Do we need inhaled anaesthetics to blunt arousal, haemodynamic responses to intubation after i.v. induction with propofol, remifentanil, rocuronium?

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Background. The aim of this study was to determine whether, after propofol, rocuronium and remifentanil rapid sequence induction, inhaled anaesthetic agents should be started before intubation to minimize autonomic and arousal response during intubation.

Methods. One hundred ASA I and II patients were randomized to receive 1 MAC of desflurane or sevoflurane during manual ventilation or not. Anaesthesia was induced with an effect-site-controlled infusion of remifentanil at 2 ng ml⁻¹ for 3 min. Patients then received propofol to induce loss of consciousness (LOC). Rocuronium (0.6 mg kg⁻¹) was given at LOC and the trachea was intubated after 90 s of manual breathing support (=baseline) with or without inhaled anaesthetics. Vital signs and bispectral index (BIS) were recorded until 10 min post-intubation to detect autonomic and arousal response.

Results. A significant increase in BIS value after intubation was seen in all groups. The increases were mild, even in those not receiving pre-intubation inhaled anaesthetics. However, in contrast to sevoflurane, desflurane appeared to partially blunt the arousal response. Heart rate, systolic and diastolic pressure increase similarly in all groups.

Conclusions. Desflurane and sevoflurane were unable to blunt the arousal reflex completely, as measured by BIS, although the reflex was significantly less when desflurane was used. Rapid sequence induction with remifentanil, propofol and rocuronium and without inhaled anaesthetics before intubation can be done without dangerous haemodynamic and arousal responses at intubation after 90 s.

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laryngoscopy and intubation in combination with propofol, remifentanil and rocuronium.

Methods

After Institutional Ethics Committee (Ghent University Hospital, Ghent, Belgium) approval, informed consent was obtained from 100 ASA I patients, aged 18–60 yr, scheduled for surgery requiring general anaesthesia. Exclusion criteria included weight <70% or >130% of ideal body weight, neurological disorder and recent use of psychoactive medication, including alcohol.

Heart rate, pulse-oximetry ($SpO_2$) and capnography were recorded continuously using a S/5 Anaesthesia Monitor (GE Healthcare, Helsinki, Finland). Non-invasive arterial pressure was monitored at 1-min intervals using the same monitor. Bispectral index (BIS) (version 4.0) was derived from the frontal EEG (At-Fpzt) and calculated by the A-2000 BIS® monitor using a BIS-sensor® (Aspect Medical Systems, Inc., Newton, MA, USA). The smoothening time of the BIS-monitor was set at 15 s.

No patient received pre-anaesthetic medication. All i.v. study drugs were given through a cannula placed in a large left forearm vein. Patients were pre-oxygenated for 5 min via face mask delivering oxygen at 6 litre min$^{-1}$. In all patients, induction was with an effect compartment-controlled infusion of remifentanil, targeted at 2 ng ml$^{-1}$ started 3 min before the start of propofol and maintained for the duration of the study. Remifentanil was administered via a computer-assisted continuous infusion device RUGLOOP (RUGLOOP, written by Tom De Smet, MSc (Electronic Engineering) and Michel MRF Struys, MD, PhD (Professor in Anaesthesia). More information at http://www.anesthesia-uzgent.be) to a target effect-site concentration (CeREMI) using a three compartment model enlarged with an effect-site compartment. 3 Propofol was administered at a rate of 600 ml h$^{-1}$ until loss of consciousness (LOC), defined as an Observers’ Assessment of Alertness/Sedation (OAA/S) score less than 2.8. At LOC, all patients received a bolus of rocuronium of 0.6 mg kg$^{-1}$. After induction of anaesthesia, controlled ventilation was done with an ADU ventilator (Datex-Ohmeda®, Helsinki, Finland), with a tidal volume aiming at a $P_{CO_2}$ between 4.4 and 4.6 kPa, a fresh gas flow of 6 litre min$^{-1}$ and an $F_{O_2}=1.00$. An out-of-circle vapour admission Aladin cassette (Datex-Ohmeda®, Helsinki, Finland) was used. Controlled ventilation was performed manually using a tight-fitting face mask until intubation at 90 s after LOC. In all patients, manual breathing support and orotracheal intubation was performed by one of the co-authors (M.J.C.).

