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SHORT COMMUNICATION

Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia

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Background. Esmolol, a short-acting β_1-antagonist, can reduce anaesthetic requirements and decrease seizure activity during electroconvulsive therapy even after a single dose of 80 mg. We studied the effect of esmolol on the bispectral index scale (BIS), which is a processed EEG recently introduced to monitor depth of anaesthesia.

Methods. We gave esmolol 80 mg to 30 healthy male patients after induction of anaesthesia using propofol, with either fentanyl (group 1) or placebo (group 2). Patients were ventilated mechanically through a laryngeal mask airway and anaesthesia was maintained using propofol to keep the BIS value between 55 and 60.

Results. Esmolol did not affect the BIS index value in either group. In group 1, the areas (mean (SD)) under the BIS *vs* time curve 3 min before and 3 min after esmolol administration were 145 (9) and 146 (8) respectively (P=0.116). In group 2 values were 147 (8) and 146 (7) respectively (P=0.344). In contrast, in group 1 the area under the systolic arterial pressure (SAP) curve was 299 (31) before and 270 (29) after esmolol (P<0.001), and 156 (17) and 141 (17) respectively for heart rate (P<0.001). In group 2 values were 326 (36) and 302 (41) for SAP (P<0.001) and 182 (25) and 155 (22) for heart rate (P<0.001).

Conclusions. The results suggest that a single dose of esmolol affects the SAP and heart rate but does not affect BIS values.

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The potentially harmful effects of autonomic nervous system activity during anaesthesia and surgery have led to the use of beta-blockers in the perioperative period.[1 2] Esmolol, a short-acting β_1-antagonist, is used to treat and prevent cardiovascular responses at this time. In addition to its effect on the sympathetic nervous system, esmolol, if given at the same time as opiates, reduces the anaesthetic requirement to suppress the response to skin incision.[3 4] Esmolol did not affect the propofol requirement for loss of responsiveness,[5] but esmolol, even in a single i.v. dose of 80 mg, reduced both clinical and EEG-detected seizure duration during electroconvulsive therapy,[6] and a single dose of epinephrine increased EEG activity.[7] As esmolol is a peripherally acting drug that does not penetrate the blood–brain barrier, the mechanism of its effects on the depth of anaesthesia and on EEG activity is not clear.

Because esmolol appears to affect EEG activity, we studied its effects by using the bispectral index scale (BIS; Aspect Medical Systems, Natick, MA, USA), which is a processed EEG recently introduced to monitor the depth of anaesthesia.[7]

Methods and results

After ethics committee approval and informed consent, we enrolled 30 male patients, aged 18–50 yr and scheduled for

elective knee arthroscopy. Exclusion criteria were ischaemic heart disease, hypertension, use of β-adrenergic or calcium-channel blocking drugs, second- or third-degree atrioventricular block, sinus bradycardia, chronic obstructive pulmonary disease and cardiac, renal or hepatic failure.

Patients were monitored during the study using ECG, a pulse oximeter and a capnograph. Systolic arterial pressure (SAP) was measured at 1-min intervals and heart rate (HR) was monitored continuously. The BIS (version 3.12; Aspect Medical Systems, Natick, MA, USA) was measured continuously.

On arrival in the operating room, patients were randomly assigned to one of two groups by an independent observer. Group 1 received fentanyl 2 μg i.v. and group 2 patients received placebo, in a double-blind fashion. In both groups a dose of propofol 2.5 mg kg^{-1} was followed by a continuous infusion of 5 mg kg^{-1} h^{-1}. Additional propofol was given in doses of 0.5 mg kg^{-1} to keep the BIS between 55 and 60. After insertion of a laryngeal mask airway, patients were ventilated using pressure-controlled mode with an initial pressure of 16 cm H_2O, a respiratory rate of 10, an inspiratory to expiratory ratio of 1:2 and 50% oxygen with 50% nitrous oxide. The ventilator was adjusted to keep end-tidal carbon dioxide at 28–32 mm Hg.

When SAP, HR and BIS values had been stable for 5 min, esmolol 80 mg was given in both groups and recordings were made for 3 min. During this period surgery was not allowed to progress.

