British Journal of Anaesthesia **96** (**5**): 602–7 (2006)
doi:10.1093/bja/ael069 Advance Access publication March 27, 2006

BJA

Landiolol, an ultra-short-acting beta 1-adrenoceptor antagonist, does not alter the electroencephalographic effect of isoflurane in swine model

T. Kurita*, K. Morita, K. Fukuda, K. Takata, M. Uraoka, Y. Sanjo and S. Sato

Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan

**Corresponding author. E-mail: tadkur@hama-med.ac.jp*

Background. β-Adrenergic blocking agents may interact with anaesthetics, and several studies suggest that β-blockers attenuate electroencephalographic responses during general anaesthesia. We have investigated the influence of landiolol, an ultra-short-acting beta 1-adrenoceptor antagonist, on the electroencephalographic effect of isoflurane in pigs.

Methods. Ten swine were anaesthetized through inhalation of 2% isoflurane. The inhalational concentration was then decreased to 0.5% and maintained for 25 min, before being returned to 2% and maintained for a further 25 min (control period). After control measurements, infusion of landiolol (at 0.125 mg kg^{-1} min^{-1} for 1 min, and then at 0.04 mg kg^{-1} min^{-1}) was started. After a 20 min stabilization period, the inhalational concentration was varied as in the control period (40 γ landiolol). Finally, infusion of landiolol was increased from 0.04 to 0.2 mg kg^{-1} min^{-1}, and after a 20 min stabilization period, the inhalational concentration was again varied as in the control period (200 γ landiolol). End-tidal isoflurane concentrations and spectral edge frequencies were recorded throughout the study. Analysis of the pharmacodynamics was performed using a sigmoidal inhibitory maximal effect model for spectral edge frequency *vs* effect-site concentration.

Results. There were no significant differences in the effect of isoflurane among the conditions used. Landiolol did not shift the concentration–effect relationship [the effect-site concentration that produced 50% of the maximal effect was 1.35 (0.17)% under control conditions, 1.30 (0.12)% at 40 γ landiolol, and 1.38 (0.30)% at 200 γ landiolol].

Conclusion. Landiolol does not alter the electroencephalographic effect of isoflurane.

Br J Anaesth 2006; **96**: 602–7

Keywords: anaesthetic techniques, inhalation; anaesthetics volatile, isoflurane; β-blocker, landiolol; monitoring, electroencephalogram

Accepted for publication: January 26, 2006

Controversy exists over the effect of administration of β-adrenergic blocking agents (β-blockers) on anaesthetic requirements and electroencephalographic responses.[1–10] Several studies have suggested that β-blockers have an anaesthetic-sparing effect during general anaesthesia,[1–3] while others have reported that no changes in anaesthetic requirements for loss of responsiveness during propofol anaesthesia.[4 5] Similarly, several studies suggest that β-blockers attenuate electroencephalographic responses,[6–8] while others have found no change.[3 9 10] Hence, although β-blockers may increase the potency of the hypnotic aspect of anaesthesia, this issue still remains unclear.

Landiolol hydrochloride is a newly developed highly cardioselective β-blocker with a potency ratio (β_1/β_2) of 255, compared with 33 for esmolol and 0.68 for propranolol.[11] Although this agent is more potent than esmolol as a β-antagonist,[11 12] the cardiodepressant effect of landiolol is less than that of esmolol.[13] In addition, landiolol has a short duration of activity (a half-life of 4 min), enabling rapid recovery after cessation of administration, through rapid hydrolysis of its ester linkage.[11]

If β-blockers attenuate electroencephalographic responses and have an anaesthetic-sparing effect during general anaesthesia, landiolol might increase the potency of the hypnotic effect of inhalational anaesthetics. Therefore, we conducted the current study to investigate whether landiolol could alter the electroencephalographic effect of isoflurane in a swine model.

