MAC and higher end tidal concentrations, without evidence of epileptiform activity (Rampil et al., 1991). Another study (Schwender et al., 1998) found similar dose-dependent decreases in SEF for sevoflurane, isoflurane and desflurane. This was not the case in pigs where equivalent MAC dosages of sevoflurane, isoflurane (Martín et al., 2003) and desflurane did not cause a comparable decrease in SEF.

We analyzed the relationship between end-tidal concentrations of desflurane and BIS, SEF and MED values. Values for BIS decreased significantly from basal to 1, 1–1.25, 1.25–1.5, and 1.5–1.75 MAC. No human studies could be found describing BIS changes with different desflurane concentrations when this agent is used as the sole anaesthetic. However, when a desflurane end tidal concentration of 4.2% (equaling 0.7 MAC) was used in combination with 65% nitrous oxide and fentanyl for maintenance in humans, approximate BIS values recorded were 44 ± 11 (Song et al., 1997). Despite this lack of studies evaluating

BIS measurements at varying desflurane concentrations, our results indicate that BIS values in pigs may be higher than those obtained in humans at the same anaesthetic concentrations, as has been previously reported for sevoflurane and isoflurane (Martín et al., 2003; Haga et al., 1999). BIS data reported for cats (Lamont et al., 2004) shows a tendency similar to our findings, but BIS values obtained in felines were considerably lower than those obtained in pig (Martín et al., 2003) and man. However, in dogs (Greene et al., 2002), mean BIS values were similar to previously reported swine results, both by Haga et al. (1999) and in our own experience (Martín et al., 2003, 2004). Further studies are needed to dilucidate the cause of the different degree of CNS depression produced by inhalant anaesthetic in each species.

In the study reported here, mean values of BIS consistently decreased with increasing anaesthetic concentrations; however, the range of BIS values recorded at the same MAC was large, which indicates that BIS values may not always be useful for predicting anaesthetic depth in every individual. Values of BIS vary greatly between and within individuals (Martín et al., 2003; Ibrahim et al., 2001).

A mean ± SD BIS value of 57.16 ± 13.86 was obtained here when administering desflurane at 1 MAC. No reports of BIS values for 1 MAC of desflurane in pigs or any other species could be found in the literature, but BIS values reported for 1 MAC of sevoflurane and isoflurane in pigs were 61.20 ± 10.28 and 57.67 ± 10.57, respectively (Martín et al., 2003). Other BIS values reported for administration of isoflurane at 1 MAC in pigs ranged between 60 and 87 (Haga et al., 1999). In our previous study (Martín et al., 2003), BIS values were significantly higher during administration of sevoflurane than during administration of isoflurane at the same MAC. The dynamic relationship between end-tidal anaesthetic concentrations and BIS has been studied in humans (Olofsen and Dahan, 1999). In that study, investigators used a combination of an effect compartment and an inhibitory sigmoid model of maximum drug effect (E_{max}). They concluded that, although the speed of onset and offset of anaesthetic effect did not differ between isoflurane and sevoflurane, isoflurane was approximately twice as potent as sevoflurane. Apart from this difference in potency between the two anaesthetics, sevoflurane concentrations >1.5% (up to 3%) and isoflurane concentration >0.75% (up to 1.5%) yielded BIS values that reached a plateau at approximately 40. The fact that BIS values were higher during sevoflurane administration indicates that the relationship between BIS and sedation depth may not be independent of anaesthetic agent (Ibrahim et al., 2001). In another study (Ibrahim et al., 2001), BIS values were found to be a better predictor of depth of sedation with propofol anaesthesia than with sevoflurane anaesthesia. When comparing BIS values obtained during isoflurane and sevoflurane anaesthesia (Martín et al., 2003) with those obtained with desflurane at the same MAC in the present study, it can be observed that, as previously reported for isoflurane, BIS values were higher during sevoflurane administration than during desflurane administration. Moreover, both studies were conducted under the same experimental conditions and by the same research team. Desflurane and isoflurane have a similar chemical structure (Hall and Clarke, 1991), and, as shown by Rampil et al. (1988), when administered at equivalent concentrations both agents affect the porcine EEG in the same way. It could subsequently be argued that the two anaesthetics should affect BIS in the same way, as occurred in our two studies. Both SDS and BIS results indicated that desflurane anaesthetized pigs achieved a deeper anaesthetic plane. When taken into account independently, all the parameters included in the SDS confirmed this difference in anaesthetics, thus strengthening the perception that BIS was a precise indicator of anaesthetic depth.

