J Anesth (1994) 8:163–166

Journal of
Anesthesia

Effects of combined intravenous nicardipine and diltiazem administration on the circulatory response to laryngoscopy and tracheal intubation

Shin-Ichi Nakao, Kiichi Hirota, Jiro Kurata, Kenji Watanabe, Masahiro Murakawa, Toshiyuki Arai, and Kenjiro Mori

Department of Anesthesia, Kyoto University Hospital, Kawara-cho 54, Shogoin, Sakyo-ku, Kyoto, 606 Japan

Abstract: To evaluate the effect of combined intravenous administration of the calcium antagonists, nicardipine and diltiazem, on the circulatory responses to tracheal intubation, the mean arterial pressure (MAP) and rate pressure product (RPP) in response to laryngoscopy following tracheal intubation were compared in patients receiving saline placebo or nicardipine 10 $\mu g \cdot kg^{-1}$ and diltiazem 0.1 $mg \cdot kg^{-1}$ 60 s before the initiation of laryngoscopy. Each group was comprised of ten patients undergoing elective surgery. The patients receiving saline showed a significant increase in MAP and RPP associated with tracheal intubation. However, these increases were significantly attenuated ($P < 0.05$) in the patients to whom nicardipine and diltiazem were administered concurrently.

Key words: controlled hypotension, nicardipine, diltiazem, intubation, laryngoscopy

Introduction

Direct laryngoscopy and tracheal intubation induce a significant increase in blood pressure and heart rate (HR) resulting from increased sympathetic nerve activity [1,2]. These hemodynamic changes may give rise to major complications such as acute myocardial infarction and left ventricular failure, especially in patients with coronary artery disease. Pharmacologic approaches, including nitroglycerine [3], isosorbide dinitrate [4], nicardipine [5] and diltiazem [6], have been used to attenuate the pressor response to laryngoscopy and subsequent tracheal intubation.

Both nicardipine and diltiazem are calcium antagonists. Recent studies by Mikawa et al. have suggested that a bolus injection of nicardipine alone [5] or diltiazem alone [6] is highly effective for attenuating the pressor response to laryngoscopy and tracheal intubation. However, the respective advantages and adverse effects differ since their characteristics are quite different, nicardipine (a dihydropyridine derivative) is a more potent vasodilator in vivo and in vitro than diltiazem [7], and thus its hypotensive effect is also more potent. The resulting decrease in arterial blood pressure elicits sympathetic reflexes, which frequently induce tachycardia [7]. On the other hand, diltiazem, which has a rather weak hypotensive effect, has a potent intrinsic negative chronotropic and dromotropic effect [8], and therefore, responsive tachycardia rarely occurs. However, at high doses, diltiazem may cause severe heart block [9].

The present study was undertaken to evaluate the effect of combined intravenous administration of nicardipine and diltiazem at lowered doses [5,6] on the hemodynamic response to laryngoscopy and tracheal intubation.

Patients and methods

The study protocol was approved by the Ethical Committee of the Medical Faculty, Kyoto University. Informed consent was obtained from all patients.

Twenty patients (ASA I-II) without known heart disease or hypertension, and who were scheduled for noncardiac operations, were studied. The patients were divided randomly into two groups. Table 1 shows the patients' profiles. Preanesthetic medication consisted of oral diazepam (5–10 mg) and intramuscular atropine (0.5 mg) 60 min before induction of anesthesia. The experimental protocol is shown in Fig. 1.