Materials and methods

Animal preparation

This study was approved by the Institutional Ethics Committee (Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan). Ten swine [body weight range: 25.7–39.2 kg, mean (SD)=29.2 (4.2) kg] were used in this study. General anaesthesia was achieved by isoflurane inhalation (5%) in oxygen at 6 litre min^{-1}, using a standard animal mask. After tracheostomy, anaesthesia was maintained with a 2% inhalational concentration of isoflurane and an oxygen–air mixture (oxygen:air=3 litre min^{-1}:3 litre min^{-1}) via mechanical ventilation. Exhaled gases were analysed using a Capnomac Ultima (ULT-V-31-04, Datex-Ohmeda, Helsinki, Finland), and these data were recorded every 10 s throughout the study. A ventilator was set to maintain end-tidal carbon dioxide between 4.7 and 5.3 kPa during the animal preparation period, and this setting was maintained throughout the study. Lead II of an ECG was monitored with three cutaneous electrodes. A pulmonary artery catheter (5 F, 4 lumen, Nihon Kohden, Tokyo, Japan) and a central venous catheter (16 gauge) were inserted via the right jugular vein, and another catheter (16 gauge) was placed in the right femoral artery. The blood temperature of the swine was maintained between 38 and 39°C throughout the study. After these preparation steps, electroencephalogic monitoring was started by preparing the skin over the fronto-occipital regions bilaterally and positioning four cutaneous electrodes (Zipprep, Aspect Medical Systems, Natick, MA, USA). Four channels of the EEG were amplified and digitally recorded using an Aspect A-1000 EEG instrument, with software version 3.0 (Aspect Medical Systems, Natick, MA, USA). The low-pass and high-pass filters were set at 2 and 70 Hz, respectively. Digitized raw electroencephalographic waveform data and processed electroencephalographic values were collected electronically at intervals of 5 s.

Experimental protocol

After completion of animal preparation, baseline measurements were taken after a further 30 min, and then the inhalational isoflurane concentration was decreased from 2 to 0.5% and maintained at this level for 25 min, before being returned to 2% and maintained at this level for a further 25 min (control conditions). After measurement of the control data, landiolol hydrochloride was administered with an infusion pump via a central venous catheter at a rate of 0.125 mg kg^{-1} min^{-1} for 1 min, and then at 0.04 mg kg^{-1} min^{-1} (a comparable dose to that administered to humans). After 20 min, and after confirming the stability of the EEG, the inhalational isoflurane concentration was decreased from 2 to 0.5% and maintained at this level for 25 min, before being returned to 2% and maintained at this level for a further 25 min, in a similar manner to the control (40 γ landiolol conditions). The landiolol hydrochloride dose was then increased from 0.04 to 0.2 mg kg^{-1} min^{-1}, and after a further 20 min the same inhalational concentration procedure to that described above was performed (200 γ landiolol conditions). Heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure, central venous pressure and cardiac output (CO) were recorded at each inhalational concentration under all conditions. CO was determined with a thermodilution computer (Cardiac Output Computer, MTC6210, Nihon Kohden, Tokyo, Japan) using 5 ml of cold 5% glucose injected into the right atrium. Each CO measurement was made four times, and the mean of the last three values was recorded.

