European Journal of Anaesthesiology 2006; **23:** 305–310

doi: 10.1017/S0265021505001997

Original Article

The effect of a remifentanil bolus on the bispectral index of the EEG (BIS) in anaesthetized patients independently from intubation and surgical stimuli

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Summary

Background and objective: Remifentanil boluses are used in different clinical situations and the effects on bispectral index monitoring are unclear. We analysed the effect of a remifentanil bolus on the bispectral index of the electroencephalogram (bispectral index) under total intravenous anaesthesia with propofol and remifentanil. *Methods:* ASA I–III patients were included in this study. All patients received a 2 $\mu g\,kg^{-1}$ remifentanil bolus in a period free from stimuli. Bispectral index and haemodynamic data were collected from an A-2000XP bispectral index monitor (every second) and an AS/3 Datex monitor (every 5 s). Bispectral index data were analysed using the area under the curve. Mean arterial pressure and heart rate were averaged at each 30-s period and analysed using analysis of variance. *Results:* A total of 240 bispectral index values were obtained per patient. The area under the curve between 90 and 120 s after the bolus was significantly lower than the basal area under the curve (average of all areas before the bolus, $P < 0.05$). Mean arterial pressure and heart rate were significantly reduced from 96.4 $\pm$ 19.9 mmHg at the time of the bolus to 74.2 $\pm$ 16.6 mmHg 120 s after, and from 70 $\pm$ 16.4 bpm at the time of the bolus to 61 $\pm$ 13.6 bpm after ($P < 0.001$), respectively. *Conclusions:* There was a significant reduction in the areas under the curve between 90–120 s following the bolus. Heart rate and blood pressure also showed significant reductions. Thus, remifentanil bolus given under total intravenous anaesthesia with propofol and remifentanil decreases bispectral index, an effect independent of intubation and surgical stimuli.

Keywords: OPIOIDS, remifentanil; ANAESTHETICS INTRAVENOUS, propofol; HAEMODYNAMIC PHENOMENA, heart rate, blood pressure; ANAESTHESIA, GENERAL, depth monitoring; ELECTROENCEPHALOGRAPHY, bispectral index.

Introduction

Remifentanil boluses are frequently used in various clinical situations such as prevention of haemodynamic responses to laryngoscopy and tracheal intubation with [1–3] and without muscles relaxants [4,5] and to control undesirable haemodynamic responses during craniotomy procedures [6]. More recently, remifentanil bolus safety was tested in awake subjects breathing room air [7].

The bispectral analysis of the electroencephalogram (EEG) (bispectral index, BIS), a signal processing technique, is used to monitor the level of unconsciousness during anaesthesia and sedation [8] and has been proposed as a pharmacodynamic measure of anaesthetic effects on the central nervous system (CNS) [9]. BIS has

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Accepted for publication 5 December 2005 EJA 3304
First published online 10 February 2006

been correlated with the hypnotic component of anaesthesia and can be used as a guide for the administration of volatile and intravenous anaesthetics [9–11].

There have been several studies regarding the effect of remifentanil on BIS in various clinical situations and with different remifentanil effect concentrations [12–15]. However, the results did not give the same conclusions. To our knowledge, there are no studies of the effects of a remifentanil bolus on BIS under a propofol–remifentanil-based general anaesthesia, in a period free from stimuli.

In this study we evaluated the effect of a remifentanil bolus on BIS and haemodynamic variables at deep levels of hypnosis during general anaesthesia, in a stimuli-free period.

Methods

Patients and monitoring

Twenty-five neurosurgical patients, ASA I–III were included in this study. Data were collected during neurosurgical interventions (Research Committee approved and informed consent), under general anaesthesia using propofol and remifentanil. Patients with pathologies, such as advanced cardiac, pulmonary, hepatic or renal dysfunction, epilepsy, uncontrolled hypertension or taking medication influencing the CNS were excluded. Patients that showed obvious alteration of mental status, with BIS under normal values when entering the surgery room or obese patients (body mass index (BMI) >32) were also excluded. If headpins, incision, severe hypotension as consequence of the remifentanil bolus that needed pharmacological treatment or other stimuli that could influence the results occurred during the study period, patients would be excluded from data analysis.