On arrival at the operating room, a radial artery catheter was placed for continuous monitoring of mean arterial pressure (MAP). The ECG lead II was monitored continuously, and heart rate (HR) was calculated from

Address correspondence to: S. Nakao
Received for publication on April 22, 1993; accepted on August 20, 1993

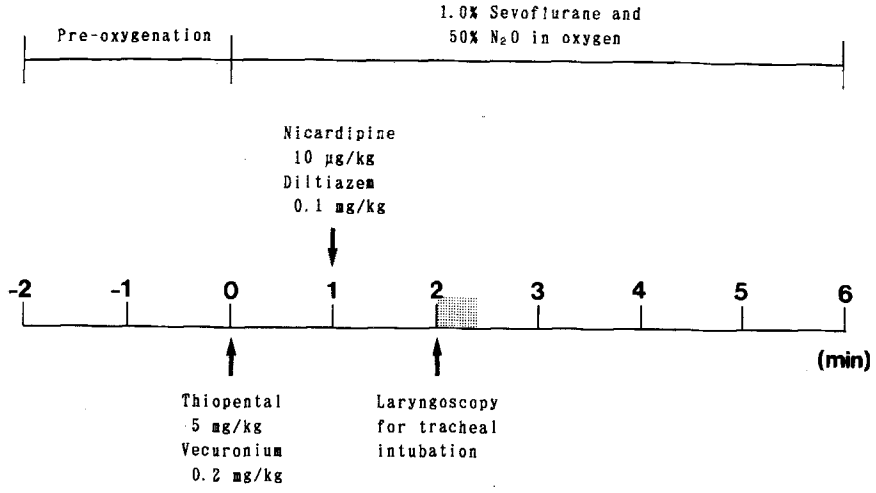

Fig. 1. Schematic diagram of the protocol for the study of the effects of combined intravenous nicardipine and diltiazem administration on the hemodynamic responses to laryngoscopy and tracheal intubation

a 15-s portion of the record obtained. After stabilization of blood pressure and HR, while breathing 100% oxygen, all patients received thiopental 5 mg·kg^{-1} followed by vecuronium 0.2 mg·kg^{-1} to facilitate tracheal intubation. Ventilation was controlled via mask with 1% sevoflurane and 50% nitrous oxide in oxygen. Two minutes after the administration of thiopental and vecuronium, direct laryngoscopy was begun and tracheal intubation was completed within 25 s. Intubations were performed by the same anesthesiologist. Nicardipine 10 μg·kg^{-1} and diltiazem 0.1 mg·kg^{-1} (ND group) or saline (control group) was injected 60 s (1 min after thiopental-vecuronium) before the start of laryngoscopy. The doses of the calcium antagonists and the time of drug administration were determined according to the reports by Mikawa et al. [5,6]. Serial HR and AP measurements were obtained before induction (at 0 time) and at 30, 60, 90, 120, 155, 175, 205, 265, and 325 s after induction.

Data were expressed as the mean ± SEM and analyzed statistically by Bonferroni's multiple comparison after repeated-measures analysis of variance and by unpaired *t*-test for comparison of the groups that were given saline (control) or nicardipine and diltiazem Differences at $P < 0.05$ were considered statistically significant.

Results

Figures 2 and 3 show MAP and RPP changes during and after tracheal intubation with nicardipine and diltiazem or saline administration 1 min before the start of laryngoscopy. Decreases in MAP and RPP 1 min after thiopental-vecuronium (just before the administration of nicardipine and diltiazem) were similar in both groups. The MAP and RPP of the ND group 1 min after administration of nicardipine and diltiazem (just before the start of laryngoscopy) were significantly low compared with those of the control group. Compared to the preinduction values (0 time), both MAP and RPP after tracheal intubation were significantly higher in both groups. However, the increase in MAP at 35, 55, 85, 145, and 205 s and in RPP at 35, 55, and 85 s after the start of laryngoscopy were significantly attenuated by the combined use of nicardipine and diltiazem.

During the study, no patients experienced arrhythmias or severe hypotension necessitating the use of pressor drugs.

Discussion

When using vasodilating agents for attenuating the pressor response with tracheal intubation, the time of the peak effect should correspond to that of the pressor response. Although both nicardipine and diltiazem began to decrease MAP 20–40 s after venous administration, nicardipine showed a minimum value at 2 min, and diltiazem showed a minimum value at 1.5 min [5,6]. We have confirmed these results in another study (data not shown). On the other hand, Stoelting reported that arterial pressure began to increase about 15 s after laryngoscopy, and was maximal after 30 to 45 s [10]. Thus, it is reasonable to administer nicardipine and diltiazem 1 min before the start of laryngoscopy to attenuate the pressor response.