Pharmacodynamic analysis

The pharmacological effect of isoflurane was characterized by examining the influence of isoflurane on the spectral edge frequency (SEF: the 95th percentile of the power distribution). We did not choose bispectral index (BIS) for evaluation, because in most animals BIS value remained at approximately 85 under 2% inhalational concentration of isoflurane. Furthermore, some animals failed to develop a BIS response after administration of isoflurane, despite having similar end-tidal concentration changes to those in other animals that did show a BIS response. Hence, we judged that the BIS does not adequately evaluate the pharmacodynamic effect of isoflurane in swine, at least between 2 and 0.5% inhalational concentration, and we therefore chose SEF as an alternative. SEF is related to the effect-site concentration (C_e), which was derived from the classic first-order delay of the end-tidal isoflurane concentration (E'_{iso}): $dC_e/dt = k_{e0}(E'_{iso} - C_e)$, where k_{e0} is the elimination constant from the effect site and determines the equilibration between E'_{iso} and C_e. The k_{e0} value was calculated for each animal using nonlinear least-squares fitting method in Microsoft Excel (Microsoft Excel 2000, Microsoft Corporation, Redmond, WA, USA). Optimization of k_{e0} was accomplished using the Solver tool in Excel, by minimizing the area bounded by the hysteresis loop plotted between the SEF values every 10 s and the E'_{iso} values at the respective times. Because plots of the concentration–electroencephalographic effect relationship were sigmoidal, an inhibitory sigmoid E_{max} equation (Hill equation)[14] was used to model the relationship parametrically. The following equation, $E = E_0 - (E_0 - E_{max}) \times [C_e^{\gamma}/(C_e^{\gamma} + EC_{50}^{\gamma})]$, was used, in which E is the predicted effect, E_0 is the baseline effect, E_{max} is the maximal effect, EC_{50} is the effect-site concentration that produces 50% of the maximal effect and γ is a measure of curve steepness, which was used to fit the equation to data for an individual animal. The parameters in the model were estimated using nonlinear least-squares fitting in Excel, through optimization with the Solver tool to minimize the sum of squares between the estimated and measured SEF values. We also report the coefficient

of determination (R^2) as an objective function[15]: R^2=1−SSE/SST, where SSE (sum of squared errors) represents the sum of the squares of the differences between observed measurements for a given time and the corresponding model prediction, and SST, the total sum of squares, is the sum of squares of the differences between each actual measurement and the average of all the measurements.

Statistical analysis

Data are expressed as mean values (SD). HR, MAP, mean pulmonary arterial pressure, central venous pressure, CO and pharmacodynamic parameters for each state were analysed by a repeated-measures one-way ANOVA. If the ANOVA was found to be significant, Scheffe's *F*-test was performed for multiple comparisons. *P*-values <0.05 were considered to be statistically significant.

Results

The averaged haemodynamic parameters in each state are shown in Table 1. HR, MAP and CO tended to increase when the inhalational concentration was decreased to 0.5%, and then decreased after the concentration returned to 2%. Landiolol tended to attenuate the haemodynamic changes. Landiolol decreased HR and CO, and increased mean pulmonary arterial pressure dose-dependently. MAP and central venous pressure did not change upon landiolol administration. Figure 1 shows the changes in mean ratio of E'_{iso} to inspired isoflurane concentration (E'_{iso}/FI_{iso}) for a decrease in inhalational concentration from 2 to 0.5% and for an increase in inhalational concentration from 0.5 to 2%. The decline in the E'_{iso}/FI_{iso} ratio observed after landiolol administration occurred more slowly than that during the concentration-decrease phase under control conditions. The increase in the E'_{iso}/FI_{iso} ratio observed after landiolol administration appeared to be more rapid than that under control conditions, but because the initial values of the E'_{iso}/FI_{iso} ratio (or the E'_{iso} values 25 min after the inhalational concentration decreased from 2 to 0.5%) after landiolol administration were greater than those under control conditions, the increase in the E'_{iso}/FI_{iso} ratio did not actually differ between conditions. It is probable that an increase in tissue partial pressure of isoflurane, induced by exposure to isoflurane for a long period, caused slow washout after landiolol administration. Figure 2 shows the time course of both E'_{iso} and SEF for a typical animal. Isoflurane decreased SEF between inhalational concentrations of 0.5 and 2%, and an increase or decrease in SEF was observed shortly after a respective decrease or increase in E'_{iso}. Both addition and an increase in the dose of landiolol infused at 2% inhalational concentration did not change SEF values. When SEF values were plotted against E'_{iso}, hysteresis was observed in all animals, as illustrated in Figure 3A, using the data for the same animal as shown in Figure 2. Hysteresis was collapsed by estimating the elimination constant from the effect site (k_{e0}), resulting in the effect-site concentration–SEF effect relationship for isoflurane as shown in Figure 3B. The individual curves for all animals in each condition are shown in Figure 4. Correlations of SEF to the effect-site concentration were good in all conditions and the correlation coefficients (R^2) were 0.95 (0.04) under control, 0.93 (0.08) at 40 γ landiolol, and 0.92 (0.06) at 200 γ landiolol. The EC_{50} values (with 95% confidence intervals) were 1.35 (1.45–1.24) under control conditions, 1.30 (1.37–1.22) at 40 γ landiolol, and 1.38 (1.57–1.20) at 200 γ landiolol. There were no significant differences in the EC_{50} values

