Comparison of different doses of remifentanil on the cardiovascular response to laryngoscopy and tracheal intubation†

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We have compared three bolus and infusion regimens of remifentanil on the cardiovascular response to laryngoscopy and orotracheal intubation in three groups of 20 ASA I–II female patients, in a randomized, double-blind study. Patients in group 1 received glycopyrrolate 200 μg i.v. followed by a bolus dose of remifentanil 1 μg kg^{-1} over 30 s and an infusion of remifentanil at a rate of 0.5 μg kg^{-1} min^{-1}. The other patients received remifentanil 0.5 μg kg^{-1} over 30 s and an infusion of 0.25 μg kg^{-1} min^{-1} with (group 2) or without (group 3) pretreatment with glycopyrrolate 200 μg. All patients then received a sleep dose of propofol, rocuronium 0.6 mg kg^{-1} and 1% isoflurane with 67% nitrous oxide in oxygen. Laryngoscopy and tracheal intubation were performed 3 min later. Heart rate and arterial pressure were recorded at 1-min intervals from before induction of anaesthesia until 5 min after intubation. Baseline heart rate was similar in all groups, but decreased in group 3 (no glycopyrrolate) after induction and remained significantly lower after intubation compared with the other groups ($P<0.05$). Heart rate and arterial pressure increased slightly after intubation in each group but there were no significant differences in mean arterial pressure between groups at any time. The incidence of bradycardia (one patient in group 2) and hypotension (two patients in groups 1 and 2 and three patients in group 3) was low.

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Laryngoscopy and tracheal intubation can cause tachycardia, hypertension, arrhythmias, increased plasma catecholamine concentrations and myocardial ischaemia in susceptible individuals.[1] These responses may be attenuated by i.v. opioids, vasodilators, calcium channel and β-blockers, or deepening of anaesthesia.[1] Remifentanil is a new opioid with a rapid onset (1–2 min) and short duration of effect, which makes it ideal for attenuation of brief but noxious stimuli. The dose of remifentanil recommended at induction of anaesthesia is 1 μg kg^{-1} followed by an infusion of 0.25–1.0 μg kg^{-1} min^{-1}.[2] We have shown previously that this dose attenuates the haemodynamic response to laryngoscopy and tracheal intubation in healthy adults.[3] However, bradycardia and hypotension occurred in five of 10 patients who did not receive pretreatment with glycopyrrolate and we postulated that a lower dose of remifentanil might be effective, without these side effects. We have therefore compared the haemodynamic response to laryngoscopy and tracheal intubation in patients receiving the recommended remifentanil regimen (with glycopyrrolate) or half this dose, both with and without glycopyrrolate pretreatment.

Methods and results

After obtaining approval from the Local Research Ethics Committee and informed written consent, we studied 60 ASA I–II female patients, aged 20–56 yr, presenting for elective surgery. Patients were allocated to one of three groups in a randomized, double-blind manner. The groups were: glycopyrrolate 200 μg i.v. followed by a bolus dose of remifentanil 1 μg kg^{-1} given over 30 s, and a subsequent infusion of remifentanil 0.5 μg kg^{-1} min^{-1} (group 1); and remifentanil 0.5 μg kg^{-1} given over 30 s and an infusion of remifentanil 0.25 μg kg^{-1} min^{-1} preceded by glycopyrrolate 200 μg (group 2) or saline (group 3). All drugs were prepared by an independent anaesthetist; the investigators were blinded to the identity of the drugs.

Immediately after the bolus dose of remifentanil, anaesthesia was induced with propofol 0.5 mg kg^{-1} followed by 10 mg every 10 s to loss of verbal contact, and rocuronium

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Table 1 Mean (SD) cardiovascular variables before and after induction of anaesthesia and laryngoscopy and intubation in group 1 (1 μg bolus/0.5 μg kg^{-1} min^{-1} infusion, glycopyrrolate pretreatment), group 2 (0.5 μg bolus/0.25 μg kg^{-1} min^{-1} infusion, glycopyrrolate pretreatment) and group 3 (0.5 μg bolus/0.25 μg kg^{-1} min^{-1} infusion, no glycopyrrolate). *P<0.05 between groups