Mikawa et al. have already reported that nicardipine [5] or diltiazem alone [6] are effective for attenuating the pressor response after tracheal intubation. Although the hypotensive effect of nicardipine is potent, the tendency to induce responsive tachycardia has been a cause of concern. Despite the intrinsic negative chronotropic effect of diltiazem, its potency to induce hypotension is rather low and a high dose of diltiazem may cause severe heart block, especially in the elderly

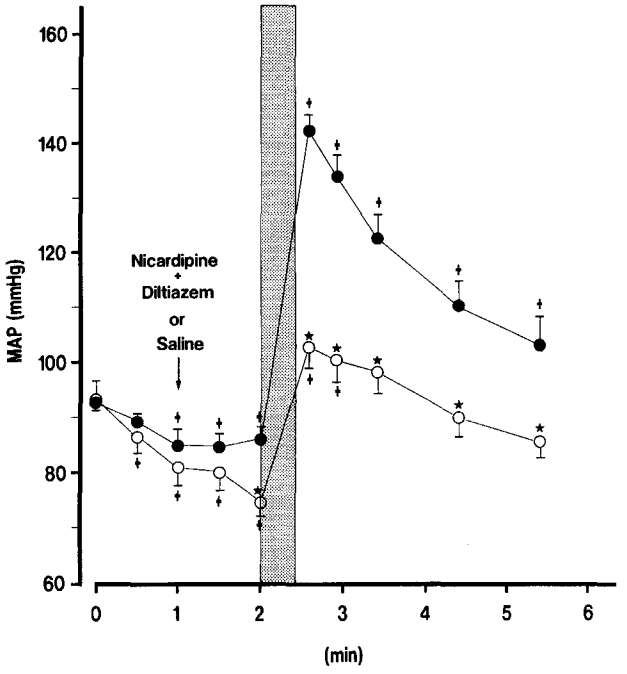

Fig. 2. Changes in mean arterial pressure (MAP) after thiopental-vecuronium and in response to direct laryngoscopy and tracheal intubation with saline (*open circles*) or with nicardipine and diltiazem (*closed circles*). The *shaded area* represents the duration of laryngoscopy for tracheal intubation. $^{+}P < 0.05$ significantly different from the value at 0 time (Bonferroni's multiple comparison after the repeated-measure analysis of variance). $^{*}P < 0.05$ significantly different from the control group (unpaired *t*-test)

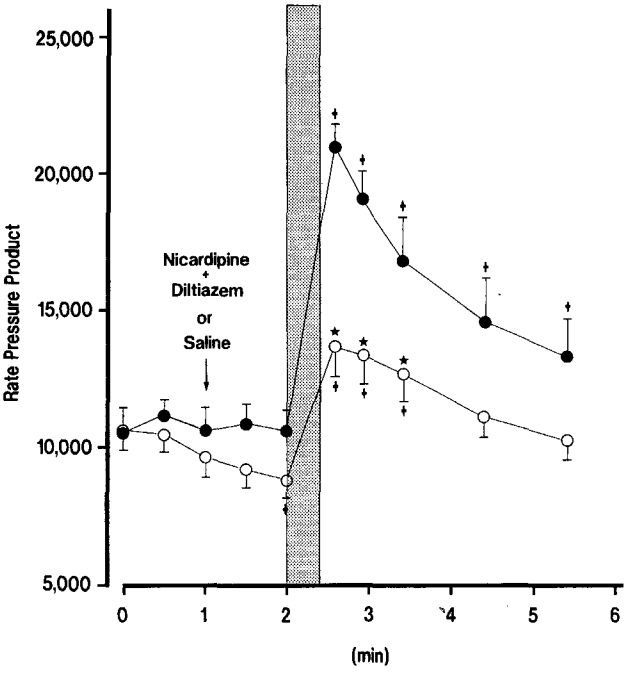

Fig. 3. Changes in rate pressure product after thiopental-vecuronium and in response to direct laryngoscopy and tracheal intubation with saline (*open circles*) or with nicardipine and diltiazem (*closed circles*). The *shaded area* represents the duration of laryngoscopy for tracheal intubation. $^{+}P < 0.05$ significantly different from the value at 0 time. $^{*}P < 0.05$ significantly different from the control group