Table 1 Haemodynamic parameters in each state. CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial blood pressure; MPA, mean pulmonary arterial pressure; CO 2%, CVP 2%, HR 2%, MAP 2% and MPA 2%, CO, CVP, HR, MAP and MPA at the first inhalational isoflurane concentration of 2%, respectively; CO 0.5%, CVP 0.5%, HR 0.5%, MAP 0.5%, and MPA 0.5%, CO, CVP, HR, MAP and MPA at an inhalational isoflurane concentration of 0.5%, respectively; CO $2\%_2$, CVP $2\%_2$, HR $2\%_2$, MAP $2\%_2$, and MPA $2\%_2$, CO, CVP, HR, MAP and MPA at the second inhalational isoflurane concentration of 2%, respectively; *significant difference *vs* control; **significant differences *vs* control and 40 γ landiolol; †significant difference *vs* the first 2% state; ‡significant differences *vs* both 2% states; #significant differences *vs* the second 2% state

	Control	40 γ landiolol	200 γ landiolol
HR 2% (beats min^{-1})	127 (16)	120 (13)	113 (8.2)*
HR 0.5% (beats min^{-1})	159 (22)†	146 (18)*,‡	131 (16)**,‡
HR $2\%_2$(beats min^{-1})	141 (28)	123 (12)*	122 (14)*
MAP 2% (mm Hg)	67 (12)	74 (11)	74 (7)
MAP 0.5% (mm Hg)	98 (13)‡	96 (12)‡	96 (10)‡
MAP $2\%_2$ (mm Hg)	76 (12)	76 (11)	74 (8)
MPA 2% (mm Hg)	26 (6.7)	29 (9.0)	33 (8.8)*
MPA 0.5% (mm Hg)	26 (4.6)	31 (8.2)*	32 (9.0)*
MPA $2\%_2$ (mm Hg)	27 (5.9)	30 (7.4)	35 (8.2)*
CVP 2% (mm Hg)	9.7 (1.3)	9.3 (1.6)	9.6 (1.5)
CVP 0.5% (mm Hg)	8.4 (1.8)	8.5 (1.3)#	9.3 (1.2)
CVP $2\%_2$ (mm Hg)	9.6 (1.7)	9.9 (1.1)	9.9 (1.3)
CO 2% (litre min^{-1})	3.2 (0.6)	3.1 (0.5)*	2.8 (0.7)*
CO 0.5% (litre min^{-1})	3.9 (0.7)†	3.2 (0.8)*	2.9 (0.7)*
CO $2\%_2$ (litre min^{-1})	3.4 (0.5)	2.9 (0.6)*	2.6 (0.3)*