The patients were allocated randomly to one of the four study groups. In the first group, patients received desflurane at a set concentration of 1 MAC (=2 vol%) at LOC (Group D). After intubation, a similar concentration of desflurane was continued. In the second group, patients only received 1 MAC of desflurane after the intubation (Group ND). In the third group, patients received sevoflurane at a set concentration of 1 MAC (=2 vol%) at LOC (Group S). After intubation, a similar concentration of sevoflurane was continued. In the fourth group, patients only received 1 MAC of sevoflurane after intubation (Group NS). In all groups, stable anaesthesia conditions were maintained for 10 min after tracheal intubation. No changes in drug concentrations were made. For the duration of the study, a quiet operation theatre was obtained to avoid external stimuli. Every patient received about 200 ml of crystalloid fluid during the study period. No fluid load was given before induction.

All electronic data were recorded digitally every 5 s and subsequently extracted and time synchronized using Labgrab® data-management software (Demed, Temse, Belgium). Propofol plasma and effect-site concentrations (CePROP) were calculated post hoc using RUGLOOP software. For propofol, the pharmacokinetic-dynamic model previously published$^9$ was used. For all measures, specific values at specific timepoints were defined and used for comparative analysis. For BIS, $BIS_{BL}=$ mean value of BIS values measured between 30 s before start laryngoscopy and start laryngoscopy, $BIS_{peak}=$ highest BIS value observed after intubation (for 2 min after intubation), $BIS_{diff}=BIS_{peak}−BIS_{BL}$, and $T_{BIS,peak}=time at BIS_{peak}$.

For heart rate (HR), $HR_{BL}=$ mean value of HR measured between 30 s before start laryngoscopy and start laryngoscopy, $HR_{peak}=$ highest HR value observed after intubation (for 2 min after intubation), $HR_{diff}=HR_{peak}−HR_{BL}$, $T_{HR,peak}=time at HR_{peak}$. For systolic arterial pressure (SYS), $SYS_{BL}=$ mean value of SYS measured between 30 s before start laryngoscopy and start laryngoscopy, $SYS_{peak}=$ highest SYS value observed after intubation (for 2 min after intubation), $SYS_{diff}=SYS_{peak}−SYS_{BL}$, $T_{SYS,peak}=time at SYS_{peak}$. For diastolic arterial pressure (DIA), $DIA_{BL}=$ mean value of DIA measured between 30 s before start laryngoscopy and start laryngoscopy,

### Table 1 Groups. Data are mean (SD)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Group D</th>
<th>Group ND</th>
<th>Group S</th>
<th>Group NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36 (10)</td>
<td>35 (12)</td>
<td>35 (9)</td>
<td>37 (10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 (12)</td>
<td>68 (12)</td>
<td>67 (12)</td>
<td>69 (13)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 (10)</td>
<td>170 (9)</td>
<td>174 (9)</td>
<td>171 (8)</td>
</tr>
</tbody>
</table>

### Table 2 Time to loss of consciousness (LOC), BIS at LOC and propofol effect-site concentrations (CePROP) at LOC, at start laryngoscopy, intubation and at the highest CePROP defined as CePROP$\_peak$ [mean (SD)]