A peripheral venous line was inserted in the forearm of each patient and connected to a ramp of three stopcocks. An anti-reflux system was connected to the ramp where two lines delivered propofol 1% (Fresenius Kabi®; Bad Homburg, Germany) and remifentanil (Ultiva®; GSK, Middlesex, UK) at a concentration of 20 $\mu g\,mL^{-1}$ to the patient, pumped by two Asena Alaris GH syringes (Alaris Medical Systems, San Diego, CA, USA). Other needed medication and fluid were administered in a separate venous line. A 0.9% sodium chloride solution was administered to provide a continuous infusion rate of 400 $mL\,h^{-1}$ by an Infusomat infusion pump (B. Braun®; Melsungen, AG, Germany). After induction of anaesthesia, patients received rocuronium 1 $mg\,kg^{-1}$ intravenously and were intubated. A catheter was placed in the left radial artery for blood pressure (BP) monitoring in patients submitted to neurosurgery; continuous non-invasive BP monitoring was used in patients submitted to spinal surgery. Neuromuscular function was recorded using the electromyographic response to ulnar nerve stimulation. Haemodynamic and neuromuscular activity data were collected by the AS/3 Datex monitor (Datex-Ohmeda, Helsinki, Finland) every 5 s. BIS data were collected every second from an Aspect Medical A-2000XP BIS monitor (Aspect Medical Systems, Newton, MA) by a cutaneous electrode placed according to manufacturer instructions (Aspect Medical Systems, Newton, MA). Signal quality index and suppression ratio were monitored continuously. Rugloop II® software (written by Tom De Smet (Demed Engineering, Temse, Belgium) and Michel Struys (Ghent University, Gent, Belgium)) using Minto and colleagues [16], and Schnider and colleagues [17] TCI pharmacokinetic models was used to control the Asena syringe pumps. The BIS and the Datex AS/3 monitors, and the syringe pumps were connected to a personal computer via an RS-232 interface.

Clinical protocol

After intubation, propofol concentrations were adjusted to a BIS target level for hypnosis of 40–60 in all patients and remifentanil concentrations were diminished to a minimum, maintaining heart rate (HR) and mean arterial pressure values stabilized according to the individual patient's needs. After completing the necessary preparatory anaesthetic procedures for neurosurgery, the patients were not stimulated for a minimum period of 5 min in order to stabilize the BIS values. Propofol and remifentanil target concentrations remained unaltered for a minimum period of 3 min before remifentanil bolus. All patients were mechanically ventilated with an air and oxygen mixture. A 2 $\mu g\,kg^{-1}$ remifentanil bolus from a saline solution concentration of 20 $\mu g\,mL^{-1}$ was administered at time zero (T0). Data were collected as referred above and the 2 min prior and after the remifentanil bolus were analysed; no stimulus was applied at any time. After 2 min, headpins were applied (without local anaesthetic) or an incision was performed. If severe hypotension occurred during the study period following the remifentanil bolus, it was treated with ephedrine and the patient excluded from data analysis.

Statistical analysis

Statistical analysis was performed using MATLAB 6.5.1 (The MathWorks®, Natick, MA). For BIS values (recorded every second) the area under the curve (AUC) was calculated for all patients, for each period of 30 s before (120–90 s, 90–60 s, 60–30 s, 30–0 s) and after (0–30 s, 30–60 s, 60–90 s, 90–120 s) the remifentanil bolus. The trapezoidal rule was used to estimate

the area under the BIS curve for each sampling period. The average between two consecutive measurements multiplied by the time interval between them (1 s) was used to obtain 30 isolated AUC values. These values were summed to obtain the single AUC value for each period of 30 s.

The AUC obtained were compared within the group, using repeated measurements analysis of variance (ANOVA). The four AUC periods before the bolus were averaged to a single value per patient, the AUC basal. The relation between the basal AUC and each AUC after the remifentanil bolus was analysed by individual paired two-tailed *t*-tests. $P < 0.05$ was considered significant.

Mean arterial pressure and HR were averaged at each 30-s period in the 2 min after the remifentanil bolus and analysed using repeated measurements ANOVA. Data are presented as mean ± SD.

Results

Twenty-four patients, (15 female), ASA I–III, age 50 ± 13 yr (range 20–73), height 163.2 ± 9.7 cm, weight 68.9 ± 15.3 kg with a BMI of 25.6 ± 3.7 were analysed. One patient was excluded from analysis due to the need of ephedrine administration during the study period. Eight patients had non-invasive BP measurements and 16 patients had continuous invasive measurements.