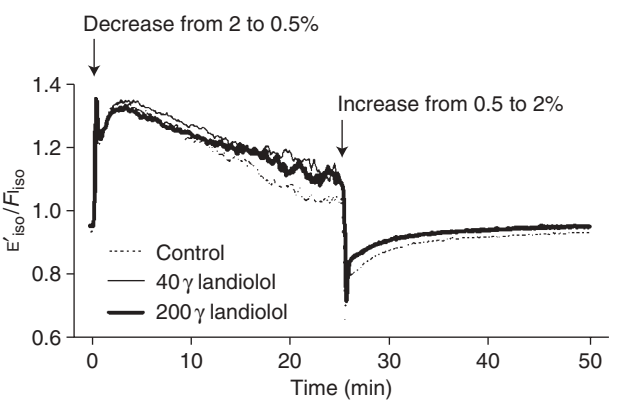

Fig 1 Changes in the mean ratio of end-tidal isoflurane concentration to inspired isoflurane concentration (E'_{iso}/FI_{iso}) during a decrease in inhalational concentration from 2 to 0.5% and during an increase from 0.5 to 2%.

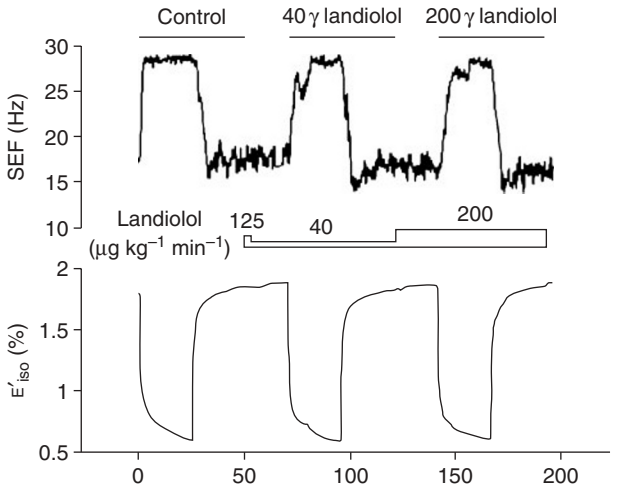

Fig 2 Changes in SEF and end-tidal isoflurane concentration (E'_{iso}) during a typical experiment.

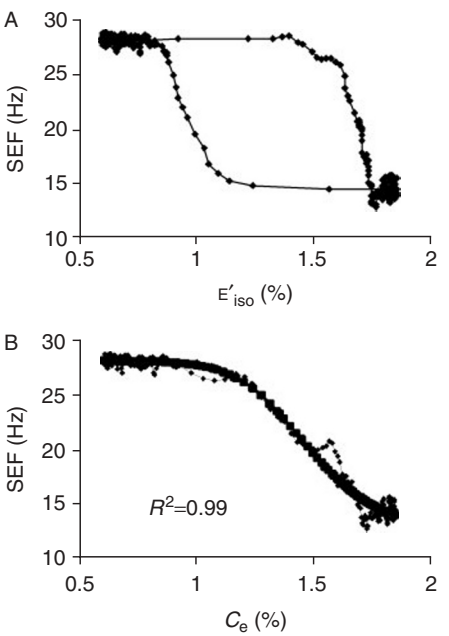

Fig 3 (A) Relationship between SEF and end-tidal isoflurane concentration (E'_{iso}) during a decrease in inhalational concentration from 2 to 0.5% (the lower limb of the loop) and then during an increase back to 2% (the upper limb) under control conditions for the pig shown in Figure 2. (B) Relationship between SEF and effect-site isoflurane concentration (C_e) after hysteresis minimization.

among the three conditions. SEF values (with 95% confidence intervals) at each EC_{50} were 20.6 (21.9–19.2) under control conditions, 20.2 (21.2–19.2) at 40 γ landiolol, and 18.9 (20.5–17.3) at 200 γ landiolol. Pharmacodynamic parameters are presented in Table 2. E_0, E_{max} and γ showed a decreasing trend with increasing landiolol, with the exception of γ the differences were not significant. Landiolol did not significantly change the effect of isoflurane on SEF.