A high individual variability was found in BIS values, up to a 40% range of variability around the mean. An individual variability to MAC of desflurane has also been recently reported in cats (Barter et al., 2004). Both studies suggest that a certain degree of individual sensitivity to a variety of inhaled anaesthetics exists. For this reason, the main limitation of the present study is to have selected the level of anaesthesia based on a desflurane MAC value reported previously in other paper. In order to improve our results, individual MAC values for each pig could have been calculated before measuring EEG parameters.

Spontaneous ventilation was maintained in our study. Although this situation may elicit some respiratory depression, we did not detect a decrease in tidal volume, suggesting that $ETCO_2$ and end-tidal recordings of volatile agent measured by the capnograph were correct. Lockhart et al. (1991) described a decrease in tidal volume and increased breath rate, along with a decreased ventilatory response to CO_2 with increasing anaesthetic depth in desflurane anaesthetized men. In our study, however, the highest breathing rates registered occurred with the lower desflurane concentrations. $ETCO_2$ increased significantly with increasing concentrations of desflurane but without reaching clinically important hypercapnia. Intermittent positive-pressure ventilation was not used in this study, because no animal showed a degree of respiratory depression to justify its use.

Mean arterial blood pressure decreased significantly when 1 MAC was administered, and it remained significantly lower than baseline at 1.25, 1.5 and 1.75 MAC. In swine, desflurane-related hypotension appeared when the agent was administered at 1 MAC, whereas sevoflurane and isoflurane caused significant hypotension at 1.75 MAC (Martín et al., 2003). Sevoflurane- and isoflurane-induced hypotension is usually related to a decrease in systemic vascular resistance (Steffey, 2001). Weiskopf (1995) reported that desflurane has two different cardiovascular effects. Firstly, it decreases systolic and diastolic function at a left ventricular level, causing a dose-dependant decrease in peripheral vascular resistance and mean arterial blood pressure. Low stable concentrations do not affect heart rate, but higher concentrations increase it. Secondly,

desflurane increases sympathetic activity, heart rate and mean arterial blood pressure when exhaled agent concentrations increase suddenly over 1 MAC if no premedication has been administered. In the present study, the first cardiovascular effect of desflurane observed was similar to that described by Weiskopf (1995) in man. However, the circulatory hyperdynamic response secondary to a fast increase in end tidal concentration was not evidenced, despite an increasing agent concentration in some instances. In this same research field, previously published data state that a sudden increase in inhaled desflurane in swine does not cause a hyperdynamic circulatory response (Karzai et al., 1997). Desflurane anaesthesia in dogs causes an increase in heart rate and a decrease in mean arterial blood pressure which is not related either to desflurane end-tidal concentration or to the ventilation regimen maintained (Clarke et al., 1996).

Koitabashi (2004) presented the relationship between BIS and suppression rate (SR) at deeper anaesthesia and identified how the SR is incorporated into BIS. According to his study, BIS is only affected by SR when the later exceeds 40%. In the present study, no burst suppression over 14% was observed, so we considered that it did not have any import on the calculated parameters.

On the other hand, electromyographic activity increases BIS values (Riess et al., 2002). However, the BIS monitor used for the present study did not register EMG activity, a feature available in newer versions. Thus, electromyographic activity was not recorded, but a low amount of muscular activity was consistently seen in all pigs, so it is our opinion that our results were not affected by it. To validate this conclusion, however, electromyographic activity should have been recorded.

