Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation

K. MIKAWA, K. NISHINA, N. MAEKAWA AND H. OBARA

Summary
We have compared the efficacy of three calcium channel blockers, nicardipine, diltiazem and verapamil, in attenuating the cardiovascular responses to laryngoscopy and intubation in 60 normotensive patients (ASA I) undergoing rapid sequence induction of anaesthesia with thiopentone and fentanyl. We also examined whether or not these blockers inhibited catecholamine release induced by intubation. The patients were allocated to one of four groups \((n = 15\) for each): saline (control), nicardipine \(30 \mu g kg^{-1}\), diltiazem \(0.2 mg kg^{-1}\) or verapamil \(0.1 mg kg^{-1}\). Verapamil and the three other drugs were administered 45 s and 60 s before the start of direct laryngoscopy, respectively, in a double-dummy design. Anaesthesia was induced with thiopentone \(4 mg kg^{-1}\) i.v. and fentanyl \(2 \mu g kg^{-1}\) i.v. Tracheal intubation was facilitated with vecuronium \(0.2 mg kg^{-1}\). During anaesthesia, ventilation was assisted or controlled with \(1%\) isoflurane and \(50%\) nitrous oxide in oxygen. Laryngoscopy lasting \(30 s\) was attempted \(2 min\) after administration of thiopentone and vecuronium. Patients receiving saline exhibited significant increases in systolic and diastolic arterial pressures (AP), heart rate (HR) and plasma concentrations of catecholamines associated with tracheal intubation. The increase in AP was attenuated in patients treated with any calcium channel blocker. The greatest effect was elicited by verapamil, which attenuated the increase in HR, although nicardipine seemed to enhance tachycardia. All three drugs failed to suppress the increase in plasma catecholamine concentrations in response to tracheal intubation. These findings suggest that bolus injection of verapamil \(0.1 mg kg^{-1}\) was a more effective method of controlling hypertension and tachycardia associated with intubation than diltiazem \(0.2 mg kg^{-1}\) or nicardipine \(30 \mu g kg^{-1}\), and that these prophylactic effects were not caused by inhibition of the catecholamine response. (Br. J. Anaesth. 1996; 76: 221–226)

Key words
Intubation tracheal responses. Calcium channel block, diltiazem. Calcium channel block, nicardipine. Calcium channel block, verapamil. Complications, hypertension. Cardiovascular system, effects.

Laryngoscopy and tracheal intubation after a standardized induction dose of thiopentone often provoke a reflex increase in both sympathetic and sympathoadrenal activity, which may result in hypertension, tachycardia and arrhythmias [1–7]. These responses, although transient, may be harmful in some patients, particularly those suffering from myocardial or cerebrovascular disease. Many pharmacological techniques have been devised to reduce the extent of the haemodynamic events, including the use of high-dose opioids [1], local anaesthetics [1], adrenergic blocking agents [1] and vasodilating agents such as nitroglycerin [2] and sodium nitroprusside [3]. Several studies have shown that calcium channel blockers such as nicardipine [4], diltiazem [5] or verapamil [6, 7] are also effective. However, the effects of these calcium channel blockers have been examined separately with different anaesthetic induction techniques, including different anaesthetics and neuromuscular blockers. Thus the aim of the present study was to compare the efficacy of single rapid administration of verapamil, diltiazem and nicardipine for controlling these haemodynamic responses to tracheal intubation under the same anaesthetic techniques.

A good correlation has been demonstrated between the cardiovascular responses to intubation and changes in plasma catecholamine concentrations [8–11]. Calcium ions exert a major role in the release of catecholamines from the adrenal gland and adrenergic nerve endings, which affects plasma concentrations of catecholamines, in response to sympathetic stimulation [12]. Animal experiments have shown that calcium channel blockers inhibited catecholamine release from the sympathetic nerve ending by electrical stimulation [13–15]. In a study in healthy volunteers, the blocker inhibited the increase in plasma adrenaline induced by exercise [16]. These observations suggest that calcium channel blockers interfere with catecholamine release after tracheal intubation. In addition, therefore, plasma concentrations of catecholamines were measured before and after intubation with or without prior administration of the calcium channel blockers.

Patients and methods
The study was approved by the Ethics Committee of Kobe University Hospital. We studied 60 normo-
tensive patients (ASA I) undergoing elective surgery; all gave informed consent. They were allocated randomly to one of four groups (n = 15 for each group) to receive saline (control), nicardipine 30 \( \mu \text{g kg}^{-1} \) (Perdipine, Yamanouchi, Japan), diltiazem 0.2 \( \mu \text{g kg}^{-1} \) (Herbesser, Tanabe, Japan) or verapamil 0.1 \( \mu \text{g kg}^{-1} \) (Vasolan, Eisai, Japan). Patients with anticipated difficult tracheal intubation, hypertension, renal, hepatic or gastrointestinal disease, or weight exceeding 120 % of ideal for height were excluded (Table 1).