<table>
<thead>
<tr>
<th>Group D</th>
<th>Group ND</th>
<th>Group S</th>
<th>Group NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to LOC (s)</td>
<td>96 (25)</td>
<td>100 (21)</td>
<td>104 (32)</td>
</tr>
<tr>
<td>BIS at LOC</td>
<td>72 (16)</td>
<td>63 (18)</td>
<td>69 (14)</td>
</tr>
<tr>
<td>CePROP$_peak$ at LOC (µg ml$^{-1}$)</td>
<td>5.0 (1.9)</td>
<td>5.5 (1.7)</td>
<td>5.4 (1.9)</td>
</tr>
<tr>
<td>CePROP at start laryngoscopy (µg ml$^{-1}$)</td>
<td>6.8 (1.4)</td>
<td>7.4 (1.6)</td>
<td>6.7 (1.45)</td>
</tr>
<tr>
<td>CePROP at stop intubation (µg ml$^{-1}$)</td>
<td>6.4 (1.4)</td>
<td>6.5 (1.5)</td>
<td>5.9 (1.6)</td>
</tr>
</tbody>
</table>
DIA_{peak}=\text{highest DIA value observed after intubation (for 2 min after intubation)}, \quad \text{DIA}_{\text{diff}}=\frac{\text{DIA}_{\text{peak}}}{\text{DIA}_{\text{BL}}}, \quad T_{\text{DIA}_{\text{peak}}}=\text{time at DIA}_{\text{peak}}.

Power analysis was based on previous work with BIS.\textsuperscript{10} If we considered a difference in BIS increase at intubation (arousal) between groups of 5 (5) clinically significant, 21 patients would be needed per group with a Type-I error of 0.05 and a Type-II error of 0.10. Taking into account possible drop-outs, we randomized 25 patients to each group.

For BIS, HR, SYS and DIA at baseline and at peak values and their derived data ('diff'), intergroup comparison was done using ANOVA statistics and post hoc test, if required (Tukey-test). For intra-group comparison, differences between baseline and peak measures were calculated using a paired t-test. Differences in the overall time courses of the measured vs time were analysed using repeated measures ANOVA test. For all statistical analysis, Graphpad Instat version 3.05 (Graphpad Software, San Diego, CA, USA) was used.

**Results**

The groups were similar with respect to age, weight and height (Table 1). For technical reasons or protocol violation, 4 out of the 100 patients were excluded from

![Fig 1](https://academic.oup.com/bja/article-abstract/97/6/835/358644 by guest on 26 February 2018)

**Fig 1** Time course of the bispectral index (BIS) and end-tidal concentrations [mean (SD)] for all groups. (A) Groups D and ND and (B) Groups S and NS. L = moment of loss of consciousness, B = baseline moment (defined as the start of intubation), T = end of the tracheal intubation. *P<0.05.
Table 3  Bispectral index (BIS), heart rate (HR), systolic (SYS) and diastolic (DIA) blood pressure at baseline (BL) (time period between 30 and 0 s before start laryngoscopy), at the moment (T) of the highest value after intubation (PEAK), diastolic-PEAK–BL. *P<0.05 between group D and ND; $P<0.05 between baseline and peak measure in the same group.

