Comparison of effects of remifentanil and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients

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In a randomized double-blind study, we compared the effect of remifentanil and alfentanil on the cardiovascular response to laryngoscopy and tracheal intubation in patients on long-term treatment for hypertension. Forty ASA II–III patients were allocated to receive (i) remifentanil 0.5 μg kg^{-1} followed by an infusion of 0.1 μg kg min^{-1} or (ii) alfentanil 10 μg kg^{-1} followed by an infusion of saline; all patients received glycopyrrolate 200 μg before the study drug. Anaesthesia was induced with propofol and rocuronium and maintained with 1% isoflurane and 66% nitrous oxide in oxygen. Laryngoscopy and tracheal intubation were performed after establishment of neuromuscular block. Arterial pressure and heart rate (HR) were measured non-invasively at 1 min intervals from 3 min before induction until 5 min after intubation. Systolic (SAP), diastolic and mean arterial pressure decreased significantly after induction in both groups ($P<0.05$). Maximum increases in mean SAP after laryngoscopy and intubation were 35 and 41 mm Hg in the remifentanil and alfentanil groups, respectively. After intubation, arterial pressure did not increase above baseline values in either group. HR remained stable after induction of anaesthesia, but increased above baseline values after intubation. Mean maximum HR was 87 beats min^{-1} for the remifentanil group (12 beats min^{-1} above baseline; $P=0.065$) and 89 beats min^{-1} for the alfentanil group (15 beats min^{-1} above baseline; $P<0.05$). There were no significant differences between groups in HR or arterial pressure at any time. There were no incidences of bradycardia. Seven patients in the remifentanil group and four in the alfentanil group received ephedrine for hypotension (i.e. SAP<100 mm Hg).

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Laryngoscopy and tracheal intubation may be accompanied by hypertension, tachycardia and raised intracranial pressure and can be associated with myocardial ischaemia in susceptible individuals.[1] This response may be exaggerated in patients with treated or untreated essential hypertension[2] who have a greater incidence of coexisting coronary artery and cerebrovascular disease. Many drugs have been shown to be effective in modifying this haemodynamic response in healthy patients, including remifentanil[3] and alfentanil.[4 5] Remifentanil is an opioid drug with a pharmacological profile ideal for the treatment of brief noxious stimuli.[6 7] Few studies of the haemodynamic response to intubation have been carried out in hypertensive patients or those at risk of developing myocardial ischaemia[8] and none have used remifentanil. In this randomized double-blind study, we compare the relative efficacy of remifentanil with that of alfentanil in modifying the haemodynamic response to intubation in patients receiving long-term treatment (>6 months) for hypertension.

Patients and methods

After hospital ethics committee approval and informed consent, 40 ASA II–III patients aged 33–78 yr, receiving long-term treatment (>6 months) for hypertension and undergoing elective surgery requiring tracheal intubation were recruited. They were allocated at random to two groups using a sealed envelope technique. Criteria for exclusion were: ASA grade III or greater; hiatus hernia or significant gastro-oesophageal reflux; obesity (body mass

Table 1 Patient characteristics: mean (SD or range) or number. Baseline arterial pressures and heart rate are the mean of three values taken immediately before induction of anaesthesia

	Remifentanil (*n*=20)	**Alfentanil (*n*=20)**
Age (yr)	64 (33–78)	63 (49–78)
Gender (male/female)	10/10	10/10
Weight (kg)	76.2 (14.7)	77.0 (11.9)
Propofol dose (mg)	95.3 (26.3)	95.3 (24.8)
Baseline arterial pressure (mm Hg)		
SAP	159 (26)	162 (20)
MAP	106 (19)	111 (15)
DAP	85 (15)	88 (10)
Baseline heart rate (beats min^{-1})	75 (14)	74 (12)
Duration of laryngoscopy (s)	17.5 (13)	21.0 (16)

Table 2 Concurrent antihypertensive medication and requirements for escape medication, according to treatment group; figures in brackets refer to the numbers of patients who required ephedrine to treat hypotension (SAP<100 mm Hg)

	Remifentanil (*n*=20)	**Alfentanil (*n*=20)**
Diuretic	1	2 (1)
Beta blocker	2 (1)	4 (1)
ACE inhibitor	3 (2)	1
Calcium channel blocker	4	3
Combination therapy	10 (4)	10 (2)

index >30); anticipated difficulty with airway maintenance or intubation; recent myocardial infarction, congestive cardiac failure or ECG evidence of heart block; or the presence of a cardiac pacemaker.