During the entire study period (2 min prior to the remifentanil bolus and 2 min following it) the average propofol predicted effect site concentration was 2.9 ± 0.7 μg mL^{-1}. During the 2-min period prior to T0, the average remifentanil predicted cerebral concentration was 1.4 ± 0.8 ng mL^{-1}. At T0, a 2 μg kg^{-1} remifentanil bolus was delivered over 24 ± 4.2 s, resulting in a remifentanil predicted effect site concentration of 9.3 ± 1.3 ng mL^{-1} at T120, a 6.6-fold average increase from baseline. Remifentanil predicted cerebral concentrations reached a plateau between 90 and 110 s after the bolus.

Rocuronium 1 mg kg^{-1} was given on average 34.4 ± 24.4 min before T0. At T0 the first response of the train-of-four was 11.7 ± 18.2% of its initial reference. During the study period, $ETCO_2$ was 4.5 ± 0.5%.

Mean arterial pressure was significantly reduced from 96.4 ± 19.9 mmHg at T0 to 74.2 ± 16.6 mmHg at T120 ($P < 0.001$). HR was also significantly decreased from 70 ± 16.4 min^{-1} at T0 to 61 ± 13.6 min^{-1} at T120 ($P < 0.001$) (Table 1).

A total of 240 BIS values obtained during a 4 min recording period were obtained per patient. Averaged individual BIS values prior to the bolus varied between 36 and 54 (42 ± 6); after the bolus varied between 32 and 57 (41.1 ± 6). Average BIS variability (difference between maximum and minimum) prior and after the remifentanil bolus was 14 ± 5 and 15.4 ± 5, respectively.

Table 1. Haemodynamic values compared between the moment of remifentanil bolus (T0) and 30, 60, 90 and 120 s after (T30, T60, T90 and T120, respectively) using repeated measurements ANOVA.

Time	BP	MAP	HR
T0	130.2 ± 27	96.4 ± 19.9	70 ± 16.4
T30	128 ± 23.1	94.4 ± 16.5	69 ± 15.9
T60	120.6 ± 22.8*	87.8 ± 18.1**	66 ± 13.1*
T90	111 ± 20.5**	80.6 ± 16.3**	63 ± 14.1**
T120	105 ± 20**	74.2 ± 16.6**	61 ± 13.6**

Mean arterial pressure (MAP) (mmHg) and heart rate (HR) (bpm) were significantly reduced by the remifentanil bolus: *$P < 0.01$; **$P < 0.001$. BP: systolic blood pressure (mmHg).

The AUCs between each of the four 30-s period before the bolus were not statistically different ($P = 0.7$). Since there were no differences among these four periods before the bolus, the average of AUCs for each 30-s period was calculated for each patient: AUC basal. The AUC basal was used for comparisons with the four AUCs obtained following the bolus. The 0–30 AUC, 30–60 AUC and the 60–90 AUC periods following the bolus were not significantly different from basal AUC. AUC between 90 and 120 s after the bolus was significantly lower than basal AUC ($P = 0.04$) (Fig. 1). This time period (90–120 s) reflects BIS activity recorded during maximum predicted remifentanil concentrations.

Discussion

Remifentanil given as a bolus (2 μg kg^{-1}) to patients during total intravenous anaesthesia caused significant reductions in BIS, arterial pressure and HR. The study of the effects of remifentanil on BIS may be influenced by whether the patients were awake or under anaesthesia, by the presence of noxious stimulation and by the co-administration of other drugs. In the present study we examined the effect of a large bolus of remifentanil given during stable general anaesthesia, in a period free from stimulation, surgical or other.

The effect of opioids on the EEG, when used as single drugs in awake patients is well described by several authors [10,18–20]. However, when combined with hypnotic drugs, some authors report depressant effects [15,21], no effect at all [12–14] or even excitatory effects [22]. Recent studies in humans [23,24] found an increase in the BIS of the EEG when propofol was supplemented with fentanyl.

Only two studies [15,21] have described depressant effects of remifentanil on BIS; however none of them