		After induction			After laryngoscopy and intubation				
	Baseline	1 min	2 min	3 min	1 min	2 min	3 min	4 min	5 min
Group 1 (n=20)									
SAP	125 (13)	111 (17)	100 (13)	94 (10)	105 (20)	100 (15)	96 (11)	93 (10)	93 (9)
MAP	88 (11)	77 (18)	67 (13)	62 (11)	73 (16)	69 (14)	65 (10)	54 (9)	62 (8)
DAP	72 (9)	62 (16)	56 (12)	50 (11)	61 (14)	57 (12)	53 (10)	52 (9)	51 (8)
HR	84 (17)	86 (17)	82 (15)	81 (15)	86 (16)	86 (17)	84 (16)	82 (15)	80 15)
Group 2 (n=20)									
SAP	127 (16)	110 (16)	98 (14)	92 (13)	109 (17)	102 (12)	94 (12)	92 (11)	91 (12)
MAP	91 (14)	75 (13)	66 (12)	59 (11)	75 (13)	71 (10)	64 (10)	62 (10)	61 (10)
DAP	76 (11)	62 (13)	53 (11)	47 (9)	63 (13)	58 (9)	52 (8)	48 (9)	50 (10)
HR	85 (12)	86 (15)	85 (13)	81 (16)	90 (17)	86 (15)	83 (15)	81 (15)	78 (15)
Group 3 (n=20)									
SAP	123 (13)	108 (13)	99 (9)	92 (9)	102 (12)	97 (11)	94 (9)	91 (9)	89 (8)
MAP	88 (10)	75 (11)	64 (7)	60 (8)	71 (11)	65 (8)	61 (8)	58 (8)	57 (7)
DAP	76 (10)	63 (13)	53 (8)	47 (7)	60 (12)	54 (9)	49 (8)	46 (7)	46 (7)
HR	77 (13)	77 (12)	72 (12)	69 (11)*	79 (15)	73 (13)*	69 (12)*	65 (12)*	63 (11)*

0.6 mg kg^{-1}. Patients' lungs were ventilated manually with 1% isoflurane with 67% nitrous oxide in oxygen until intubation, and mechanically thereafter using a Manley ventilator (tidal volume 10 ml kg^{-1}, end-tidal carbon dioxide partial pressure 4.0–4.5 kPa). Arterial pressure was measured non-invasively by an automatic oscillometer (Datex Cardiocap) and heart rate was recorded from the ECG trace. Intubation was performed 3 min after induction of anaesthesia.

Heart rate (HR), systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were recorded at 1-min intervals from before induction of anaesthesia to 5 min after intubation. Hypotension (SAP <80 mm Hg for >60 s) was treated with increments of ephedrine 3 mg i.v. or atropine 300 μg i.v. (if HR <50 beat min^{-1}). Bradycardia (HR <45 beat min^{-1} for >60 s) was treated with atropine in increments of 300 μg.

Power calculations based on our previous data[3] showed that 20 patients per group would be required to demonstrate a difference in MAP of 15 mm Hg or HR of 15 beat min^{-1} (α=0.05, β=0.1), or a reduction in the incidence of bradycardia or hypotension to 10% (α=0.05, β=0.2). Statistical analysis was performed using two-way and multivariate analysis of variance for repeated measures (ANOVA, MANOVA with treatment group and time as the between- and within-group factors) and paired and unpaired t tests with Bonferroni post-test analysis as appropriate using SPSS for Windows computer software (release 6.0, 1993).

Mean ages were 34.4 (range 21–45) yr, 35.3 (24–56) yr and 32.1 (20–48) yr in groups 1, 2 and 3, respectively. Mean weights were 67.6 (SD 11.6) kg, 69.2 (15.3) kg and 65.9 (15.7) kg, and propofol doses were 1.97 (0.46) mg kg^{-1}, 2.01 (0.42) mg kg^{-1} and 2.04 (0.54) mg kg^{-1} in the three groups, respectively. Baseline SAP, MAP, DAP and HR were similar (Table 1). Heart rate decreased in group 3 after induction of anaesthesia and remained lower after tracheal intubation compared with the other groups (P<0.05). MAP increased by 11–16 mm Hg and mean HR increased by 6–11 beat min^{-1} after intubation, but within- or between-group differences in arterial pressure (SAP, MAP and DAP) were not statistically significant. Hypotension requiring escape medication occurred in two patients in groups 1 and 2 and in three patients in group 3. One patient in group 2 developed bradycardia requiring treatment.