In the study reported here, values for BIS were the most accurate EEG indicators for predicting the depth of anaesthesia in pigs during desflurane anaesthesia. It was difficult to assess anaesthetic depth by use of only SEF and MED values. Variability among individuals must be taken into account when monitoring anaesthetic depth by BIS values in clinical settings. A deeper plane of anaesthesia was achieved with desflurane than with sevoflurane or isoflurane when used at equipotent concentrations in swine, as demonstrated both by SDS scores and by EEG BIS values.

Appendix. Variables used to determine depth of anaesthesia in pigs

Variable	Plane of anaesthesia				
	1	2	3	4	5
Conscious	Yes	No	No	No	No
Breathing rate	Normal	Irregular and increased	Moderately decreased	Moderately decreased	Slow and irregular
Type of breathing	Thoracic and abdominal	Thoracic and abdominal	Thoracic and abdominal	Thoracic but predominantly abdominal	Abdominal
Pupil	Normal	Dilated	Normal	Moderately dilated	Dilated
Eyeball position	Normal	Variable	Fixed ventromedially	Normal	Normal
Heart rate	Normal	Increased	Moderately decreased	Moderately decreased	Decreased
Arterial blood pressure	Normal	Increased	Normal	Decreased	Decreased
Palpebral reflex	Weak response	Strong response	Weak response	Not detected	Not detected
Corneal reflex	Weak response	Strong response	Weak response or not detected	Weak response or not detected	Not detected
Pedal reflex	Strong response	Strong response	Weak response	Not detected	Not detected
Muscular tone	Yes	Yes	Decreased	Decreased	Not detected
Nociceptive response	Strong response	Strong response	Weak response	Not detected	Not detected

The original Guedel classification included four stages: I = analgesia; II = delirium; III = surgical anaesthesia; IV = coma with stage III (surgical) being separated in four planes (1 = light; 2–3 = medium; 4 = deep).In this modification, five stages are included, with plane 1 corresponding to Guedel's stage II (delirium), plane 2 = III,1 (light anaesthesia), plane 3 = III,2,3 (medium anesthesia), plane 4 = III,4 (deep anaesthesia) and plane 5 = IV (coma).

Acknowledgements

We acknowledge Miss Patricia Embree from Aspect Medical System for her expert assistance.

This work has been funded by the Ministerio de Sanidad y Consumo. Fondo de Investigación Sanitaria. Instituto de Salud Carlos III (Ref 01/304).

References

Antognini, J.F., Wang, X.W., Carstens, E., 2000. Isoflurane anaesthetic depth in goats monitored using the bispectral index of the electroencephalogram. Vet. Res. Commun. 24, 361–370.

Barter, L.S., Ilkiw, J.E., Steffey, E.P., Pypendop, B.H., Imai, A., 2004. Animal dependence of inhaled anaesthetic requirements in cats. Br. J. Anaesth. 92 (2), 275–277.

Billard, V., Gambus, P.L., Chamoun, N., et al., 1997. A comparison of spectral edge, delta power, and bispectral index as EEG measures of alfentanil, propofol, and midazolam drug effect. Clin. Pharmacol. Ther. 61, 45–58.

Chen, C.L., Liu, C.C., Chen, T.L., et al., 1994. Recovery from propofol anaesthesia: a quantitative electroencephalographic analysis. Acta Anaesth. Sin. 32, 77–82.

Clarke, K.W., Alibhai, H.I., Lee, Y.H., Hammond, R.A., 1996. Cardiopulmonary effects of desflurane in the dog during spontaneous and artificial ventilation. Res. Vet. Sci. 61, 82–86.

Drummond, J.C., Brann, C.A., Perkins, D.E., et al., 1991. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anaesthesia. Acta Anaesth. Scand. 35, 693–699.

Dwyer, R.C., Rampil, I.J., Eger II, E., et al., 1994. The electroencephalogram does not predict depth of isoflurane anaesthesia. Anesthesiology 81, 403–409.

Eger Jr., E.I., Johnson, B.H., Weiskopf, B., Holmes, M.A., Yasuda, N., Targ, A., Rampil, I.J., 1988. Minimum alveolar concentration of I-653 and isoflurane in pigs: Definition of a supramaximal stimulus. Anesth. Analg. 67, 1174–1177.