Premedication consisted of oral diazepam 0.1 mg kg\(^{-1}\) and atropine 0.01 mg kg\(^{-1}\) i.m., given at 60 min and 30 min, respectively, before induction of anaesthesia, which started at 08:30 in all subjects. On arrival in the operating room, two (right and left) radial arterial cannulae were inserted under local anaesthesia for continuous monitoring of systolic arterial pressure (SAP) and diastolic (DAP) arterial pressure using a radial arterial cannula. All intubations were performed with the aid of a standard Macintosh laryngoscope blade. All intubations were performed by the same anaesthetist (K.M.). A double–dummy technique was used to maintain a double-blind design (Table 2). All patients received two injections. In the verapamil group, saline and verapamil were administered i.v. 60 s and 45 s before the start of direct laryngoscopy, respectively. In the diltiazem and nicardipine groups, the calcium channel blocker and saline were injected 60 s and 45 s before starting laryngoscopy. These doses and timings were based on our previous data [4–6]. In these reports, the three calcium channel blockers were shown to attenuate the pressor response to tracheal intubation to a similar extent (16–18 % attenuation of mean arterial pressure). Furthermore, the doses of the calcium channel blockers used in the present study produced a similar degree of hypotension in patients anaesthetized with enflurane and nitrous oxide, without noxious surgical stimulation [4–6]: nicardipine 30 \( \mu \text{g kg}^{-1} \), verapamil 0.1 mg kg\(^{-1}\) and diltiazem 0.2 mg kg\(^{-1}\) decreased mean arterial pressure by 30 %, 27 % and 24 %, respectively. Other investigators administered nicardipine and diltiazem for the treatment of hypertension during surgery [17, 18]. Nicardipine 25–30 \( \mu \text{g kg}^{-1} \) produced a 25 % reduction in SAP [17] while diltiazem 10 mg (0.2 mg kg\(^{-1}\) i.v.) decreased SAP by 21 % [18]. Verapamil 0.1 mg kg\(^{-1}\) or 5 mg i.v. caused a 25 % decrease in SAP in patients with renal hypertension [19]. These findings determined our selection of the doses of the three calcium channel blockers.

After administration of thiopentone and vecuronium until 10 min after induction, ventilation was assisted as required or controlled with 1 % isoflurane and 50 % nitrous oxide in oxygen, and end-tidal partial pressure of carbon dioxide was maintained at 4.1–5.1 kPa, monitored with a Datex Capnometer (Helsinki, Finland) by means of a catheter placed in the nostril. After insertion of the tracheal tube, sampling of expired air was performed from a T-piece connected to the tube. Additional blood samples and haemodynamic measurements were obtained immediately before induction, and 1, 2, 2.5, 2.75, 3, 4 and 5 min after administration of thiopentone–vecuronium by independent observers who were blinded to the nature of the experimental treatment. All measurements and blood sampling were completed before surgical skin incision. SAP, DAP, HR and plasma concentrations of catecholamines were compared with corresponding measurements in the four groups and with measurements

### Table 1 Patient characteristics (mean [sn] [range] or number). No significant differences between groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Saline</th>
<th>Nicardipine 30 ( \mu \text{g kg}^{-1} )</th>
<th>Diltiazem 0.2 ( \mu \text{g kg}^{-1} )</th>
<th>Verapamil 0.1 ( \mu \text{g kg}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>4/11</td>
<td>6/9</td>
<td>8/7</td>
<td>7/8</td>
</tr>
<tr>
<td>Age (yr)</td>
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<td>47</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>[21–68]</td>
<td>[26–67]</td>
<td>[21–64]</td>
<td>[25–65]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>[159 (7)]</td>
<td>[160 (8)]</td>
<td>[162 (9)]</td>
<td>[160 (9)]</td>
</tr>
</tbody>
</table>

### Table 2 Timing of administration of calcium channel blockers and saline in the four groups (double-dummy technique). All doses of drug were prepared in 10 ml

<table>
<thead>
<tr>
<th>Group</th>
<th>First drug</th>
<th>Second drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 s after thiopentone–vecuronium (60 s before laryngoscopy)</td>
<td>75 s after thiopentone–vecuronium (45 s before laryngoscopy)</td>
</tr>
<tr>
<td>Control</td>
<td>Saline</td>
<td>Saline</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Nicardipine 30 ( \mu \text{g kg}^{-1} )</td>
<td>Saline</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Diltiazem 0.2 ( \mu \text{g kg}^{-1} )</td>
<td>Saline</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Saline</td>
<td>Verapamil 0.1 ( \mu \text{g kg}^{-1} )</td>
</tr>
</tbody>
</table>
before induction (operating room baseline) within the same group. Maximal values of SAP, DAP and HR after intubation were also recorded.

**CATECHOLAMINE MEASUREMENT**

Arterial blood for measurement of plasma concentrations of catecholamine, was collected in lithium heparin tubes and centrifuged within 10 min at 0°C. Plasma was separated and stored at −70°C until assay by reverse phase high-pressure liquid chromatography with electrochemical detection and an internal standard using the method described by Krstulovic [20] and Causon and Carruthers [21]. The lower limits of sensitivity of the method were 54.6 pmol litre⁻¹ and 0.0591 nmol litre⁻¹ for adrenaline and noradrenaline, respectively. The intra- and inter-assay coefficients of variance were, respectively, 4.4 % and 8.0 % for adrenaline and 4.8 % and 8.4 % for noradrenaline.