<table>
<thead>
<tr>
<th></th>
<th>Group D</th>
<th>Group ND</th>
<th>Group S</th>
<th>Group NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BISpeak</td>
<td>35 (7)$</td>
<td>35 (6)$</td>
<td>36 (10)$</td>
<td>35 (6)$</td>
</tr>
<tr>
<td>BISdiff</td>
<td>7 (6)$</td>
<td>15 (10)$</td>
<td>10 (8)$</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Tmax (s)</td>
<td>17 (17)$</td>
<td>19 (44)$</td>
<td>16 (42)$</td>
<td>172 (31)</td>
</tr>
<tr>
<td>HRmax (beats min$^{-1}$)</td>
<td>78 (17)$</td>
<td>76 (14)$</td>
<td>76 (18)$</td>
<td>73 (10)$</td>
</tr>
<tr>
<td>HRmax (beats min$^{-1}$)</td>
<td>98 (20)$</td>
<td>98 (8)$</td>
<td>95 (21)$</td>
<td>90 (15)$</td>
</tr>
<tr>
<td>THR-peak (s)</td>
<td>139 (21)</td>
<td>150 (33)</td>
<td>139 (39)</td>
<td>151 (26)</td>
</tr>
<tr>
<td>SYSpeak (mm Hg)</td>
<td>117 (13)$</td>
<td>112 (14)$</td>
<td>116 (15)$</td>
<td>112 (15)$</td>
</tr>
<tr>
<td>DIAPeak (mm Hg)</td>
<td>130 (21)$</td>
<td>125 (16)$</td>
<td>131 (26)$</td>
<td>135 (27)$</td>
</tr>
<tr>
<td>DIAmax (mm Hg)</td>
<td>15 (15)</td>
<td>15 (13)</td>
<td>15 (20)</td>
<td>24 (23)</td>
</tr>
<tr>
<td>THRpeak (s)</td>
<td>161 (35)</td>
<td>182 (45)</td>
<td>185 (17)</td>
<td>164 (41)</td>
</tr>
<tr>
<td>THRpeak (s)</td>
<td>79 (16)$</td>
<td>80 (15)$</td>
<td>82 (18)$</td>
<td>84 (22)$</td>
</tr>
<tr>
<td>DIAmax (mm Hg)</td>
<td>14 (12)</td>
<td>17 (14)</td>
<td>16 (15)</td>
<td>19 (16)</td>
</tr>
<tr>
<td>THRpeak (s)</td>
<td>155 (42)</td>
<td>167 (85)</td>
<td>163 (46)</td>
<td>162 (40)</td>
</tr>
</tbody>
</table>

HR, SYS and DIA increased significantly and in a similar way among groups after intubation (Table 3, Fig. 2). The number of patients with post-intubation HR, SYS or DIA values higher than 20% above or below baseline measures (BL) were similar in all groups, as was the percentage of post-intubation time (defined as time interval between end of intubation until 10 min post-intubation) with HR, SYS or DIA values higher or lower than 20% of baseline (Table 5).

### Discussion

The aim of this study was to determine whether the use of desflurane or sevoflurane is required during the period of manual breathing support between LOC and the tracheal intubation to blunt the autonomic and hypnotic arousal responses to laryngoscopy and intubation. We found that, in the presence of a steady-state concentration of remifentanil before induction, a bolus of propofol and rocuronium without inhaled anaesthetics before tracheal intubation did not cause dangerous arousal or haemodynamic changes. When using 1 MAC equivalent of inhaled anaesthetics before intubation, we found, using BIS, that neither sevoflurane nor desflurane were able to blunt the arousal reflex completely, although this was significantly less when desflurane was used. The haemodynamic responses were not influenced by the administration of an inhaled anaesthetic. This study contributes to the discussion between the avoidance of pollution during mask ventilation and the prevention of stress response at laryngoscopy/intubation when using a ‘balanced anaesthesia technique’. Inhaled anaesthetics are delivered to ‘deepen’ anaesthesia before tracheal intubation in order to avoid arousal or haemodynamic changes. However, during rapid sequence induction when inhaled anaesthetics cannot be delivered or when the clinician wishes to avoid pollution in the operation room, the question remains whether it is safe not to deliver inhaled anaesthetics before intubation when using a combination of fast onset drugs such as propofol, remifentanil and rocuronium. Although various studies report on the haemodynamic and electroencephalographic responses to tracheal intubation with both i.v.11 and inhalation induction10 methods, no data exist for propofol followed by inhaled anaesthetic administration. In a study comparing the neuroendocrine stress response during total i.v. anaesthesia or ‘balanced anaesthesia’, the drug administration strategy before tracheal intubation was not reported.12

Although data on sevoflurane and desflurane are limited, long-term occupational exposure to trace concentration of inhaled anaesthetics is thought to have adverse effects on the health of exposed personnel.13 A recent study found that delivering inhaled anaesthetics through a breathing mask for only 3 min caused significant operation room pollution,5 even when modern scavenging systems are present. Others have confirmed their findings.6,14 There is a wide variation in individual anaesthetists’ performance on the levels of...
environmental exposure. Gray and Spence\textsuperscript{15} reported that anaesthetist’s exposure varied by a factor of 17 on a day-to-day basis.