Flaishon, R., Windsor, A., Sigl, J., et al., 1997. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. Anesthesiology 86, 613–619.

Gajraj, R.J., Doi, M., Mantzaridis, H., et al., 1999. Comparison of bispectral EEG analysis and auditory evoked potentials for monitoring depth of anaesthesia during propofol anaesthesia. Br J. Anaesth. 82, 672–678.

Gan, T.J., Glass, P.S., Windsor, A., et al., 1997. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anaesthesia. Anesthesiology 87, 808–815.

Glass, P.S., Bloom, M., Kearse, L., et al., 1997. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology 86, 836–847.

Greene, S.A., Benson, G.J., Tranquilli, W.J., et al., 2002. Relationship of canine bispectral index to multiples of sevoflurane minimal alveolar concentration, using patch or subdermal electrodes. Comp. Med. 52, 424–428.

Guedel, AE., 1936. Anesthesia: a teaching outline. Stage of anesthesia. Anesth. Analg. 15, 1–4.

Haga, H.A., 2001. Electroencephalographic and cardiovascular indicators of nociception during isoflurane anaesthesia in pigs. Vet. Anaesth. Analg. 28, 126–131.

Haga, H.A., Dolvik, N.I., 2002. Evaluation of the bispectral index as an indicator of degree of central nervous system depression in isoflurane-anesthetized horses. Am. J. Vet. Res. 63, 438–442.

Haga, H.A., Tevik, A., Moerch, H., 1999. Bispectral index as an indicator of anaesthetic depth during isoflurane anaesthesia in the pig. J. Vet. Anaesth. 26, 3–7.

Hall, L.W., Clarke, K.W., 1991. General pharmacology of the inhalation anaesthetics. In: Saunders, W.B. (Ed.), Veterinary Anaesthesia, ninth ed. Bailliere Tindall, London, England, pp. 98–112.

Ibrahim, A.E., Taraday, J.K., Kharasch, E.D., 2001. Bispectral index monitoring during sedation with sevoflurane, midazolam and propofol. Anesthesiology 95, 1151–1159.

Karzai, W., Haberstroh, J., Muller, W., Pruebe, H.J., 1997. Rapid increase in inspired desflurane concentration does not elicit a hyperdynamic circulatory response in the pig. Lab. Anim. 31, 279–282.

Katoh, T., Suzuki, A., Ikeda, K., 1998. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anaesthesia induced by sevoflurane. Anesthesiology 88, 642–650.

Kearse, L.A., Manberg, P., Chamoun, N., et al., 1994. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anaesthesia. Anesthesiology 81, 1365–1370.

Koitabashi, T., 2004. Integration of suppression ratio in the bispectral index. J. Anesth. 18, 141–143.

Lamont, L.A., Greene, S.A., Grimm, K.A., Tranquilli, W.J., 2004. Relationship of bispectral index to minimum alveolar concentration multiples of sevoflurane in cats. Am. J. Vet. Res. 65 (1), 93–98.

Liu, J., Singh, H., White, P.F., 1996. Electroencephalographic bispectral analysis predicts the depth of midazolam-induced sedation. Anesthesiology 84, 64–69.

Liu, J., Singh, H., White, P.F., 1997. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol induced sedation. Anesth. Analg. 84, 185–189.

Lockhart, S.H., Rampil, I.J., Yasuda, N., Eger II, E.I., Weiskopf, R.B., 1991. Depression of ventilation by desflurane in humans. Anesthesiology 74 (3), 484–488.

Manohar, M., Parks, C.M., 1984. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anaesthesia without and with 50% nitrous oxide. J. Pharmacol. Ther. 234, 640–648.

Martín, M.F., Lima, J.R., Luis, L., Crisóstomo, V., Ezquerra, L.J., Carrasco, M.S., Usón-Gargallo, J., 2003. Bispectral index, Spectral Edge Frequency 95% and Median Frequency recorded at varying isoflurane and sevoflurane concentrations in pigs. Am. J. Vet. Res. 64 (7), 866–873.

