EFFECT OF VERAPAMIL ON THE CARDIOVASCULAR RESPONSES TO TRACHEAL INTUBATION

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

SUMMARY
We have studied the efficacy of verapamil in attenuating the cardiovascular responses to tracheal intubation in three groups of ASA grade I patients given verapamil 0.05 mg kg$^{-1}$ or 0.1 mg kg$^{-1}$ or saline 45 s before the start of laryngoscopy. Anaesthesia was induced with thiopentone 5 mg kg$^{-1}$ i.v. and tracheal intubation was facilitated with vecuronium 0.2 mg kg$^{-1}$. During anaesthesia, ventilation was assisted or controlled with 1% enflurane and 50% nitrous oxide in oxygen. In patients who received saline, there was a significant increase in mean arterial pressure and rate-pressure product associated with tracheal intubation. The increases were significantly less in verapamil-treated patients compared with those in the control group, although verapamil failed to prevent tachycardia caused by laryngoscopy and intubation.

KEY WORDS
Complications: hypertension, intubation, tracheal cardiovascular response, verapamil.

Laryngoscopy and tracheal intubation often provoke a marked sympathetic response, which may result in hypertension, tachycardia and arrhythmias [1]. Such cardiovascular disturbances, although transient, may be dangerous in some patients, particularly those suffering from myocardial or cerebrovascular disease. This stress response may be attenuated by opioids [1], α- or β-adrenergic blocking agents [1], ganglionic block [2] and vasodilating agents including nitroglycerine [3], sodium nitroprusside [4] and prostaglandin E$_1$ [5]. Recently, calcium antagonists such as nifedipine [6], nicardipine [7] and diltiazem [8], have also been shown to be effective. We undertook the present study, which was conducted in two parts, to examine the time course and magnitude of changes in mean arterial pressure (MAP) after administration of verapamil during anaesthesia, and to assess its value in attenuating the cardiovascular response to laryngoscopy and tracheal intubation.

PATIENTS AND METHODS
This randomized, placebo-controlled, double-blind study was approved by the Human Investigation Committee of Kobe University School of Medicine and informed consent was obtained. All patients were ASA physical status I, undergoing elective gynaecological or orthopaedic surgery. The present study comprised two parts, as did those of Stoelting [4], and Mikawa, Obara and Kusunoki [7].

Part 1
The time course and magnitude of changes in MAP and heart rate (HR) after a single rapid i.v. injection of verapamil (Vasolan, Eisai, Japan) were determined in 20 patients during anaesthesia but in the absence of stimulation produced by tracheal intubation. Premedication comprised diazepam 0.1 mg kg$^{-1}$ orally and atropine 0.01 mg kg$^{-1}$ i.m. Anaesthesia was induced with thiopentone 5 mg kg$^{-1}$ and the trachea was intubated after administration of vecuronium 0.2 mg kg$^{-1}$. Anaesthesia was maintained with 1% enflurane and 50% nitrous oxide in oxygen and end-tidal carbon dioxide partial pressure ($P_{\text{ETCO}}$) was measured using a Datex Capnometer (Datex, Helsinki, Finland). Ventilation of the lungs was controlled to maintain $P_{\text{ETCO}}$ at 4.0–5.1 kPa. After MAP and HR had stabilized, the patients were allocated randomly to two groups and given either verapamil 0.05 mg kg$^{-1}$ (group A) or 0.1 mg kg$^{-1}$ (group B) as a single rapid i.v. injection. MAP, monitored via a radial artery cannula, was recorded before injection of verapamil and then for 6 min after administration of the drug. HR was calculated from a 15-s portion of the electrocardiogram (ECG). All measurements were completed before skin incision.

Part 2
Thirty normotensive patients were allocated randomly into three groups of 10. Premedication comprised diazepam 0.1 mg kg$^{-1}$ orally and atropine 0.01 mg kg$^{-1}$ i.m. 60 and 30 min, respectively, before induction of anaesthesia.

