Relationship of bispectral index values, haemodynamic changes and recovery times during sevoflurane or propofol anaesthesia in rabbits

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Summary

The aim of this study was to determine and compare the degree of hypnosis achieved during propofol or sevoflurane anaesthesia in rabbits using bispectral index (BIS), and to evaluate its usefulness as a predictor of both haemodynamic changes during anaesthesia and recovery times. Twenty adult male New Zealand White rabbits, average weight 4.4 ± 0.4 kg, were used for this study. Animals were randomly allocated to one of two groups with 10 rabbits/group. An electroencephalographic recording was obtained from each conscious rabbit prior to drug administration. All animals received buprenorphine as a preanaesthetic medication (0.05 mg/kg, intravenous [i.v.]). Anaesthesia was induced with propofol (8 mg/kg, i.v.) in all animals; 10 rabbits were maintained with sevoflurane via inhalation (1 minimum alveolar concentration – end-tidal sevoflurane concentration of 3.7% – at a fresh gas flow rate of 3 L/min; group I), and 10 were maintained with i.v. propofol (0.6 mg/kg/min; group II). The rabbits were orotracheally intubated and spontaneous ventilation was maintained throughout the study (100% oxygen). After abdominal surgery through a ventral midline laparotomy, rabbits were allowed to recover from anaesthesia. Cardiovascular variables and BIS values were recorded at intervals throughout the procedure, as was the duration of recovery from anaesthesia.

In both groups, mean BIS values were significantly decreased immediately after induction, compared with baseline values obtained during consciousness. Anaesthetic depth (evaluated by clinical observation) was similar in both groups; however, group II rabbits had significantly higher ($P < 0.001$) BIS values from 30 s before incision until anaesthesia was discontinued. There was no significant difference in BIS recorded 1 and 5 min after incision as compared with values obtained 30 s before incision in either group.

During sevoflurane or propofol administration, correlations were found between BIS values and mean arterial blood pressure (MABP), and between BIS values and heart rate (HR).

Mean BIS values at discontinuation of administration of the anaesthetic agent were greater in group II (69.1 ± 6.0) than in group I (49.3 ± 2.2). However, recovery from anaesthesia was significantly longer in group II (38.4 ± 7.2 min) than in group I (11.5 ± 2.5 min).

In conclusion, BIS can be used to differentiate between conscious and unconscious states during anaesthesia in rabbits. BIS values derived from an electroencephalogram at the end of anaesthesia were not useful for predicting the speed of anaesthetic recovery in sevoflurane or propofol-anaesthetized rabbits undergoing abdominal surgery. Despite the correlation found

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between BIS and haemodynamic parameters, its usefulness as a predictor of clinically important changes in arterial blood pressure and HR in anaesthetized rabbits was limited.

Keywords Bispectral index; rabbit; sevoflurane; propofol

A variable derived from the electroencephalogram (EEG), the bispectral index (BIS), has been reported to be useful for measuring the hypnotic component of the anaesthetic state (Kearse *et al.* 1994, Sebel *et al.* 1995, Vernon *et al.* 1995, Gan *et al.* 1997, Liu *et al.* 1997). It is a dimensionless number from 0 to 100, and decreasing values indicate more sedation and hypnosis. The EEG, as recorded from the skin of the head, gives a measurement of electrical activity in the brain cortex, thus changing with variations in anaesthetic depth, as has been demonstrated in several species (Prynn & Redding 1968, Rose *et al.* 1972, Otto & Short 1991, Martín-Cancho *et al.* 2003). BIS is calculated from an algorithm empirically derived from EEG studies in anaesthetized humans. This algorithm takes into account power spectral parameters, burst suppression and the degree of phase coupling assessed through bispectral analysis, generating an index ranging from 0 to 100, that is known as BIS (Sigl & Chamoun 1994).

Rabbits are used extensively in biomedical research and may undergo major surgery. It has been suggested that minimum alveolar concentration (MAC) cannot accurately indicate anaesthetic depth due to individual responses to the anaesthetic agents (Haskins 1996). For this reason, an objective and reliable system to measure anaesthetic depth would be very valuable in rabbits. During propofol anaesthesia, an excessive depth of sedation may be associated with clinically significant cardiovascular and respiratory depression, whereas less intense levels of sedation may be associated with intraoperative recall (Aeschbacher & Webb 1993a,b, Smith *et al.* 1994). Similarly, sevoflurane depresses respiratory system function and causes dose-dependent myocardial depression and a decrease in sympathoadrenal activity (Park *et al.* 1996, Steffey 1996, Flecknell *et al.* 1999).