Martín, M.F., Carrasco, M.S., Lima, J.R., Ezquerra, L.J., Crisóstomo, V., Usón-Gargallo, J., 2004. Assessment of the relationship of bispectral index values, hemodynamic changes, and recovery times associated with sevoflurane or propofol anaesthesia in pigs. Am. J. Vet. Res. 65 (4), 409–416.

Olofsen, E., Dahan, A., 1999. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. Anesthesiology 90, 1345–1353.

Pypendop, B.H., Ilkiw, J.E., 2005. The effects of intravenous lidocaine administration on the minimum alveolar concentration of isoflurane in cats. Anesth. Analg. 100 (1), 97–101.

Rampil, I.J., Weiskopf, R.B., Brown, J.G., Eger II, E.I., Johnson, B.H., Holmes, M.A., Donegan, J.H., 1988. I-653 and isoflurane produce similar dose-related changes in the electroencephalogram of pigs. Anesthesiology 69, 289–302.

Rampil, I.J., Lockhart, S.H., Eger II, E.I., Yasuda, N., Weiskpof, R.B., Calahan, M.K., 1991. The electroencephalographic effects of desflurane in humans. Anesthesiology 74, 434–439.

Riess, M.L., Graefe, U.A., Goeters, C., et al., 2002. Sedation assessment in critically ill patients with bispetral index. Eur. J. Anaesthesiol. 19, 18–22.

Schweder, D., Daunderer, M., Klasing, S., et al., 1998. Power spectral analysis of the electroencephalogram during increasing end-expiratory concentrations of isoflurane, desflurane and sevoflurane. Anaesthesia 53, 335–342.

Schwender, D., Daunderer, M., Klasing, S., Finsterer, U., Peter, K., 1998. Power spectral analysis of the electroencephalogram during increasing

end-expiratory concentrations of isoflurane, desflurane and sevoflurane. Anaesthesia 53, 335–342.

Schwilden, H., Schuttler, J., Stoeckel, H., 1987. Closed-loop feedback control of methohexital anaesthesia by quantitative EEG analysis in humans. Anesthesiology 67, 341–347.

Sebel, P.S., Bowles, S.M., Saini, V., et al., 1995. EEG bispectrum predicts movement during thiopental/isoflurane anaesthesia. J. Clin. Monit. 11, 83–91.

Sigl, J.C., Chamoun, N.G., 1994. An introduction to bispectral analysis for the electroencephalogram. J. Clin. Monit. 10, 392–404.

Song, D., Joshi, G.P., White, P.F., 1997. Titration of volatile anaesthetics using bispectral index facilitates recovery after ambulatory anaesthesia. Anesthesiology 87 (4), 842–848.

Steffey, E.P., 1996. Inhalation anesthetics. In: Thurmon, J.C., Tranquilli, W.J., Benson, G.J. (Eds.), Veterinary Anesthesia, third ed. Williams & Wilkins, Baltimore, p. 314.

Steffey, E.P., 2001. Anestésicos por inhalación. In: Adams, H.R. (Ed.), Veterinary Pharmacology and Therapeutics, Eigth ed. Iowa State University Press, Ames, Iowa, USA, pp. 195–224.

Thurmon, J.C., Tranquilli, W.J., Benson, G.J., 1996. Consideration for general anaesthesia. In: Thurmon, J.C., Tranquilli, W.J., Benson, G.J. (Eds.), Lumb and Jones Veterinary Anaesthesia, third, ed. Williams and Wilkins, Baltimore, pp. 11–16.

Vernon, J., Lang, E., Sebel, P., et al., 1995. Prediction of movement using BIS electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anaesthesia. Anesth. Analg. 80, 780–785.

Weiskopf, R.B., 1995. Cardiovascular effects of desflurane in experimental animals and volunteers. Anaesthesia 50 (Suppl.), 14–17.

Werry, C., Neulinger, A., Eckert, O., et al., 1996. Age-related correlation between EEG parameters and depth of anaesthesia under propofol. Effect of fentanyl. Anaesthesist 45, 722–730.