In the operating room, a radial arterial cannula was inserted under local anaesthesia for continuous monitoring of MAP. HR was calculated from 15-s portions of lead II of the ECG. After a 10-min stabilization period, the patients breathed 100% oxygen via a mask for 3 min. Immediately before induction of anaesthesia, MAP and HR were re-
corded by an independent observer. Anaesthesia was induced with thiopentone 5 mg kg\(^{-1}\) followed by vecuronium 0.2 mg kg\(^{-1}\) to facilitate tracheal intubation. Direct laryngoscopy was attempted 2 min after induction, and tracheal intubation was completed within 30 s in all patients, with the aid of a standard Macintosh laryngoscope blade. Verapamil 0.05 mg kg\(^{-1}\) (group D), verapamil 0.1 mg kg\(^{-1}\) (group E) or saline (group C) was injected 45 s before direct laryngoscopy was commenced (75 s after induction). All tracheal intubations were performed by the first author, who was blinded to the nature of the injection. After induction of anaesthesia, ventilation of the lungs was assisted as required or controlled with 1.0% enflurane and 50% nitrous oxide in oxygen and \(PECO_2\) was maintained at 4.1–4.9 kPa. \(PECO_2\) was measured by means of a catheter placed in the nostril until after insertion of the tracheal tube, when sampling took place from a T-piece connected to the tube. Further measurements were taken at 1, 2, 2.5, 2.75, 3, 3.5, 4, 4.5 and 5 min after induction. MAP, HR, and rate–pressure product (RPP) were compared with corresponding measurements among the three groups (C–E) and with preinduction measurements within the same group.

**Statistical analysis**

Data were analysed by analysis of variance followed by multiple \(t\) test with Bonferroni correction when indicated using the super ANOVA (Abacus Concepts, Inc., CA, 1989) computer software package. \(P < 0.05\) was deemed significant.

**RESULTS**

The five groups were comparable in age, weight and gender (Table I).

**Part 1**

MAP decreased significantly after verapamil in a dose dependent manner 20 s after administration, reached its minimum after 90 s and a return toward control was apparent by 4 min (Fig. 1). HR increased slightly but significantly, but there was no difference between the two doses. Confidence intervals (95%) for these haemodynamic variables are summarized in Table II.
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**Table II.** Confidence intervals (95%) of means of haemodynamic variables in Part 1. For clarity, only eight points are shown. A = Verapamil 0.05 mg kg\(^{-1}\) i.v.; B = verapamil 0.1 mg kg\(^{-1}\) i.v. \(P < 0.05\): + group A compared with group B; * compared with basal values within groups

<table>
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<tr>
<th>Time after administration of verapamil (min)</th>
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<td>A</td>
<td>92-104</td>
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<td>66-78*+</td>
<td>64-76*+</td>
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HR (beat min\(^{-1}\))

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**Fig. 2.** Mean (SEM) changes in mean arterial pressure (MAP) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation, after verapamil 0.05 mg kg\(^{-1}\) (●), 0.1 mg kg\(^{-1}\) (○) or saline (control) (■) administered i.v. 45 s before starting laryngoscopy. Arrow indicates injection of saline or verapamil and the stippled area indicates duration of laryngoscopy and tracheal intubation. \(P < 0.05\): * compared with control; † 0.05 mg kg\(^{-1}\) compared with 0.1 mg kg\(^{-1}\).

**Part 2**

There was no significant difference in MAP immediately before the start of laryngoscopy or before induction between the three groups (Fig. 2). In response to laryngoscopy and tracheal intubation, MAP increased significantly in all groups, but the increase was significantly less in the verapamil-treated groups than in the control group. The larger dose of verapamil was associated with significantly greater attenuation of MAP than the smaller dose. HR increased after induction of anaesthesia and immediately after tracheal intubation in all three groups, and there was no significant difference between the groups (Fig. 3). After laryngoscopy and tracheal intubation, RPP was significantly smaller in both verapamil-treated groups than in the control group (Fig. 4). Verapamil 0.1 mg kg\(^{-1}\) had a greater inhibitory effect than 0.05 mg kg\(^{-1}\) on the increase in RPP after tracheal intubation. Confidence limits (95%) for these haemodynamic variables are summarized in table III.

No patient was sufficiently hypotensive to require pressor drugs. The least MAP was 60 mm Hg (systolic 82 mm Hg, diastolic 49 mm Hg). No abnormal ECG was observed in any patient.