We are not aware of any study reporting the use of BIS in rabbits, despite reports that state that rabbits can be used to study the EEG effects of anaesthetics (Hartikainen *et al.* 1995). Furthermore, Vachon *et al.* (1999) suggested that EEG recordings may be used to evaluate the depth of anaesthesia when using injectable drug combinations in rabbits. Previously conducted studies using swine have shown that BIS values change between consciousness and light anaesthesia, and can also be used to detect excessive depth of anaesthesia (Haga *et al.* 1999). On the other hand, BIS does not seem to change according to anaesthetic depth at clinically useful isoflurane concentrations (Haga *et al.* 1999), nor does it appear to indicate nociception in isoflurane-anaesthetized swine (Haga 2001). However, in our own experience (Martín-Cancho *et al.* 2003), BIS was useful for predicting changes in anaesthetic depth at clinically used dosages of inhalant anaesthetics (sevoflurane and isoflurane), although some variability was seen among individuals. Johnson and Taylor (1998) demonstrated that the isoflurane-mediated EEG depression in horses was of sudden onset and maximal at all concentrations of agent studied. Haga and Dolvik (2002) reported that BIS cannot be used to measure the central nervous system depression in isoflurane-anaesthetized horses. These authors measured BIS in sedated and anaesthetized horses, finding no significant differences between groups.

The aim of this study was to evaluate the BIS in rabbits during sevoflurane–buprenorphine and during propofol–buprenorphine anaesthesia for abdominal surgery to compare the degree of hypnosis achieved using each anaesthetic regimen in this species. The possible role of BIS as a predictor of haemodynamic changes during anaesthesia, namely its usefulness in predicting and preventing heart rate (HR) and

blood pressure increases during triggering events, was also studied. BIS values at the end of anaesthesia were evaluated to determine if this monitor can be used to predict the speed of anaesthetic recovery after surgery.

Material and methods

Animals

The experimental protocol was approved by the Centre Ethical Committee for Animal Research. Twenty healthy male New Zealand White rabbits, average weight 4.4 ± 0.4 kg, were anaesthetized for this study. All rabbits underwent a complete physical examination, serum biochemical analyses, and thoracic radiography prior to inclusion in the study to assure their good health.

During the study, animals were housed indoors in stainless steel cages with free access to food and water, except during the 2 h prior to anaesthesia, when they were allowed water only.

Animals were randomly assigned to one of two experimental groups with 10 rabbits per group. Group I received inhalant anaesthesia with sevoflurane (Sevorane, Abbott Laboratories, Madrid, Spain) and group II was anaesthetized with intravenous (i.v.) propofol (Recofol, Schering España SA, Madrid, Spain). Buprenorphine (Buprex, Schering Plough, Madrid, Spain) was administered as an analgesic drug in all animals.

During this study, abdominal surgery was performed in all animals as part of an unrelated project. Access to the abdominal aorta was achieved through a midline laparotomy, and the infrarenal segment of this vessel was dissected, from the level of the renal arteries to the origin of the iliac arteries. Continuous infusion of physiological saline at a rate of 5 mL/kg/h was maintained during surgery.

Electroencephalographic monitoring

Before induction of anaesthesia, all animals' heads were shaved and defatted by use of diethyl ether. Gel-coated disposable silver–silver chloride electrodes (Zipprep, Aspect Medical Systems Inc, Natick, MA, USA) were applied to record the EEG. Two electrodes (one for each eye) were placed 1 cm caudal to the lateral eye cantus; a central or reference electrode was placed on the midline on the frontal bone 3 cm away from each previously applied electrode, and a ground electrode was placed 2 cm to the left or right edge of the central electrode, following a configuration previously reported in people (Gan *et al.* 1997). Impedance was checked and maintained below 10,000 Ohms at 128 Hz before each recording. The electrodes were connected to an EEG monitor (A-1050TM, version 3.05.05, Aspect Medical Systems Inc, Natick, MA, USA), setting the low-frequency filter to 2 Hz and the high-frequency filter to 70 Hz. The unsedated animals were placed in a rabbit-restraining cage and BIS values were recorded during a 5 min period of conscious state.

Rabbits were then anaesthetized, following the protocol described below for each group. The monitor used automatically detected only high-quality signals. Artefact-processing algorithms in the monitor detected and corrected (or rejected) patient-induced artefacts 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. BIS was recorded from a conscious state (awake) throughout induction, maintenance and recovery from anaesthesia. BIS values were registered during 60 s for each study time point (Figures 1 and 2).

Anaesthesia

Rabbits were anaesthetized in a randomized order. After registering baseline BIS values in the conscious animal as described above, the fur on the outside of both pinnae was clipped and the skin cleaned with alcohol, while the animals were still kept in the rabbit-restraining cage. A 22 G catheter was placed in the marginal ear vein and another 22 G catheter was inserted percutaneously into the central ear artery. Both auricular catheter

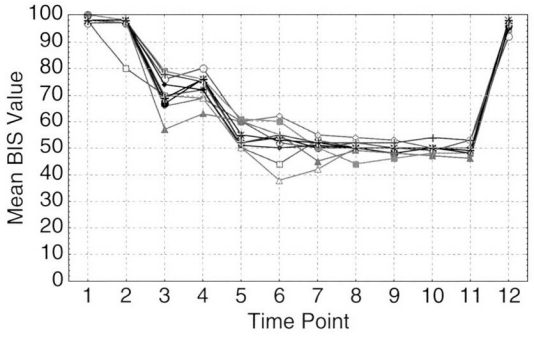

Figure 1 Bispectral index (BIS) obtained for each rabbit at the different time points during sevoflurane anaesthesia. Each rabbit is indicated by a unique symbol