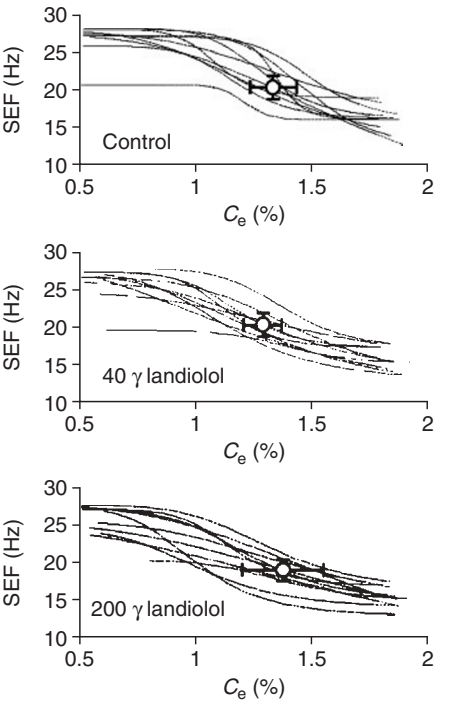

Fig 4 Individual relationships between SEF and effect-site isoflurane concentration (C_e) at each state. Open circles are EC_{50} values with 95% confidence intervals.

Table 2 Pharmacodynamic parameters. E_0, baseline spectral edge effect level; E_{max}, maximal spectral edge effect; EC_{50}, effect-site concentration that produces 50% of the maximal spectral edge effect; γ, a measure of curve steepness; k_{e0}, elimination constant from the effect site; *significant difference *vs* control

	Control	40 γ landiolol	200 γ landiolol
k_{e0} (min^{-1})	0.47 (0.12)	0.39 (0.09)	0.45 (0.20)
E_0 (Hz)	26.7 (2.3)	26.1 (2.6)	25.8 (2.3)
E_{max} (Hz)	14.4 (4.0)	14.2 (2.5)	12.0 (4.8)
γ	11.2 (6.6)	6.7 (2.7)	5.5 (2.3)*
EC_{50} (%)	1.35 (0.17)	1.30 (0.12)	1.38 (0.30)

Discussion

This study indicates that landiolol does not influence the encephalographic effect of isoflurane, suggesting that landiolol does not alter the hypnotic effect of isoflurane. Pharmacokinetic changes associated with uptake and distribution, induced by the decrease in CO, are also minimal. The clinical implication of our study is that landiolol will not modify the hypnotic effect of isoflurane when used for attenuating haemodynamic responses during anaesthetic induction, recovery from anaesthesia or both.

Landiolol hydrochloride is a new β-adrenergic blocker that has pharmacological similarities to esmolol. It was synthesized by ONO Pharmaceutical Co. Ltd (Osaka, Japan), and several preliminary studies have shown that it has some unique characteristics. Landiolol hydrochloride is a highly cardioselective β-blocker with a potency ratio (β_1/β_2) of 255, compared with 33 for esmolol and 0.68 for

propranolol.[11] It has a short duration of action (a half-life of 4 min) as a result of rapid hydrolysis of its ester linkage, enabling rapid recovery after cessation of administration.[11] In addition, although landiolol exerts a more potent negative chronotropic effect than esmolol,[11 12] its cardiodepressant effect is less than that of esmolol.[13] In fact, in this study, although HR and CO decreased after administration of landiolol, CO decreased by approximately 25% even at 200 γ landiolol, and furthermore MAP was unchanged (Table 1).