**STATISTICS**

Statistical analysis was performed using analysis of variance followed by Bonferroni’s modification of t test for parametric data, and Fisher’s exact test for non-parametric (distribution) data. Differences were considered statistically significant at P < 0.05. The power of the present study was 75 % provided that d (mean/SD) is 1.0 (where μ = mean and σ = std). Thus the number of patients in the present study (n = 15) was sufficient to detect such a difference between groups.

**Results**

The four groups were comparable in age, weight and sex (table 1).

There were no significant differences between the four groups in SAP immediately before the start of laryngoscopy or before induction. In response to laryngoscopy and tracheal intubation with prior calcium channel blockers (figs 1, 2). Administration of verapamil 0.1 mg kg⁻¹ completely inhibited the increase in arterial pressures associated with intubation. Diltiazem 0.2 mg kg⁻¹ seemed to be less effective than the two other calcium channel blockers. Conversely, in the verapamil group, arterial pressures decreased 5 min after induction compared with before induction, although the two other blockers did not cause such hypotension.
Although there was an increase in HR after induction, there was no significant difference in pre-induction values of HR or that immediately before laryngoscopy between the four groups. Verapamil successfully attenuated the HR increase after intubation (fig. 3). In contrast, nicardipine failed to do so. HR was lower in the verapamil and diltiazem groups than in the nicardipine group.

There were no significant differences in plasma adrenaline and noradrenaline concentrations between the four groups at the pre-induction and pre-intubation times. Plasma adrenaline concentrations increased significantly after intubation, with return towards baseline by 5 min after induction in all groups (fig. 4). The calcium channel blockers failed to attenuate the increase. Plasma noradrenaline concentrations increased in response to intubation in the control group. The increase was enhanced in patients receiving nicardipine (fig. 5). Verapamil and diltiazem showed changes similar to those in the control group.

A significantly smaller number of patients receiving calcium channel blockers demonstrated an SAP > 170 mm Hg and a DAP > 110 mm Hg (table 3). The number of patients with HR > 100 beat min⁻¹ seemed to be smaller in the verapamil than in the control group, although this was not significant. HR > 100 beat min⁻¹ was observed less frequently in patients receiving verapamil than in those receiving nicardipine.

No abnormal changes in ECG were observed in any patient in the diltiazem and verapamil groups. In contrast, one patient in the control and nicardipine groups had short-lived ventricular premature con-
tractions. During this study, no patient developed hypotension (SAP < 80 mm Hg) or bradycardia (HR < 50 beat min⁻¹) severe enough to require pressor, anticholinergic or sympathomimetic agents: the lowest SAP/DAP values were 82/49, 82/50 and 85/52 mm Hg in the verapamil, nicardipine and diltiazem groups, respectively, and the lowest HR were 57, 79 and 63 beat min⁻¹ in the verapamil, nicardipine and diltiazem groups, respectively.

**Discussion**

Consistent with previous reports [4–7], we have confirmed that these calcium channel blockers attenuated hypertension associated with tracheal intubation. Verapamil successfully blunted tachycardia, unlike nicardipine and diltiazem. These findings may be explained by the difference in pharmacological characteristics between dihydropyridines and phenylalkylamines. In our previous study [6], verapamil failed to attenuate the increase in HR. This discrepancy may result from different anaesthetic induction techniques: we administered fentanyl as a supplement in the present study. The combination of thiopentone and a neuromuscular blocking agent cause significant increases in plasma concentrations of catecholamines. No calcium channel blocker attenuated the catecholamine response to intubation, and conversely nicardipine enhanced the increase. Some investigators have documented that short-term treatment using dihydropyridine-type drugs increases plasma concentrations of noradrenaline as a result of baroreceptor-mediated reflex in sympathetic nervous activity [25, 26]. Furthermore, verapamil and diltiazem had no effect on plasma concentrations of noradrenaline [27, 28]. These reports support our observations. In the present study, despite higher plasma concentrations of noradrenaline in patients receiving nicardipine than in the control after intubation, the increase in arterial pressure was lower in the nicardipine group during the study period. Philipp, Distler and Cordes documented that an important determinant of the level of arterial pressure may be plasma noradrenaline and reactivity to noradrenaline [29]. Calcium channel blockers have been shown to reduce the pressor effect of circulating noradrenaline on resistance vessels [30], resulting from inhibition of the calcium influx that accompanies stimulation of α₂ receptors [31], leading to attenuation of the increase in arterial pressure after elevated concentrations of noradrenaline.

No patient in the present study developed severe hypotension: the lowest SAP and DAP recorded were 82 mm Hg and 49 mm Hg, respectively, in a patient receiving verapamil 5 min after induction. There were no differences between the three groups in clinical outcome (e.g. intra- and postoperative mortality and morbidity), possibly because we studied only otherwise healthy ASA I patients without cardiovascular or cerebrovascular disease.

**References**