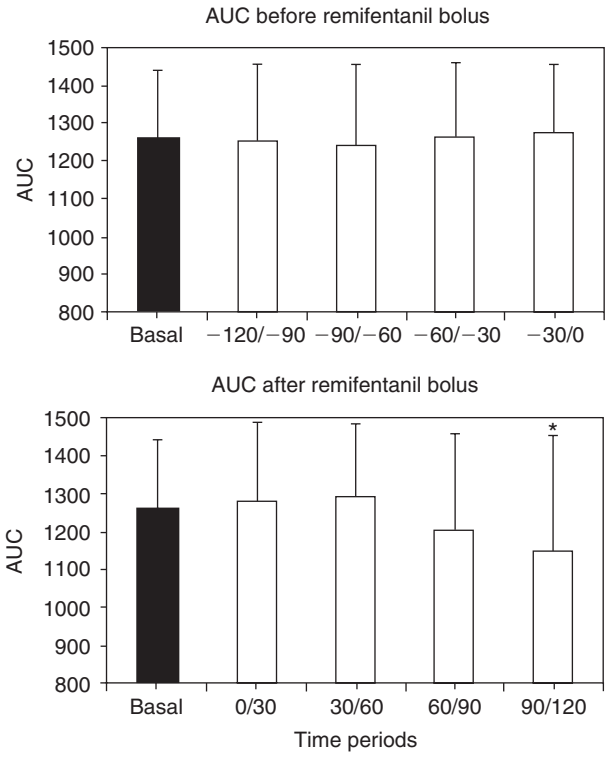

Figure 1.
Basal AUC and 30 s AUC periods prior (−120/−90, −90/−60, −60/−30, −30/0) and after (0/30, 30/60, 60/90, 90/120) the 2 μg kg^{-1} remifentanil bolus given at time 0. $^{*}P < 0.05$.

demonstrated a direct effect of remifentanil on BIS in anaesthetized patients. Strachan and colleagues [21] demonstrated that BIS was reduced by increasing infusion rates of remifentanil when combined with sedative doses of propofol (BIS $>$ 71.6) and not under general anaesthesia. Koitabashi and colleagues [15] described increasing doses of remifentanil under stable propofol anaesthesia to be significantly correlated with decreasing BIS. This author studied patients intubated following propofol anaesthesia who later received remifentanil. The modest decrease in BIS values described by these authors could be due to the removal of the stimulus caused by the presence of the endotracheal tube [25]. Although airway instrumentation had taken place 25–40 min before the study, no opioids had been administered. Remifentanil administration may have decreased BIS because of a reduction of nociception and not a direct effect on BIS [25]. In our study patients were free from surgical stimulation and the stimulus caused by the presence of the tracheal tube was attenuated by an infusion of remifentanil that provided a predicted cerebral concentration of 1.4 ± 0.8 ng mL^{-1}. The addition of an opioid to a hypnotic prevents the somatic and autonomic responses to a noxious stimulus [12]. Additionally, our study was performed with adequate muscle relaxation and 63.4 ± 35.9 min after airway instrumentation. These conditions allowed us to examine the direct effect of a bolus of remifentanil on BIS.

At induction of anaesthesia, Finianos and colleagues [13] and Lysakowski and colleagues [14] found no increased hypnotic effect of opioids on BIS. Finianos and colleagues [13] reported that remifentanil had no effect in the relationship between propofol and BIS, and showed that BIS measured only the hypnotic effect of propofol. However higher doses of remifentanil than usual clinical ones could be necessary to produce changes in EEG [13]. Similarly, Lysakowski and colleagues [14] reported that opioids in analgesic concentrations produce minimal electrophysiological alterations on the cerebral cortex [14]. The dose that we chose to administer was 2 μg kg^{-1} and can be considered a high dose. Since our patients were already on a remifentanil infusion, the bolus resulted in higher predicted remifentanil concentrations. Predicted remifentanil concentrations in our study were half the concentration required to achieve a 50% reduction of EEG activity in awake subjects [19]. Another indication that the dose that we tested was high was the finding that the remifentanil bolus caused significant reductions in both BP and HR.

Guignard and colleagues [12] observed that remifentanil, even at large doses, produced no modification on BIS under a constant level of propofol infusion, related to orotracheal intubation. They also reported a significant increase in BIS, HR and mean arterial pressure with a predicted remifentanil effect concentration of 2 ng mL^{-1} during laryngoscopy and orotracheal intubation, with a maximum expression within the first 2 min in all cases. Muncaster and colleagues [26] also observed no significant changes in BIS with the change in opioid concentrations, in a sevoflurane–remifentanil based anaesthesia.

All these studies were carried out with superficial levels of sedation and anaesthesia (BIS $>$ 60) or in periods with the presence of stimuli; only Koitabashi and colleagues [15] described studies with lower BIS values (BIS near 60). Before the bolus, our patients had an average BIS of 42 ± 6 which can be considered an adequate surgical level of anaesthesia and would therefore allow us to identify both a depressive effect with a reduction in BIS, and excitation with an increase in BIS. Our study showed that large doses of remifentanil, combined with propofol, do seem to modify the BIS level when there is no painful stimulation, in agreement with the work of Koitabashi and colleagues [15].