β-Blockers have been used for many years to control perioperative haemodynamic responses. In particular, esmolol, a short-acting β_1-blocker, is used in anaesthesia to attenuate the stress response to orotracheal intubation, to control postoperative hypertension, and to manage unstable coronary syndromes and tachyarrhythmias.[16] Because of the potential of drug interactions to lead to central nervous system depression[17 18] and acute haemodynamic effects, possible interactions of esmolol with anaesthetics have been investigated.[1–10 19 20] Menigaux and colleagues[7] demonstrated that esmolol prevents movement and BIS arousal reactions in response to orotracheal intubation in propofol-anaesthetized patients. Similarly, Oda and colleagues[8] showed that landiolol prevents BIS arousal reactions in response to orotracheal intubation at 1 minimum alveolar concentration sevoflurane. These results imply that β-blockers may increase the hypnotic effect of anaesthetics under noxious stimulation (during surgery). Menigaux and colleagues[7] speculated that esmolol may modify BIS during general anaesthesia only when substantial sympathetic activation is likely, because addition of esmolol during propofol general anaesthesia did not affect BIS before laryngoscopy. Indeed, several reports[7–9] have shown that addition of β-blockers under stable conditions does not influence the EEG, as observed in the current study. β-Adrenoceptors are present in various parts of the reticular activating system, particularly in the medial septal region of the basal forebrain.[21] Infusion of β-adrenoceptor agonists into this region elicits enhancement of behavioural and electroencephalographic indices of waking in animals.[21] Conversely, infusion of β-adrenoceptor antagonists decreases electroencephalographic indices of arousal.[21] Similarly, the infusion of epinephrine in humans causes clinical signs of arousal associated with an increase in BIS.[22] In our study, we examined the electroencephalographic effect of isoflurane under surgical stimulation, and further changed the inhalational concentrations between 2 and 0.5% (between approximately 1.2 and 0.4 minimum alveolar concentration isoflurane in swine[23]) to evaluate hypnotic effects. Hence, the study was performed under relatively light anaesthesia, in which central catecholamine concentrations tend to increase. However, the addition of landiolol infusion under 2% isoflurane anaesthesia did not affect SEF, and landiolol did not alter the encephalographic effect of isoflurane under light anaesthesia.

Johansen and colleagues[2] have demonstrated that even high-dose esmolol has no effect on isoflurane requirements for skin incision. This might lead to the conclusion that β-blockers do not have an anaesthetic-sparing effect during use of inhalational anaesthetics alone. However, Johansen and colleagues also demonstrated that high-dose esmolol increases the anaesthetic-sparing effect of alfentanil during isoflurane anaesthesia, leading to the suggestion that esmolol interacts with opioids to produce an anaesthetic-sparing effect. However, Haidar and colleagues[10] showed that there is no pharmacokinetic or pharmacodynamic interaction between esmolol and remifentanil in an animal study. If β-blockers have an interaction with opioids, it remains possible that landiolol might alter the encephalographic effect of isoflurane when it is used in combination with opioids.

Several limitations of the study need to be addressed. In our experiments, the particular inhalational concentration range was chosen because 0.5% is the minimal dose for sedation and an inhalational concentration of 2% is approximately equivalent to a 1.8% end-tidal concentration (approximately 1.2 minimum alveolar concentration of isoflurane in swine[23]). Hence, this range appears to be appropriate for examining hypnotic effects. In pilot studies, the decrease of SEF tended to reach a maximum at an inhalational concentration of approximately 2.5%. Strictly speaking, when using an inhibitory sigmoid E_{max} model for an inhalational concentration between 0.5 and 2%, the EC_{50} value may be arbitrary, even if SEF is well correlated with isoflurane concentration over this range. In addition, increased reliability of interpretation of data obtained under the different conditions in the study may have been facilitated by inclusion of a placebo group (no landiolol administration throughout the study period). We also note that although we administered doses of landiolol comparable to that administered to humans and 5-fold the human dose, the distribution of β-adrenoceptors in swine may differ from that in humans and β-blockers may not necessarily produce the same effects in swine and humans.

In summary, landiolol, an ultra-short-acting beta 1-adrenoceptor antagonist, does not alter the potency of isoflurane. Although further investigation of the effects of landiolol on isoflurane when used in combination with opioids is necessary, this study indicates that β-blockers do not appear to influence the hypnotic effect of inhalational anaesthetics.

Acknowledgements

Landiolol hydrochloride was provided by ONO Pharmaceutical Co. Ltd, and other support was provided from departmental sources.