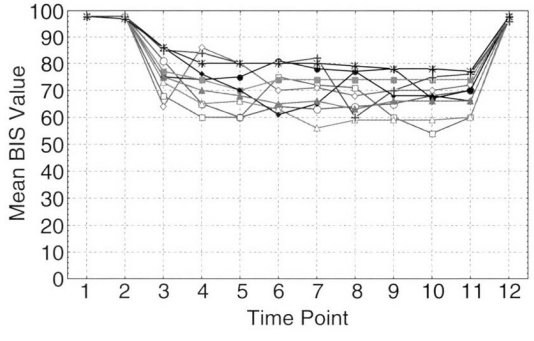

Figure 2 Bispectral index (BIS) obtained for each rabbit at all time points during propofol anaesthesia. Each rabbit is indicated by a unique symbol

systems were flushed with heparin saline and fixed to the skin. All the animals were premedicated with i.v. administration of buprenorphine (0.05 mg/kg) (Flecknell 2002). After premedication, rabbits were oxygenated with 100% oxygen via a facial mask at 5 L/min for 5 min.

Anaesthesia was induced with propofol (8 mg/kg) administered i.v. over 60 s in both groups. This dose was chosen because it had been previously used in rabbits with good results (Aeschbacher & Webb 1993a). Following blind orotracheal intubation with a cuffed endotracheal tube (Sims Portex Inc, Keene, NH, USA) 3 mm in internal diameter, two anaesthetic protocols were employed for anaesthetic maintenance. Group I: Sevoflurane – The agent's end-tidal concentration was adjusted to 1 MAC (3.7%) (Scheller *et al.* 1988a) sevoflurane at a fresh gas flow rate of 3 L/min in 100% oxygen for maintenance. Group II: Propofol – Anaesthesia was maintained with an i.v. infusion of propofol at a rate of 0.6 mg/kg/min (Blake *et al.* 1988) and oxygen (3 L/min). Spontaneous ventilation was maintained in both groups.

The rabbits were placed in dorsal recumbency. A heating system in the operating table was used to assure that body temperature ranged from 37–38 °C.

At the end of surgery, the vaporizer was switched off or propofol infusion was discontinued, and fresh gas flow rate was increased to 5 L/min of 100% oxygen. Once the rabbits regained swallowing reflexes, extubation was performed. Animals were considered recovered from anaesthesia when they exhibited an alert stance and had regained ambulation.

Further measurements

Anaesthetic 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 positioning the probe (Clip Tip sensor, Oximeter Sensor, Datex-Ohmeda, Louisville, KY, USA) on the tongue or on the previously shaved tail, rectal temperature (digital thermometer), tidal volume, end-tidal sevoflurane concentration, 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 face mask in conscious animals and at the oral end of the endotracheal tube in anaesthetized rabbits. Arterial blood pressure and HR were also measured using a blood pressure module (Hewlett Packard Press M 1006B, Hewlett Packard, Geneva, Switzerland) connected to a haemodynamic monitoring system (Hewlett Packard model 86S, Hewlett Packard, Geneva, Switzerland). Cardiovascular recordings were obtained by connecting the arterial catheter to the monitoring system via a transducer

(Ohmeda transducer DT-XX, Ohmeda, Madrid, Spain). Although all variables were continuously monitored during the study, cardiovascular values were recorded every 5 min.

An anaesthetist, blinded to the EEG signal, assessed the animal for the type of reflexes present, and their strength. The following reflexes were evaluated: eyeball position and movement, photomotor reflexes and pupillary size, lacrimation, palpebral and corneal reflexes, laryngeal reflex, muscle tone and ear pinch and digital (pedal) reflexes. This evaluation was always performed by the same investigator. The information obtained, in conjunction with the physiological variables being monitored (HR and arterial blood pressure), was used to create a subjective judgement of the depth of anaesthesia. Anaesthetic recovery time was determined by recording the following times: extubation, first movement, sternal recumbency and standing.

Data processing

All the data registered, including BIS values, were computerized and means and standard deviations were calculated for the following times:

Time 1: baseline (awake).
Time 2: immediately before induction (post-premedication).
Time 3: immediately after induction.
Time 4: 30 s after intubation.
Time 5: 30 s prior to incision.
Time 6: 1 min after incision.
Time 7: 5 min after incision.
Time 8: 15 min after incision.
Time 9: 30 min after incision.
Time 10: 60 min after incision.
Time 11: end of surgery (discontinuation of anaesthesia).
Time 12: extubation.

Statistics

Results are given as means ± standard deviations. A Kolmogorov–Smirnov test (Sokal & Rohlf 1995) was used to assure that data were normally distributed, and a Bonferroni procedure for multiple comparisons was conducted to minimize the possibility of finding significant results by chance. Analysis of variance (ANOVA) for repeated measures was used to study changes with time, followed by a Tukey's test to examine the deviation from control values in each group. Intergroup differences were analysed by two-way ANOVA. Stepwise multiple-regression analysis was performed to evaluate the relationship between BIS as the dependent variable and mean arterial blood pressure (MABP) and HR. For all analyses, values of $P<0.05$ were considered significant. Statistical analyses were performed with the SPSS 10.0 statistical package for Windows (SPSS 10.0 statistical package for Windows, SPSS Inc, Chicago, IL, USA).