With regard to the drug regimen used in this study, we used steady-state infusion of remifentanil in all patients during the study period, to avoid fluctuations in opiate concentration. A large bolus of opioid could be used at induction to prevent response, but this could result in haemodynamic instability. A better quality of anaesthesia has been demonstrated when continuous infusions of opiates were given instead of repeated bolus doses.\textsuperscript{16} A higher remifentanil concentration could have been used, but we balanced our choice between the use of a clinical relevant concentration and the ability to show a possible difference between groups during the transition period between propofol and inhaled anaesthetic administration. Ce\textsubscript{PROP} was between 5 and 7 µg ml\textsuperscript{-1} at the time of intubation and Ce\textsubscript{REMI} was 2 ng ml\textsuperscript{-1}, both of which are within the therapeutic range.\textsuperscript{17,18} Propofol was administered at 600 ml h\textsuperscript{-1}, which does not produce a large overshoot at the effect-site level when stopped at LOC.\textsuperscript{19}

To enable comparisons between sevoflurane and desflurane, a 1 MAC-equivalent dose was used under similar fresh gas flow and anaesthesia equipment conditions. No higher concentration was targeted as this could cause possible burst-suppression patterns in the EEG, biasing our BIS readings during arousal.\textsuperscript{20} An ‘overpressure’ technique could be used to deliver high inspired concentrations of inhaled anaesthetics to reach higher end-tidal concentrations at intubation. However, we did not use this technique as,
for desflurane, there is an increased potential for side-effects with rapidly increasing concentrations.\(^{21}\) Rocuronium was used as it has the shortest onset of non-depolarizing neuromuscular blocking agents,\(^{4}\) thus minimizing the time between LOC and intubation.

BIS can be used to detect arousal responses at laryngoscopy/intubation.\(^{1,2,23}\) We showed a significant increase in BIS at intubation after an i.v. induction with propofol, remifentanil and rocuronium. Although this was significant in all groups, BIS values above 60, which is considered at risk for awareness,\(^{24}\) occurred for only a short time and few patients. Arousal (defined by an increase in BIS) was significantly less with desflurane than with sevoflurane. However, the number of patients reaching BIS levels which can be considered at risk for pending awareness and the time spent at this level was similar between groups (Table 4). At 90 s after bolus injection of propofol, the \(C_{PRED}\) was still high enough to be protective against a potentially dangerous arousal reflex at the time of laryngoscopy/intubation. However, the haemodynamic and arousal responses could have been different if a neuromuscular blocking agent, such as cisatracurium, or opioids, such as sufentanil and fentanyl, with a slower onset was used. In such a setting inhaled anaesthetics may be required before tracheal intubation. This should be investigated in future studies.

In high risk patients, it is important to maintain haemodynamic stability by avoiding the onset of surgical stress at laryngoscopy/intubation and optimizing anaesthetic drug delivery may help to achieve this. In our study involving ASA I and II patients, the haemodynamic responses were not influenced by the administration of an inhaled anaesthetic. The number of patients with haemodynamic changes greater than 20% above baseline and the amount of time they were above this limit were similar between groups. However, no dangerous tachycardia or hypertension was observed. In our study, 1 MAC equivalent of sevoflurane or desflurane did not blunt the haemodynamic stress response completely. The switch between propofol and inhaled anaesthetics did not result in a dangerous hypotonic instability.

In conclusion, the drug regimen used in this study allowed the anaesthetist to avoid the use of inhaled anaesthetics while manually ventilating the patient before tracheal intubation. A rapid induction with remifentanil, propofol and rocuronium did not result in dangerous haemodynamic and arousal responses to tracheal intubation after 90 s.

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