References

1 Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. *Anesthesiology* 1997; **86**: 364–71

2 Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar Isoflurane concentration by alfentanil. *Anesth Analg* 1998; **87**: 671–6

3 Zaugg M, Tagliente T, Silverstein JH, Lucchinetti E. Atenolol may not modify anesthetic depth indicators in elderly patients—a second look at the data. *Can J Anaesth* 2003; **50**: 638–42

4 Orme R, Leslie K, Umranikar A, Ugoni A. Esmolol and anesthetic requirement for loss of responsiveness during propofol anesthesia. *Anesth Analg* 2002; **93**: 112–16

5 Wilson ES, McKinlay S, Crawford JM, Robb HM. The influence of esmolol on the dose of propofol required for induction of anaesthesia. *Anaesthesia* 2004; **59**: 122–6

6 Johansen JW. Esmolol promotes electroencephalographic burst suppression during propofol/alfentanil anesthesia. *Anesth Analg* 2001; **93**: 1526–31

7 Menigaux C, Guignard F, Adam F, Sessler DI, Joly V, Chauvin M. Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. *Br J Anaesth* 2002; **89**: 857–62

8 Oda Y, Nishikawa K, Hase I, Asada A. The short-acting beta1-adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. *Anesth Analg* 2005; **100**: 733–7

9 Berkenstadt H, Loebstein R, Faibishenko I, Halkin H, Keidan I, Perel A. Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia. *Br J Anaesth* 2002; **89**: 509–11

10 Haidar SH, Moreton JE, Liang Z, Hoke JF, Muir KT, Eddington ND. The pharmacokinetics and electroencephalogram response of remifentanil alone and in combination with esmolol in the rat. *Pharm Res* 1997; **14**: 1817–23

11 Iguchi S, Iwamura H, Nishizaki M, *et al.* Development of a highly cardioselective ultra short-acting β-blocker, ONO-1101. *Chem Pharm Bull* 1992; **40**: 1462–9

12 Muraki K, Nakagawa H, Nagano N, *et al.* Effects of ONO-1101, a novel beta-antagonist, on action potential and membrane currents in cardiac muscle. *J Pharmacol Exp Ther* 1996; **278**: 555–63

13 Sasano J, Tarver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting β-blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth* 2001; **48**: 985–9

14 Hill AV. The possible effect of the aggregation of the molecules of hemoglobin on its dissociation curves. *J Physiol* 1910; **40**: iv–vii

15 Bowerman B, O'Connell R. *Linear Statistical Models (An Applied Approach)*. Boston: PWS-KENT, 1990; 174–83

16 Wiest D. Esmolol: a review of its therapeutic efficacy and pharmacokinetic characteristics. *Clin Pharmacokinet* 1995; **28**: 190–202

17 Waal HJ. Propranolol-induced depression. *Br Med J* 1967; **2**: 50

18 Granville GK, Turner P. The effect of propranolol on anxiety. *Lancet* 1966; **1**: 788–90

19 Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. *Anesth Analg* 2001; **92**: 352–7

20 Szmuk P, Ezri T, Chelly JE, Katz J. The onset time of rocuronium is slowed by esmolol and accelerated by ephedrine. *Anesth Analg* 2000; **90**: 1217–19

21 Berridge CW, Foote SL. Enhancement of behavioral and electroencephalographic indices of waking following stimulation of noradrenergic β-receptors within the medial septal region of the basal forebrain. *J Neurosci* 1996; **16**: 6999–7009

22 Andrzejowski J, Sleigh JW, Johnson IAT, Sikiotis L. The effect of intravenous epinephrine on the bispectral index and sedation. *Anaesthesia* 2000; **55**: 761–3

23 Lerman J, Oyston JP, Gallagher TM, *et al.* The minimum alveolar concentration (MAC) and hemodynamic effects of halothane, isoflurane, and sevoflurane in newborn swine. *Anesthesiology* 1990; **73**: 717–21