Results

No significant differences were shown in age (group I: 154 ± 12 days and group II: 150 ± 8 days), weight (group I: 4.5 ± 0.4 and group II: 4.3 ± 0.4) or baseline values in the two treatment groups. Anaesthetic duration was not significantly different between groups, with a mean length of anaesthesia of 82.5 ± 4.8 min in group I, and 84.6 ± 4.0 min in group II. The interval from baseline to incision was 17.6 ± 3.1 min in group I and 19.8 ± 3.2 min in group II. During anaesthetic maintenance, depth of anaesthesia as determined by clinical observation was similar in all rabbits (negative reaction to ear pinch, palpebral and limb withdrawal reflexes, and positive corneal reflex). No animals showed nystagmus or spontaneous eyelid reflex.

Anaesthetic induction was smooth in all cases, without any excitatory movements. No excessive salivation was observed during this phase. All animals were intubated blindly without difficulty after propofol administration, and no episodes of apnoea secondary to anaesthetic induction were observed. The time needed from induction to achieve a correct anaesthetic plane that allowed for animal intubation was 2.6 ± 0.7 min.

Recovery from anaesthesia was similarly uneventful. The first signs of anaesthetic recovery were limb movements and head lifting. No signs of excitement or other complications were observed during this period. All rabbits appeared friendly, curious and interested in their surroundings.

SpO_2 throughout the study period was >97% in all rabbits; body temperature did not decrease at any point, as compared with baseline values. No significant blood loss was caused by the surgical procedure in any of the rabbits, and the surgical technique and stimulus were the same in both groups. Both anaesthetic regimens provided adequate anaesthesia during long abdominal surgical procedures, as judged by the stability in blood pressure and HR measurements and BIS values. Anaesthetic depth at the end of surgery and discontinuation of anaesthesia was similar in all rabbits.

Group I – Compared with baseline, MABP decreased significantly ($P<0.001$) from 5 min after incision onwards. HR increased significantly ($P<0.001$) after induction. This increased HR was maintained during endotracheal intubation and incision, and from 5 min after incision onwards it reverted to values statistically similar to baseline. Although MABP decreased from this time point (5 min after incision) to extubation, no significant changes in HR were noted during that interval (Table 1).

During the period of anaesthesia, mean BIS values decreased significantly ($P<0.001$) (Table 1). Compared with baseline, a significant decrease in mean BIS was detected immediately after induction of anaesthesia. Mean BIS at 1, 5, 15, 30 and 60 min after incision did not differ significantly from the value recorded 30 s prior to incision (Table 1).

Although ventilatory depression was observed following propofol administration, none of the rabbits developed apnoea. Respiratory rate decreased significantly ($P<0.001$) after propofol administration, but it did not vary during anaesthetic maintenance with sevoflurane (1 MAC). $ETCO_2$ did not change significantly during anaesthetic induction, nor during the rest of the studied intervals. SpO_2 values were consistently >95% in all animals (Table 2).

After the vaporizer supplying sevoflurane was turned off, the mean recovery time was 11.5 ± 2.5 min (Table 3).

Group II – MABP values measured 30 s prior to incision in group II rabbits showed a significant ($P<0.01$) decrease from baseline. This decreasing trend in MABP lasted until the end of surgery. A significant increase in HR was seen after induction. This increased HR persisted for the whole anaesthetic period (Table 1).

A significant ($P<0.001$) decrease in BIS was detected immediately after induction of anaesthesia. There was no significant change in BIS measured 30 s after intubation and 1 min after incision as compared with immediately after induction and 30 s before incision. Mean BIS values decreased further at subsequent data collection points, reaching 67.9 ± 7.2 at 60 min after incision. On discontinuation of anaesthesia at the end of surgery, the mean BIS in this group was 69.1 ± 6.0.

No episodes of apnoea were observed following propofol administration, despite all animals developing ventilatory depression at this time. A significant decrease in respiratory rate ($P<0.001$) was seen after propofol injection. No significant change was observed in $ETCO_2$ thorough the period of study. SpO_2 remained >98% in all animals (Table 2).

After propofol infusion was discontinued, the mean recovery time was 38.4 ± 7.2 min (Table 3).

Comparison between groups – Mean BIS values recorded in both groups were significantly decreased immediately after induction, compared with baseline values obtained during consciousness. No increase in BIS was seen 30 s after endotracheal intubation, compared with post-induction values. Anaesthetic depth (as evaluated by clinical observation) was similar in both groups. However, BIS values recorded from 30 s prior to incision to discontinuation of anaesthesia were significantly ($P<0.001$) higher in group II (Table 1). HR was also significantly ($P<0.001$) higher in group II. However, MABP values from 30 s before

Table 1 Mean ± SD and upper and lower confidence intervals of bispectral index (BIS), and mean ± SD values of heart rate and invasive mean arterial blood pressure (MABP), obtained from 10 rabbits in which anaesthesia was maintained with sevoflurane (group I) and 10 rabbits in which anaesthesia was maintained with propofol (group II) for the purpose of undergoing abdominal surgery