The BIS analysis performed in previously published remifentanil and BIS studies had a low periodicity of data sampling, when compared with the sampling frequency used in our study. Guignard and colleagues [12] used BIS values generated every 10 s and considered as a baseline the mean of six measurements

obtained 1 min before each studied period. The maximum BIS value recorded in the following 5 min was compared to that baseline. Koitabashi and colleagues [15] recorded BIS variables continuously. BIS data were averaged over a 3-min period at the end of each 15-min period, at different remifentanil predicted effect site concentrations. However, these authors do not mention how many BIS records were considered. Strachan and colleagues [21] downloaded BIS data every 5 s, and used a baseline with the BIS records of the 5 min prior to the study. Subsequently, BIS was analysed every 5-min using the average of the previous 30-s of data. Lysakowski and colleagues [14] considered three independent BIS measurements for each 2-min period after an equilibration period = 12 min. But it is not clear the time when those measurements were collected nor if they were consecutive. Finianos and colleagues [13] used BIS measurements recorded before three different periods and compared it with the lowest BIS record during propofol infusion. The duration of those time periods, the number of records performed and when those records were obtained were not described. In our study BIS was recorded every second and all BIS activity during the study period was considered for analysis.

The BIS variability observed in our study was present both before and after the bolus and may be considered high, considering that the patients were not subjected to any type of stimulation or changes in drug concentrations. The high-BIS variability poses an important methodological problem, because if we take one single measurement for analysis there is a high probability that such isolated measurement is not representative of BIS activity. Considering the average of several consecutive BIS measurements would be an alternative, but there would still be the chance that those few measurements were not representative of overall BIS activity. Furthermore, for each patient we would be analysing a value that would be a mean of several measurements, which would also have a standard deviation. By using the AUC for BIS we believe to have been able to reflect all BIS activity as well as simplify statistical analysis. Analysing isolated, maximum or minimum BIS values has a large probability of misinterpretation of BIS data. Examining the AUC instead of original BIS values overcomes the problems generated by BIS variability: each AUC reflects BIS activity during the time period considered, including all measured cerebral electric activity from BIS and has the advantage of generating an absolute number and not an average, which is more suitable for analysis. The AUC analysis is generally applied to continuous data. However, we assumed a linear correlation between every value due to the fact that BIS data was collected with a 1-s interval, allowing more confidence in data analysis.

BIS activity did not vary in the same way in all patients: whereas average AUC for BIS decreased significantly, some patients showed no change and others showed an increase. Figure 1 shows that AUC increased in the first two 30-s period after the bolus, decreasing in the next two 30-s period, although statistical significant differences were only observed in the 90–120 s period. We have no explanations for this observation. More patients will be needed to study whether other variables besides the remifentanil concentration could influence the reduction in BIS.

The observed haemodynamic effects following remifentanil bolus in our study are in agreement with Guignard and colleagues [12] who also used a 2 μg kg^{-1} remifentanil bolus in a study group, and Koitabashi and colleagues [15]. They both reported significant decrease in mean arterial pressure and HR. Glass and colleagues [27] found minimal alterations of mean arterial pressure and HR with remifentanil doses up to 2 μg kg^{-1} and Lysakowski and colleagues [14] only observed haemodynamic effects to analgesic doses of opioids in the presence of propofol. Kazmaier and colleagues [28] concluded that high remifentanil doses reduced mean arterial pressure by 30% due primarily to a 25% decrease in cardiac index, which was accompanied by a concomitant decrease in stroke volume index and HR. Rapid administration of muscle relaxants without vagolytic properties and sufentanil may also contribute to the occurrence of bradycardia, as reported Starr and colleagues [29] but in our study rocuronium was given 34.4 ± 24.4 min before the remifentanil bolus.

In conclusion, a large bolus of remifentanil given under total intravenous anaesthesia with propofol and remifentanil, in a period free from stimulation, reduces BIS activity, BP and HR. An interesting point that could be raised is that the decreases observed in the BIS values could have been related to a reduction in cerebral blood flow secondary to the reduction in either cardiac output or in BP. Our study looked specifically at the direct effect of remifentanil on BIS without the confounding influence of surgical stimulation or intubation.

Acknowledgements

The authors wish to acknowledge the Portuguese Foundation for Science and Technology (Lisbon, Portugal) for their financial support under project POSC/EEA-SRI/57607/2004.

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