The patients' age was 29 (18-49) yr in group 1 and 30 (19-50) yr in group 2 and weight was 80 (12) kg in group 1 and 81 (9) kg in group 2.

In group 1, esmolol reduced SAP from 119 (13) mm Hg to a minimum value of 105 (10) mm Hg after 2 min. In group 2 the values were 130 (16) and 120 (17) mm Hg respectively. HR decreased from 62 (7) to 55 (7) beats min^{-1} in group 1 and from 72 (10) to 61 (9) beats min^{-1} in group 2. BIS values before esmolol administration were 58 (5) in group 1 and 59 (3) in group 2. Values had not changed 3 min after esmolol administration.

Using SigmaStat software (Jadel Corporation, Access Softeck Inc., Chicago, IL, USA), the values of each variable (SAP, HR and BIS) 3 min before and 3 min after esmolol were plotted against time. The areas under the curves (AUC) before and after esmolol were then compared using a paired *t*-test.

Esmolol reduced SAP in both groups (Table 1). In group 1 the AUC for SAP *vs* time was 299 (31) before and 270 (29) after esmolol ($P<0.001$). In group 2, values were 326 (36) and 302 (41) respectively ($P<0.001$). Esmolol changed the HR. In group 1 the AUC of the HR over time was 156 (17) before esmolol, and 141 (17) after esmolol ($P<0.001$). In group 2, values were 182 (25) and 155 (22) respectively ($P<0.001$). In contrast, esmolol did not affect the BIS index. The AUC for BIS over time were 145 (9) before esmolol and 146 (8) after esmolol in group 1 ($P=0.116$), and 147 (8) and 146 (7) respectively in group 2 ($P=0.344$).

Table 1 Areas under the curve before and after esmolol administration (all values are given as mean (SD)). SAP=systolic arterial pressure (mm Hg); HR=heart rate (beats min^{-1}); BIS=bispectral index scale; AUC=area under curve (the integral of the variable over a period of 3 min)

	AUC before esmolol	AUC after esmolol	*P*
Group 1 (fentanyl, propofol)			
SAP	299 (31)	270 (29)	<0.001
HR	156 (17)	141 (17)	<0.001
BIS	145 (9)	146 (8)	0.116
Group 2 (placebo, propofol)			
SAP	326 (36)	302 (41)	<0.001
HR	182 (25)	155 (22)	<0.001
BIS	147 (8)	146 (7)	0.344

Comments

We found that a single dose of esmolol 80 mg did not affect the BIS despite the effects on HR and SAP. Previous studies found that interventions in the β-adrenergic system affect the EEG and the depth of anaesthesia. Even a single dose of esmolol 80 mg reduces seizure duration in patients undergoing electroconvulsive therapy under etomidate anaesthesia.[5] The opposite effect—increased sedation score and BIS value—was caused by a small i.v. dose (15 μg) of epinephrine.[7] The changes in EEG as well as in haemodynamic measurements in both studies were almost immediate and influenced the design of the present study. The BIS and the haemodynamic values were measured for only 3 min after esmolol administration. The lack of esmolol effect on the BIS value in the present study is not surprising as recent data show BIS suppression with an esmolol infusion, with a delay of 12–16 min between esmolol administration and the onset of half-maximal effect.[9]

How esmolol affects the depth of anaesthesia and EEG activity is unclear as the drug does not cross the blood–brain barrier. In some studies, opiates were necessary in order to achieve its effects,[4] suggesting that esmolol may affect opiate kinetics by altering cardiac function and hepatic blood flow rather than by an independent pharmacodynamic effect. In a similar way, esmolol (0.5 mg kg^{-1}) increased the onset time of rocuronium-induced muscle relaxation. The onset time was shorter after ephedrine, and the effect was attributed to the effect on cardiac output.[10] In the present study the lack of effect of esmolol on the BIS might be attributed to the dose of fentanyl (only 2 μg kg^{-1}) or to the timing of opiate administration (a few minutes before esmolol). A direct effect of esmolol, an effect of a metabolite or a secondary process are possible explanations for the change in BIS found in other studies.[9]

In conclusion, our study does not show that a single dose of esmolol affects the BIS index, even though cardiovascular effects were seen.

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