Times	BIS		HR (bpm)		MABP (mmHg)	
	Group I	Group II	Group I	Group II	Group I	Group II
1 (baseline)	98.5 ± 1.1 (97.0–100.0)	98.0 ± 0.1 (98.0–98.0)	221.0 ± 1.9	219.3 ± 1.9	102.3 ± 7.9	101.0 ± 7.5
2 (immediately before induction)	96.0 ± 5.6 (80.0–98.0)	97.9 ± 0.3 (97.0–98.0)	220.1 ± 3.9	216.2 ± 3.7	99.8 ± 8.3	100.1 ± 7.7
3 (immediately after induction)	70.6 ± 6.6* (57.0–79.0)	77.0 ± 7.6* (64.0–86.0)	250.3 ± 8.9*	257.8 ± 9.6*	100.7 ± 11.1	90.8 ± 5.9†
4 (30 s after intubation)	72.8 ± 4.9* (63.0–80.0)	73.4 ± 8.5* (60.0–86.0)	253.5 ± 6.5*	244.1 ± 14.2*	97.3 ± 7.0	93.0 ± 6.5
5 (30 s prior to incision)	55.4 ± 4.8* (50.0–61.0)	70.9 ± 7.7*† (60.0–80.0)	243.0 ± 11.6*	240.0 ± 12.9*	89.6 ± 5.1	87.4 ± 6.1*
6 (1 min after incision)	52.3 ± 7.1* (38.0–62.0)	71.3 ± 7.7*† (61.0–81.0)	238.6 ± 21.9*	241.2 ± 13.2*	91.8 ± 5.9	84.7 ± 7.9*‡
7 (5 min after incision)	50.0 ± 3.8* (42.0–55.0)	70.7 ± 8.2*† (56.0–82.0)	233.4 ± 12.3	238.5 ± 13.6*	89.9 ± 7.4*	77.9 ± 5.8*‡
8 (15 min after incision)	50.1 ± 2.6* (44.0–54.0)	69.2 ± 7.4*† (59.0–79.0)	232.5 ± 12.6	239.7 ± 14.3*	87.2 ± 6.5*	74.6 ± 5.6*‡
9 (30 min after incision)	49.5 ± 2.1* (46.0–53.0)	68.8 ± 6.6*† (59.0–78.0)	227.5 ± 16.3	239.4 ± 16.1*†	84.2 ± 8.2*	73.2 ± 6.3*‡
10 (60 min after incision)	49.8 ± 1.8* (47.0–54.0)	67.9 ± 7.2*† (54.0–78.0)	228.2 ± 12.8	239.5 ± 14.4*†	81.7 ± 8.8*	71.2 ± 6.2*‡
11 (at the end of surgery and anaesthetic off)	49.3 ± 2.2* (46.0–53.0)	69.1 ± 6.0*† (60.0–77.0)	228.6 ± 11.8	236.6 ± 15.7	79.6 ± 7.6*	68.4 ± 3.2*‡
12 (extubation)	95.8 ± 1.7 (92.0–98.0)	97.7 ± 0.7 (96.0–98.0)	225.7 ± 5.2	238.2 ± 13.1†	88.9 ± 9.4*	85.9 ± 11.3*

Data are expressed as mean ± standard deviation (SD)
*Significant changes from baseline in each group ($P<0.05$)
†Group II significantly higher than group I
‡Group II significantly lower than group I

Table 2 Mean ± SD values of respiratory rate (RR), oxygen saturation (SpO_2) and end-tidal CO_2 ($ETCO_2$) concentration, obtained from 10 rabbits in which anaesthesia was maintained with sevoflurane (group I) and 10 rabbits in which anaesthesia was maintained with propofol (group II) for the purpose of undergoing abdominal surgery

Times	RR (bpm)		SpO_2		$EtCO_2$ (mmHg)	
	Group I	Group II	Group I	Group II	Group I	Group II
1 (baseline)	47.5±1.6	47.7±1.6	98.8±0.8	99.3±0.8	37.2±2.0	37.0±1.8
2 (immediately before induction)	43.9±3.6	46.2±4.5	98.9±0.9	98.9±0.7	36.2±1.4	36.4±1.9
3 (immediately after induction)	33.9±5.2*	37.5±6.3*	98.4±1.2	99.0±0.8	38.1±4.7	36.2±1.8‡
4 (30 s after intubation)	33.8±7.0*	40.7±6.5†	97.9±1.4	98.8±0.9	39.2±3.3	37.2±1.4‡
5 (30 s prior to incision)	34.6±3.9*	39.8±4.4*	97.4±1.1	98.5±0.7	38.9±1.8	37.5±1.2
6 (1 min after incision)	36.5±8.0*	41.1±5.4†	98.0±0.9	98.8±0.9	38.4±2.9	36.6±1.6‡
7 (5 min after incision)	36.6±4.7*	43.0±4.6†	98.1±0.7	99.0±0.8	37.1±1.5	37.3±1.4
8 (15 min after incision)	37.0±4.9*	43.6±5.1†	98.2±0.8	99.0±0.8	36.7±1.9	36.5±1.6
9 (30 min after incision)	37.2±4.9*	43.2±4.7†	98.4±0.5	99.1±0.7	36.2±1.5	37.2±1.3
10 (60 min after incision)	36.4±5.2*	43.3±4.7†	98.0±0.9	98.9±0.9	36.3±1.9	36.2±1.2
11 (at the end of surgery and anaesthetic off)	36.5±5.6*	43.7±4.8†	98.3±0.5	98.9±0.7	36.2±1.7	36.4±1.4
12 (extubation)	41.4±1.9	44.7±2.4	98.2±0.8	98.9±0.6	38.7±1.5	37.5±1.6