**DISCUSSION**

We have found that verapamil 0.05 mg kg\(^{-1}\) and 0.1 mg kg\(^{-1}\) attenuated the increases in MAP and RPP after tracheal intubation; the inhibitory effect was greater with the larger dose. The maximum mean RPP after tracheal intubation in the group given verapamil 0.1 mg kg\(^{-1}\) was 14892 mm Hg beat min\(^{-1}\). This value compares favourably with those seen in patients given prostaglandin E\(_1\) [5] and buprenorphine [9]. However, this RPP value is greater than normal and indicates that the use of verapamil before intubation may not have a myocardial oxygen-sparing effect.

Since the report by Hass and Hartfelder [10] in which verapamil was shown to be a putative coronary vasodilator with negative inotropic and chronotropic
Saline or Verapamil

**Fig. 3.** Mean (SEM) changes in heart rate (HR) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation, after verapamil 0.05 mg kg\(^{-1}\) (○), 0.1 mg kg\(^{-1}\) (□) or saline (control) (●). Stippled area denotes duration of laryngoscopy and tracheal intubation. No difference among the three groups at any time. *P < 0.05 compared with basal value within group.

**Fig. 4.** Mean (SEM) changes in rate-pressure product (RPP) after thiopentone-vecuronium and in response to laryngoscopy and tracheal intubation, after verapamil 0.05 mg kg\(^{-1}\) (○), 0.1 mg kg\(^{-1}\) (□) or saline (control) (●). Stippled area denotes duration of laryngoscopy and tracheal intubation. *P < 0.05: * compared with control; †0.05 mg kg\(^{-1}\) compared with 0.1 mg kg\(^{-1}\).

effects, it has been used for treatment of supraventricular tachyarrhythmias [11]. Although the principal pharmacological effect of verapamil is on the sinoatrial and atiroventricular nodes, it also possesses vasodilating properties, in particular when administered i.v., making it useful in the treatment of angina pectoris and hypertension [11]. Verapamil dilates coronary [11], renal and hepatic arteries [12] and it is likely that these effects are advantageous.

In common with other vasodilators, verapamil failed to prevent tachycardia caused by laryngoscopy and intubation, despite the direct negative chronotropic effect of the agent which was masked by reflex sympathetic cardiac compensation induced by peripheral vasodilatation. This lack of effect limits its usefulness, because HR is a major determinant of myocardial oxygen supply.

The onset and duration of action of verapamil were rapid and transient, similar to the effects of other calcium channel blockers and vasodilators. No patient in the current study had severe hypotension with either of the two doses. The least MAP in our
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study was 60 mm Hg (systolic 82 mm Hg, diastolic 49 mm Hg). The 95% confidence interval of the mean MAP 1.5 min after the administration of verapamil was 64–76 mm Hg in the group given 0.1 mg kg⁻¹. If the “true” value of the mean MAP was 64 mm Hg, there may have been a few patients with an MAP less than 50 mm Hg, which may be hazardous even for ASA I patients. Khan and colleagues reported that a bolus injection of verapamil 0.05–0.075 mg kg⁻¹ produced dose-dependent reductions in MAP in ASA I patients undergoing general anaesthesia [13]. Thus using verapamil 0.05 mg kg⁻¹ may be safer than 0.1 mg kg⁻¹.

A single i.v. administration of verapamil 5–10 mg has been shown to decrease arterial pressure in hypertensive patients at rest and during exercise [14, 15]. The magnitude of arterial pressure decrease caused by a given dose of verapamil is greater in hypertensive than in normotensive subjects [14, 15] and is enhanced by volatile anaesthetics [16]. It is possible that this technique may be useful in hypertensive patients.

REFERENCES


### Table III. Confidence intervals (95%) of means of haemodynamic variables in Part 2. Laryngoscopy for tracheal intubation lasting 30 s was started 2 min after thiopentone-vecuronium. For clarity, only six points are shown. C = Saline i.v. (control); D = verapamil 0.05 mg kg⁻¹ i.v.; E = verapamil 0.1 mg kg⁻¹ i.v. P < 0.05 : * compared with group C; † group E compared with group D

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