Patients were not premedicated and received their usual antihypertensive drugs on the day of surgery. All patients received Hartmann's solution 5 ml kg^{-1} over 5–10 min before induction of anaesthesia. Patient's lungs were pre-oxygenated for 3 min and glycopyrrolate 200 μg i.v. was administered followed by the study drug and by an infusion, as described below.

At induction of anaesthesia, group 1 (*n*=20) received a bolus of remifentanil 0.5 μg kg^{-1} over 30 s followed by an infusion of remifentanil at 0.1 μg kg^{-1} min^{-1}. Group 2 (*n*=20) received a bolus of alfentanil 10 μg kg^{-1} over 30 s followed by an infusion of saline at the same rate. Infusions of remifentanil (group 1) and saline (group 2) continued throughout the study period. All study drugs and infusions were prepared by a third party, so that the investigators were unaware of their identity.

Immediately after the bolus of study drug, a standard general anaesthetic was administered, comprising propofol 0.5 mg kg^{-1} followed by 10 mg every 10 s until loss of verbal contact, and rocuronium 0.6 mg kg^{-1} to produce neuromuscular block. Patients' lungs were ventilated manually using a Bain circuit with 1% isoflurane and 66% nitrous oxide in oxygen, to an end-tidal carbon dioxide tension of 4.0–4.5 kPa using a Datex Capnomac. After establishment of neuromuscular blockade, confirmed with a nerve stimulator (Fisher Paykell NS272), laryngoscopy and orotracheal intubation were performed, 3 min after induction.

Heart rate (HR) and systolic, mean and diastolic arterial pressures (SAP, MAP and DAP) were recorded at 1 min intervals from pre-oxygenation to 5 min after intubation. Arterial pressure was measured non-invasively using an automatic oscillometric device (Datex Cardiocap) and ECG was monitored with electrodes in the CM5 position. The duration of laryngoscopy and any difficulties in laryngoscopy or tracheal intubation were noted.

Escape medication (ephedrine 3 mg increments) was administered for hypotension (SAP<100 mm Hg, or a decrease of >30% of baseline for >60 s) and atropine, in 300 μg increments, for bradycardia (HR<45 beats min^{-1}). For hypertension (SAP>200 mm Hg, or an increase of >30% above baseline values, for >60 s) or tachycardia (HR>130 beats min^{-1} for >60 s), the inspired isoflurane concentration was increased in increments of 0.5%. Power analysis, based on previous data,[3] suggested that 20 patients per group would give an 80% chance of detecting a difference between the groups of 15 mm Hg in the cardiovascular response to intubation. (α=0.05, β=0.2). Statistical analysis was performed using general linear model analysis of variance for repeated measures (with treatment group and time as between- and within-group factors, and Bonferroni testing to adjust for multiple comparisons of each parameter) using SPSS for Windows computer software (release 9.0, 1998).

Results

Patient characteristics, baseline haemodynamic variables (SAP, DAP, MAP and HR) and antihypertensive medication were similar between groups (Tables 1 and 2). There were significant changes over time in SAP, DAP, MAP and HR (P<0.001) but no difference at any time between groups. Changes in mean SAP, MAP and DAP occurred in parallel and are therefore reported together. Arterial pressure decreased significantly after induction of anaesthesia in both groups (P<0.05 within groups), but there was no significant change in mean HR in either group (Table 3).