*Significant changes from baseline in each group ($P<0.05$)
†Group II significantly higher than group I ($P<0.05$)
‡Group II significantly lower than group I

Table 3 Mean ± SD time to extubation, palpebral and pain or pedal reflexes recovery, detection of first movement, sternal recumbency and standing position in anaesthetized rabbits from the point at which administration of inhalant sevoflurane (group I; *n*=10) or propofol via i.v. infusion (group II; *n*=10) was discontinued, with the corresponding BIS value calculated at discontinuation of agent administration

	Group I	Group II
BIS value at the end of anaesthesia	49.3±2.2	69.1±6.0*
Palpebral reflex regained (min)	2.0±0.9	5.3±2.3*
Pedal reflex regained (min)	1.9±0.9	4.1±3.2
Extubation (min)	3.6±1.3	11.7±5.0*
First movement (min)	4.5±2.1	12.2±4.1*
Sternal recumbency (min)	8.9±1.9	29.3±7.5*
Standing (min)	11.5±2.5	38.4±7.2*

All data are expressed as means ± SD
*Group II significantly higher than group I ($P<0.05$)

incision to the end of surgery and anaesthesia were significantly ($P<0.001$) lower in this group. No significant difference was observed in BIS recorded during 1 and 5 min after incision as compared with values obtained 30 s before incision in either group.

In both groups, good correlation was found between BIS values and mean ABP and between BIS values and HR. This correlation was positive in the first case and negative in the second (Table 4).

On discontinuation of anaesthesia, mean BIS values associated with propofol anaesthesia were significantly ($P<0.001$) greater than those associated with sevoflurane anaesthesia (69.1 ± 6.0 and 49.3 ± 2.2, respectively); however, mean recovery time was significantly ($P<0.001$) longer in group II (38.4 ± 7.2 min) than in group I (11.5 ± 2.5 min; Table 3).

$ETCO_2$ values did not vary significantly over time or between groups (sevoflurane versus propofol). No significant difference was found in SpO_2 between groups, with an SpO_2 value >95% in all animals (Table 2).

Discussion

Few studies have been reported to date evaluating the use of BIS assessments in veterinary practice (Haga *et al.* 1999, Antognini *et al.* 2000, Haga 2001, Greene

Table 4 Results from multiple-regression analysis of bispectral index (BIS) values with values of mean arterial blood pressure (MABP) and heart rate (HR)

Anaesthetic agent	Variable	Coefficient	SE	*P* value	Correlation coefficient (*r*)
Sevoflurane	Intercept	76.778	29.318	0.010	
	MABP	0.779	0.153	<0.001	0.496
	HR	−0.358	0.105	0.001	−0.218
Propofol	Intercept	95.427	17.592	<0.001	
	MABP	0.519	0.080	<0.001	0.549
	HR	−0.259	0.063	<0.001	−0.410

et al. 2002, Haga & Dolvik 2002, Martín-Cancho *et al.* 2003, Lamont *et al.* 2004), despite the value of BIS monitoring having been evaluated extensively in humans (Kearse *et al.* 1994, Sebel *et al.* 1995, Lui *et al.* 1996, Billard *et al.* 1997, Flaishon *et al.* 1997, Glass *et al.* 1997, Liu *et al.* 1997, Gajraj *et al.* 1999). Further investigation to provide a comprehensive evaluation of its value in monitoring veterinary anaesthesia would be desirable. To our knowledge, no studies evaluating its usefulness in rabbits have been published. However, rabbits have been used to study the EEG effects of anaesthetics (Hartikainen *et al.* 1995), and EEG has been used to evaluate the depth of anaesthesia when using injectable combinations in this species (Vachon *et al.* 1999). In our opinion, the use of BIS may help to determine whether a correct anaesthetic plane can be achieved with a given anaesthetic protocol, thus allowing for validation of standard anaesthetic techniques in rabbits.

At present, anaesthesiologists lack a direct measure of anaesthetic effects on the brain applicable to all anaesthetics at clinically used dosages. Numerous clinical signs are normally taken into account when determining the dose of an agent to be used for induction and maintenance of anaesthesia. The main target site of action of general anaesthetics is the brain, so it would not be unreasonable to expect that a neurophysiological measure of anaesthetic effect could be found. However, the CNS is a complex system and scientists still lack a full understanding of the mechanisms of action of anaesthetic drugs. In order to be useful, this neurophysiological measure of anaesthetic effect on the brain should be sensitive enough to detect insufficient levels of anaesthesia and be able to predict recovery from anaesthesia, independently of the anaesthetic agent used. This measure should also correlate with anaesthetic concentration at the site of action (Vernon *et al.* 1995).