Comment

We found no difference between a bolus dose of remifentanil 0.5 μg kg^{-1} followed by an infusion of 0.25 μg kg^{-1} min^{-1} and twice these doses in attenuating the potential cardiovascular responses to laryngoscopy and orotracheal intubation. Heart rate decreased after induction of anaesthesia in patients who did not receive glycopyrrolate, and remained significantly lower compared with the two other groups. However, the only episode of bradycardia that fulfilled our criteria for escape medication occurred in a patient who received glycopyrrolate at induction (group 2).

A study in similar patients, using propofol, vecuronium 0.5 mg kg^{-1} and a bolus dose of remifentanil 1 μg kg^{-1} followed by an infusion of 0.5 μg kg^{-1} min^{-1}, found that remifentanil was associated with bradycardia or hypotension in five of 10 patients, compared with one of 10 in the group that also received glycopyrrolate 200 μg.[3] After a change in hospital pharmacy policy, the neuromuscular blocking drug used in the present study was rocuronium 0.6 mg kg^{-1}, which has a mild vagolytic effect and is associated with a lower incidence of bradycardia than vecuronium.[4] However, mean MAP and HR immediately before laryngoscopy in the previous study were 59 mm Hg and 80 beat min^{-1}, which were very similar to the corresponding values reported here, despite the use of rocuronium.

McAtamney and colleagues reported that after thiopental 5–7 mg kg^{-1}, a bolus dose of remifentanil 1 μg kg^{-1} was more effective in reducing the pressor response to intubation

and resulted in a more rapid return to baseline values of heart rate and arterial pressure than 0.25 or 0.5 μg kg^{-1}.[5] It is unclear if thiopental was titrated to effect. Heart rate increased in all treatment groups after induction of anaesthesia and increased further after laryngoscopy and intubation. Two of 20 patients in the remifentanil 1 μg kg^{-1} group became hypotensive, although their heart rates were not reported separately.

The same group examined the effect of remifentanil 0.5, 1.0 or 1.25 μg kg^{-1} on haemodynamic changes during rapid sequence induction of anaesthesia with thiopental 5–7 mg kg^{-1} and succinylcholine 1.0 mg kg^{-1}.[6] Remifentanil 0.5 μg kg^{-1} was ineffective in controlling the pressor response but SAP was less than 90 mm Hg in seven of 20 patients receiving remifentanil 1.25 μg kg^{-1}.

The differences between these studies and ours may be related to administration of thiopental 5–7 mg kg^{-1} before the bolus dose of remifentanil. The use of a bolus–infusion technique results in a rapid, stable concentration of remifentanil, and is logical when remifentanil is to be continued during operation. Remifentanil given before induction of anaesthesia decreases the required dose of i.v. anaesthetic agent, and propofol was titrated to loss of verbal contact in this study. The pressor response reaches a peak 1–2 min after laryngoscopy and intubation, and usually subsides within 5–6 min, although tachycardia may persist for 10 min.[7] The effect-site half-life of a remifentanil bolus is only 3.2 min, and the use of a bolus–infusion regimen is therefore rational, as acknowledged previously.[5]

This type of study may be criticized as the patients recruited were not at risk of haemodynamic responses, and no information regarding outcome was given.[8] However, we felt it important to establish the most effective regimen for remifentanil at induction of anaesthesia, especially in view of previous reports of bradycardia, before extending this work to higher risk groups. The results from this and the previous study[3] suggest that the recommended dose is excessive in healthy patients.

In summary, we observed only slight changes in heart rate and arterial pressure after laryngoscopy and tracheal intubation when remifentanil 0.5 μg kg^{-1} i.v. given over 30 s followed by an infusion of 0.25 μg kg^{-1} min^{-1} was used as part of a balanced anaesthetic technique at induction of anaesthesia in healthy adults. Heart rate was lower in patients who did not receive glycopyrrolate, but only one patient who had received glycopyrrolate developed bradycardia requiring treatment. Hypotension requiring escape medication occurred in two patients in groups 1 and 2 and in three patients in group 3.

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