SAP, MAP and DAP after intubation were significantly higher (P<0.05) than those before intubation. The increases in SAP and DAP were sustained for 4 min after intubation in the alfentanil group and for 2 min in the remifentanil group. The greatest mean increase in SAP occurred 2 min after intubation in both groups (34 and 41 mm Hg in remifentanil and alfentanil groups, respectively). However, SAP in both groups remained below pre-induction values throughout the study period (P<0.05 from 4–5 min after intubation). DAP and MAP after intubation were also significantly higher (P<0.05) than those before intubation, increasing towards baseline values in both groups, but they then decreased and values were significantly lower than baseline from 4–5 min after intubation (P<0.05).

Table 3 Mean (SD) values of heart rate (HR), systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure; **P*<0.05 compared with baseline; †*P*<0.05 compared with pre-intubation values

	Baseline	After induction	Before intubation	+1 min	+2 min	+3 min	+4 min	+5 min
Remifentanil								
SAP (mm Hg)	159 (26)	129* (33)	104* (32)	134† (26)	138† (23)	126* (23)	115* (22)	108* (22)
DAP (mm Hg)	84 (15)	71* (18)	59* (15)	82† (17)	78† (16)	69 (14)	62* (13)	59* (14)
MAP (mm Hg)	106 (19)	87* (22)	74* (18)	100† (17)	95† (18)	84 (17)	77* (15)	74* (15)
HR (beats min^{-1})	75 (14)	75 (15)	72 (14)	87† (12)	83† (11)	79 (12)	76 (13)	75 (14)
Alfentanil								
SAP (mm Hg)	162 (18)	133* (32)	103* (28)	136† (36)	144† (34)	136† (29)	125*† (24)	121* (26)
DAP (mm Hg)	88 (10)	70* (19)	57* (16)	90† (27)	87† (21)	81† (14)	73*† (14)	70*† (15)
MAP (mm Hg)	111 (15)	84* (20)	72* (21)	105† (32)	105† (24)	98† (16)	89* (17)	86* (19)
HR (beats min^{-1})	74 (12)	74 (17)	70 (15)	89*† (19)	87*† (16)	82† (15)	80† (14)	79† (15)

Changes in HR after induction of anaesthesia were minimal, but there was a significant increase in HR after intubation in both groups ($P<0.05$). Mean maximum HR occurred 1 min after intubation in both groups, and was 87 beats min^{-1} (12 beats min^{-1} above baseline; $P=0.065$) in the remifentanil group and 89 beats min^{-1} (15 beats min above baseline; $P<0.05$) in the alfentanil group. However, there were no overall differences between groups for SAP, DAP, MAP or HR.

Seven patients in the remifentanil group and four in the alfentanil group required ephedrine 3–9 mg to treat hypotension (SAP<100 mm Hg). Marked hypotension (SAP<80 mm Hg for >1 min) occurred in three patients in the remifentanil group and two in the alfentanil group. There was no clear relationship between type of antihypertensive medication and requirement for escape medication (Table 2). Three patients in the alfentanil group and none in the remifentanil group required an increase in the inspired concentration of isoflurane to treat hypertension. A SAP of >200 mm Hg occurred in only one patient in the alfentanil group. Data from all patients, including those who required escape medication, were analysed. No patient required treatment for bradycardia. Transient ST segment depression associated with tachycardia occurred after intubation in one patient in the remifentanil group. This resolved spontaneously within 3 min without specific treatment. No other ST segment changes were observed.

Discussion

We found that the effect of a bolus dose of remifentanil 0.5 μg kg^{-1} followed by a 0.1 μg kg^{-1} min^{-1} infusion was similar to that of a 10 μg kg^{-1} bolus of alfentanil in controlling the haemodynamic response to intubation in treated hypertensive patients. Although arterial pressure increased after intubation in both groups, values remained below baseline. HR after intubation was higher than that before intubation in both groups but the increases in HR and arterial pressure were not considered clinically significant. The increase in HR above pre-intubation values was sustained for 2 min after intubation in the remifentanil group, and for 5 min in the alfentanil group. This is probably because the remifentanil was being administered by intravenous infusion whereas, after only a single bolus dose, plasma and effect-site alfentanil concentrations would have been declining by this time.[9]