The ability to predict and prevent increases in blood pressure during triggering events is very important in clinical practice. In this study, the relationship between two haemodynamic variables and BIS values was analysed. Negative correlation was seen between HR and BIS (high HR values are associated with low BIS values). On the other hand, arterial blood pressure and BIS exhibited a positive correlation (high ABP values are associated with high BIS values). A significant decrease in BIS values was seen after induction of anaesthesia in both groups. Compared with baseline, a significant increase in HR was detected in both groups immediately after propofol induction. This increase in HR after induction in rabbits has been previously reported (Aeschbacher & Webb 1993a). However, no concurrent significant change in blood pressure was detected in any group. The existence of positive correlation between BIS and arterial blood pressure values detected in our study has been previously described by Masuda *et al.* (1999) and Heek *et al.* (2000), who reported that BIS may be a useful indicator of increases in arterial blood pressure during anaesthetic induction in humans. However, contradictory results were obtained in swine and dogs (Carrasco-Jiménez *et al.* 2004, Martín-Cancho *et al.* 2004), where no

correlation could be found between BIS and arterial pressure. A great interindividual variability in BIS values during anaesthesia was seen in these species. Anaesthetized rabbits did not exhibit the same degree of interindividual variability, which may probably account for the different results obtained in this study.

On the other hand, human research reported by Lui *et al.* (1996) and Mi *et al.* (1998) differs also with the results obtained in rabbits, concluding that there is no correlation between BIS and arterial blood pressure. Those investigators evaluated haemodynamic and EEG responses to intubation during propofol induction and concluded that BIS cannot be used to predict haemodynamic responses to intubation after propofol induction. Similarly, no relationship between haemodynamic responsiveness to stimulation (laryngoscopy, intubation and surgical manipulations) and changes in the EEG spectral edge frequency during general anaesthesia with propofol and nitrous oxide could be seen in the study by White and Boyle (1989).

In other studies (Baumgartner *et al.* 1998, Driessen *et al.* 1999, Kussman *et al.* 2001), a similar lack of correlation between haemodynamic changes and BIS values derived from EEG analysis during important stages of anaesthesia or triggering events has been determined. It has also been suggested that the increased MABP detected after CO_2 insufflation during laparoscopic surgery does not correlate with increased BIS values (Mavoungou *et al.* 2000). Despite most studies supporting the lack of usefulness of BIS as an indicator of cardiovascular stability during intubation and surgery in humans and swine, particularly as great inter-individual variability in BIS values has been identified (Martín-Cancho *et al.* 2003), the correlation found in rabbits may render it useful in this species, as their interindividual variability was markedly lower than that reported for pigs.

MABP decreased significantly from baseline in group II rabbits during propofol anaesthesia (at an infusion rate of 0.6 mg/kg/min). This decrease has been previously described in this species by Aeschbacher and Webb (1993b). Similarly, MABP decreased significantly in sevoflurane-anaesthetized rabbits (group I). MABP decrease in these animals was attributed to the cardiovascular effects of sevoflurane, that induces dose-dependent hypotension. The decrease in blood pressure is usually associated with a decrease in stroke volume. In some instances, a decrease in peripheral vascular resistance may also play an important, but lesser, role (Frink *et al.* 1992). Propofol-induced hypotension develops immediately after drug administration in human anaesthesia, probably due to a decrease in systemic vascular resistance (Claeys 1988).

We would like to emphasize that no significant increase in HR or ABP was seen during intubation or surgery (triggering events). Therefore, the correlation found between BIS and ABP and between BIS and HR may be attributed to the hypnotic effects of the anaesthetic agents used paralleling their haemodynamic effects. So, despite the above-mentioned correlation, the usefulness of BIS for detecting ABP and HR changes during triggering events is not proved in this study, because no increase in haemodynamic parameters was observed at these times.

Moreover, it is important to consider that neural reflexes leading to haemodynamic responses to laryngoscopic and nociceptive stimuli occur predominantly at the subcortical level, whereas BIS values reflect only cortical activity (Katoh *et al.* 1998).

Because of its low blood–gas partition coefficient, sevoflurane is eliminated rapidly from the body. Results of several studies (Davis *et al.* 1993, Hikasa *et al.* 1996, Robinson *et al.* 1999) confirm short recovery times associated with its use as an anaesthetic. In this study, sevoflurane-anaesthetized rabbits recovered faster than those anaesthetized with propofol. Nonetheless, on discontinuation of anaesthesia, BIS values were greater in the propofol group. Humans sedated or anaesthetized with propofol alone also have *higher* BIS values than when propofol is administered in conjunction with a non-depolarizing muscle relaxant. These higher values have been attributed to electromyographic (EMG) activity that

falsely increases the BIS value (Bruhn *et al.* 2000, Vivien *et al.* 2003).