or in patients with heart disease. Thus, it seems reasonable to use lower doses of both drugs in combination. In fact, combination therapy using nifedipine, a dihydropyridine derivative, and diltiazem was reported to be more effective in patients who did not respond to nifedipine or diltiazem alone with respect to anginal and exercise variables, and in reducing blood pressure [11]. Moreover, in an in vitro study, diltiazem had a positive allosteric effect on dihydropyridine derivatives such as nicardipine [12]. In the present study, the doses of nicardipine and diltiazem were less than half of those used by Mikawa et al. [5,6]. The increase in not only MAP but also RPP after tracheal intubation was significantly attenuated in the ND group. Although there was no significant difference in HR between the control and the ND groups after laryngoscopy and tracheal intubation (data not shown), the increase of HR in the ND group tended to be less than that in the control group. This tendency may be mainly due to the effects of diltiazem. Both MAP and RPP just before tracheal intubation (1 min after nicardipine and diltiazem administration) were decreased significantly in the ND group, but the effect was not severe enough to require treatment with pressor drugs.

In conclusion, combined intravenous administration of nicardipine and diltiazem is a safe, practical, and highly effective means of attenuating the pressor response to laryngoscopy and tracheal intubation.

References

1. Prys-Roberts C, Greene LT, Meloche R, et al. (1971) Studies of anaesthesia in relation to hypertension. II: Hemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 43:531–541
2. Forbes AM, Dally FG (1970) Acute hypertension during induction of anaesthesia and endotracheal intubation in normotensive man. Br J Anaesth 42:618–624
3. Fassoulaski A, Kaniaris P (1983) Intranasal administration of nitroglycerine attenuates the pressor response to laryngoscopy and intubation of the trachea. Br J Anaesth 55:49–52
4. Hatano Y, Imai R, Komatsu K, et al. (1989) Intravenous administration of isosorbide dinitrate attenuates the pressor response to laryngoscopy and tracheal intubation. Acta Anaesthesiol Scand 33:214–218
5. Mikawa K, Obara H, Kusunoki M (1990) Effect of nicardipine on the cardiovascular response to tracheal intubation. Br J Anaesth 64:240–242
6. Mikawa K, Ikegaki N, Maekawa R, et al. (1990) The effect of diltiazem on the cardiovascular response to tracheal intubation. Anaesthesia 45:289–293

7. Murad F (1990) Drugs used for the treatment of angina: organic nitrates, calcium-channel blockers, and β-adrenergic antagonists. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds) The pharmacological basis of therapeutics. Macmillan, New York, pp 764–783
8. Fujimoto T, Peter T, Mandel WJ (1981) Electrophysiologic and hemodynamic actions of diltiazem: Disparate temporal effects shown by experimental dose-response studies. Am Heart J 101:403–407
9. Kates RA, Zaggy AP, Norfleet EA, et al. (1984) Comparative cardiovascular effects of verapamil, nifedipine, and diltiazem during halothane anesthesia in swine. Anesthesiology 61:10–18
10. Stoelting RK (1977) Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. Anesthesiology 47:381–383
11. Frishman W, Charlap S, Kimmel B, et al. (1988) Diltiazem, nifedipine, and their combination in patients with stable angina pectoris: effects on angina, exercise tolerance, and the ambulatory electrocardiographic ST segment. Circulation 77:774–786
12. Garcia ML, King VF, Siegl PKS, et al. (1986) Binding of Ca^{2+} entry blockers to cardiac sarcolemmal membrane vasicles. J Biol Chem 261:8146–8157