We have recently shown that in young adults a bolus dose of remifentanil 0.5 μg kg^{-1} followed by an infusion at 0.25 μg kg min^{-1} is as effective as a remifentanil bolus of 1.0 μg kg^{-1} followed by an infusion at 0.5 μg kg min^{-1}, in attenuating the haemodynamic response to intubation.[10] The increase in SAP, DAP and MAP after intubation in young adults was approximately 10 mm Hg, compared with 30 mm Hg in the present study. This may reflect the fact that hypertensive patients demonstrate a greater cardiovascular response to laryngoscopy and orotracheal intubation, but could be related to the lower infusion regimen used in this study. However, the incidence of hypotension observed in the present study (7/20 patients in the remifentanil group required escape medication for hypotension) implies that higher doses of remifentanil would have been inappropriate in this patient population.

Previous studies have shown an unacceptable incidence of bradycardia associated with the use of remifentanil in the absence of a vagolytic drug.[3] In this study, glycopyrrolate 200 μg was given before induction of anaesthesia and no patient required treatment for bradycardia. Seven patients in the remifentanil group and four in the alfentanil group were treated for hypotension. In most cases the hypotension was moderate (i.e. SAP>80 mm Hg) and responded well to small doses of ephedrine. The incidence of hypotension in this study confirms the view that hypertensive patients demonstrate exaggerated swings in arterial pressure and HR in response to induction of anaesthesia and tracheal intubation.[2] However, hypotension occurred despite i.v. fluid preloading and glycopyrrolate, and may have been related to the use of propofol in combination with remifentanil or to the effects of antihypertensive medication.

Bolus doses of alfentanil 10–15 μg kg^{-1} have previously been shown to be effective in modifying the cardiovascular response to intubation.[4,5] Higher doses of alfentanil (⩽40 μg kg^{-1}) have been used in some studies, but these were in healthy young adult patients and such doses have been associated with bradycardia and hypotension.[4] In elderly

patients, a dose of alfentanil 10 μg kg^{-1} was effective,[11] so this dose was chosen for our study. Pharmacokinetic modelling indicates a 20- to 30-fold greater potency for remifentanil than for alfentanil.[12] A bolus dose of alfentanil 10 μg kg^{-1} approximates to remifentanil 0.5 μg kg^{-1} based on relative potencies of 20:1. We chose a lower infusion rate of remifentanil than in our previous study because in the elderly the clearance and volume of distribution of remifentanil are reduced, and the pharmacodynamic effects are greater.[13] The similarity in results between the two groups suggests that the doses of remifentanil and alfentanil chosen were comparable.

Recent data have again highlighted the problem of hypotension after induction of anaesthesia in patients receiving antihypertensive medication, in particular angiotensin-converting enzyme (ACE) inhibitors.[14] A possible criticism of this study is that the patients were receiving different types of antihypertensive medication, and this was not controlled between groups. However, Sear and colleagues found no difference in the cardiovascular response to intubation in patients receiving different monotherapies for mild to moderate hypertension,[15] and the distribution of type of antihypertensive medication between groups in this study was similar. Furthermore, the aim of this study was to establish whether remifentanil was as effective as alfentanil in a cohort of hypertensive patients, rather than examine the effects in those taking particular types of antihypertensive drugs. Although no firm conclusions can be made from a study of this size, escape medication for hypotension was required by patients taking beta blockers, ACE inhibitors, diuretics and combination therapy, with no clear association between type of antihypertensive treatment and hypotension after induction of anaesthesia. Further studies might assess the effects of opioids and specific antihypertensive medication.

This study supports the notion that hypertensive patients have an exaggerated cardiovascular response to laryngoscopy and tracheal intubation and are susceptible to episodes of hypotension after induction of anaesthesia. The occurrence of transient ST depression despite treatment measures confirms that this group is at risk of myocardial ischaemia. In conclusion, remifentanil and alfentanil in the doses described were similarly effective in reducing the cardiovascular response to laryngoscopy and orotracheal intubation.

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