Calculation of the BIS requires the inclusion of frequencies above 40 Hz, which approach frequencies generated by muscle activity (Bruhn *et al.* 2000). A high-frequency filter setting of 70 Hz was used in this study, which likely included those frequencies generated by muscle activity, so EMG activity could be a confounding factor in BIS interpretation in our study. Greif *et al.* (2002) recently reported that BIS value and EMG tone are unaffected by mivacurium administration during propofol anaesthesia, despite propofol being known to cause myoclonus. These authors also reported that BIS can be used to estimate sedation in deeply unconscious humans who are paralysed, partially paralysed, or not paralysed. It may be that propofol-anaesthetized rabbits had higher BIS values than sevoflurane-anaesthetized rabbits as a result of greater EMG activity, but it cannot be verified without administering a neuromuscular blocking agent, which was not done in this study. The possibility of differences in anaesthetic-related effects on cerebral metabolism rate could also be considered as a reason for these differences in BIS values between groups. However, studies on humans reported that both sevoflurane and propofol similarly reduce cerebral metabolic rate (Kaisti *et al.* 2003) by approximately 50–70%. This rate is similar to the one reported in anaesthetized rabbits (Scheller *et al.* 1988b). Another explanation for the higher BIS values seen in group II could be the synergic analgesic effects of combining opioids and propofol (Iselin-Chaves *et al.* 1998). Opioids on their own do not affect BIS values, but their interaction with propofol could have made the rabbits reach a correct anaesthetic plane with less hypnosis than the sevoflurane-anaesthetized animals.

A faster emergence and shorter anaesthetic recovery may be achieved by targeting a higher BIS value at the end of anaesthesia in propofol-anaesthetized women (Song *et al.* 1998). However, our data suggest that it is not possible to predict decreased recovery times in rabbits solely by maintaining a high BIS value by the end of anaesthesia. The results resemble those obtained previously in swine (Martín-Cancho *et al.* 2004).

Propofol, as a lipophilic agent, has a large volume of distribution. Previously conducted studies using propofol for rabbit's anaesthesia report slow recovery and great individual variability in surviving animals after continuous i.v. infusion of propofol over 8 h (Aeschbacher & Webb 1993b). A similar finding has been described in dogs. In this species, recovery times may be prolonged after continuous infusion of propofol for more than 30 min (Robertson *et al.* 1992). It can be assumed that the same effect could occur in rabbits, as propofol pharmacokinetics are similar in these two species (Cockshott *et al.* 1992). Reports in humans state that recovery times are not prolonged after long-duration sevoflurane anaesthesia (Ebert *et al.* 1998), although this is not entirely clear, as other data indicate that recovery times after sevoflurane anaesthesia increase with the duration of anaesthesia (Eger *et al.* 1998). The differences observed between both agents suggest that sevoflurane is associated with a more rapid recovery from anaesthesia than propofol (Robinson *et al.* 1999, Peduto *et al.* 2000, Martín-Cancho *et al.* 2004).

Anaesthetic depth may be assessed by the presence or absence of movement in response to skin incision (Thurmon *et al.* 1996). No movements were observed in any rabbit in this study during surgery, which suggested that a surgical plane of anaesthesia had been achieved in all animals. Similarly, no significant increases in BIS values, arterial blood pressure or HR were noted after skin incision.

Data from this study suggest that both sevoflurane and propofol can be used for anaesthetic maintenance in the rabbit, with good haemodynamic stability for 80–85 min long anaesthesia using 1 MAC sevoflurane or propofol infusion rate of 0.6 mg/kg/min. When using these dosages, it must be taken into account that the dose rates required in this study were reduced by the use of buprenorphine as a preanaesthetic medication (0.05 mg/kg i.v.).

Although there are no available data on rabbits, a study performed in newborn pigs (Gavilanes *et al.* 2001) indicated that the observed EEG remains stable until the MABP decreases below 30 mmHg. In this study, MABP values were not so low as to have influenced the EEG recordings.

Despite the correlation found between MABP and BIS values, MABP was lower in rabbits receiving propofol than in those anaesthetized with sevoflurane (from 1 min after incision to discontinuation of anaesthesia). However, BIS was found to be higher during propofol anaesthesia (group II rabbits) than during sevoflurane anaesthesia. The fact that BIS values were higher in group II rabbits confirms that the relationship between BIS and sedation depth is not independent of the anaesthetic agent administered. These results are similar to previously reported data in swine (Martín-Cancho *et al.* 2004). Data in people (Ibrahim *et al.* 2001) suggest that BIS may be a better predictor of depth of sedation in propofol anaesthesia than in sevoflurane anaesthesia, and that the relationship between BIS values and end-tidal sevoflurane concentration had large interindividual and intraindividual variability. Our study, however, contrasts with that study (Ibrahim *et al.* 2001). The range of BIS values recorded at each interval in our study was wider for the propofol group than for the sevoflurane group, as has been previously described in pigs (Martín-Cancho *et al.* 2004). We believe that BIS values may not be always useful for predicting anaesthetic depth in every individual.

One limitation of the study reported here was the fact that the equipment we used to conduct our study was designed to be used in humans. Additional studies are still needed to validate its use in rabbits.

Results from this study suggest that BIS cannot be used to predict the speed of recovery. Correlations were seen between BIS and ABP and between BIS and HR. However, this does not necessarily mean that BIS could be useful as a predictor of clinically important changes in arterial blood pressure and HR in anaesthetized rabbits, because these changes are related to anaesthetic agents and not to the hypnosis.

BIS appears to be useful for distinguishing between states of consciousness and unconsciousness in rabbits during the induction and maintenance of anaesthesia. Both anaesthetic regimens used provided adequate anaesthesia during long abdominal surgical procedures in rabbits.

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