HAEMODYNAMIC EFFECTS OF NICARDIPINE HYDROCHLORIDE
Studies during its use to control acute hypertension in anaesthetized patients

Y. KISHI, F. OKUMURA AND H. FURUYA

SUMMARY
Fourteen patients with vascular disease were studied to evaluate the efficacy of nicardipine hydrochloride as a hypotensive agent in the treatment of acute hypertension occurring during anaesthesia. Five patients received a bolus injection of nicardipine hydrochloride 0.5 mg. Another nine patients received bolus injections of nicardipine 1 and 2 mg. Nicardipine 0.5 mg significantly decreased systemic arterial pressure (by about 24%), systemic vascular resistance (SVR), left ventricular stroke work index (LVSWI) and rate-pressure product (RPP). Nicardipine 1 or 2 mg had twice the effect in decreasing arterial pressure as did 0.5 mg, without significant change in heart rate or right and left ventricular filling pressures. Cardiac index and stroke volume index increased and SVR, pulmonary vascular resistance, LVSWI and RPP decreased significantly.

Nicardipine hydrochloride (2,6-dimethyl-4(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2-(N-benzyl-N-methylamino))-ethyl ester 5-methyl ester hydrochloride) is a new calcium entry blocker with potent vasodilatory and hypotensive properties. Nicardipine is about 100 times more potent than papaverine in causing cerebral and coronary vasodilatation and appears to act directly on vascular smooth muscle cells without involving specific receptors such as alpha- or beta-adrenergic, cholinergic, and adenosine receptors (Takenaka et al., 1976). The mechanism of the vasodilator action of nicardipine is thought to be by means of interference with Ca²⁺ influx (Endoh, Yanagisawa and Taira, 1980; Terai, Takenaka and Maeno, 1981).

Nicardipine is a water soluble and light insensitive dihydropyridine derivative (Iwanami et al., 1979) and a preparation for i.v. use became available recently. The duration of action is short and, since complications such as severe hypotension or disturbances of atrio-ventricular conduction do not occur frequently (Seki and Takenaka, 1977), nicardipine might be useful in the management of acute hypertension occurring during anaesthesia.

The haemodynamic effects of nicardipine i.v. have been studied in anaesthetized patients during vascular surgery.

PATIENTS AND METHODS
Fourteen patients (13 male) with vascular disease were studied during vascular surgery. Their ages ranged from 13 to 74 yr. Eight patients had a history of hypertension and were receiving antihypertensive medication: trichlormethiazide, nifedipine and methyldopa. These were discontinued 24 h before surgery to avoid any interaction between these drugs and nicardipine. ECG studies confirmed the absence of myocardial infarction in all patients. No patient had congestive heart failure. Informed consent was obtained from each patient before surgery.

All patients were premedicated with atropine 0.5 mg and pethidine 50 mg i.m. 45 min before arrival in the operation theatre. Anaesthesia was induced with thiamylal, and pancuronium was given to facilitate trachea intubation. Ventilation was controlled to maintain PaO₂ above 13.3 kPa and Paco₂ at approximately 5.3 kPa. Anaesthesia was maintained with 60% nitrous oxide and increments of fentanyl and diazepam.

When the systolic arterial pressure (SAP) increased by 50% more than its preoperative value, or was more than 180 mm Hg despite the administration of fentanyl 20 μg kg⁻¹ and diazepam 20 mg, haemodynamic measurements were performed (control).

In the initial study, nicardipine 0.5 mg was administered to five anaesthetized patients and the general haemodynamic effects noted. Following the control measurements, a bolus of 0.5 mg was administered and a second series of measurements obtained once SAP had attained its lowest value.
In the subsequent study, nicardipine 1 and 2 mg was administered to nine patients during anaesthesia to determine the dose which would decrease systemic arterial pressure to its preoperative value. Nicardipine 1 mg (bolus) was administered following the control measurements. The second series of measurements was obtained as described for nicardipine 0.5 mg. The third series of measurements was obtained once SAP had returned to control. Nicardipine 2 mg (bolus) was then administered to seven of the nine patients; because of massive bleeding the study was discontinued in two patients. Haemodynamic measurements were obtained once SAP had reached its lowest value.

A 20-gauge cannula was inserted to a radial artery for measurement of the systemic arterial pressure and a triple-lumen thermodilution pulmonary artery catheter (Edwards) placed in a pulmonary artery via the right internal jugular vein. Pressure was measured with calibrated pressure transducers (Hewlett-Packard 1280C) and an eight-channel amplifying system (Hewlett-Packard). Cardiac output was determined in duplicate by thermodilution (Hewlett-Packard 78231C).

Measurements included heart rate (HR), SAP, mean arterial pressure (MAP), diastolic arterial pressure (DAP), mean pulmonary arterial pressure (MPAP), mean pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP) and cardiac output (CO). Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI), right ventricular stroke work index (RVSWI) and rate–pressure product (RPP) were derived using standard formulae.

This study was not conducted within 1 h of the commencement of surgery, nor during the period of aortic cross-clamping.

Statistical analysis was performed to compare the results with the control, using the paired Student’s t-test.

<p>| TABLE 1. Summary of haemodynamic findings (mean ± SD). Abbreviations: HR = heart rate; SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure; PCWP = mean pulmonary arterial wedge pressure; RAP = right atrial pressure; CI = cardiac index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; LVSWI = left ventricular stroke work index; RVSWI = right ventricular stroke work index; RPP = rate–pressure product. *P &lt; 0.05; **P &lt; 0.01; ***P &lt; 0.001 compared with control |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>Nicardipine 0.5 mg</th>
<th>Control</th>
<th>Nicardipine 1 mg</th>
<th>Recovery</th>
<th>Nicardipine 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>75 ± 9</td>
<td>75 ± 8</td>
<td>79 ± 10</td>
<td>79 ± 9</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>187 ± 11</td>
<td>157 ± 26*</td>
<td>189 ± 11</td>
<td>125 ± 15***</td>
<td>183 ± 4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>137 ± 5</td>
<td>113 ± 10**</td>
<td>137 ± 9</td>
<td>89 ± 13***</td>
<td>128 ± 9*</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>95 ± 6</td>
<td>78 ± 5*</td>
<td>101 ± 10</td>
<td>65 ± 11***</td>
<td>91 ± 11**</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>13 ± 5</td>
<td>12 ± 5</td>
<td>11 ± 3</td>
<td>9 ± 4</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>19 ± 5</td>
<td>19 ± 7</td>
<td>19 ± 4</td>
<td>16 ± 3</td>
<td>18 ± 3</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>7 ± 3</td>
<td>7 ± 3</td>
<td>7 ± 2</td>
<td>6 ± 2</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td>3.40 ± 0.60</td>
<td>3.68 ± 0.51</td>
<td>2.80 ± 0.43</td>
<td>3.47 ± 0.59***</td>
<td>3.17 ± 0.79</td>
</tr>
<tr>
<td>SVI (ml m⁻²)</td>
<td>45.3 ± 7.2</td>
<td>49.1 ± 3.6</td>
<td>36.0 ± 7.3</td>
<td>44.5 ± 8.1**</td>
<td>38.8 ± 6.3</td>
</tr>
<tr>
<td>SVR (dyn cm⁻⁵)</td>
<td>2001 ± 402</td>
<td>1406 ± 232*</td>
<td>2484 ± 505</td>
<td>1261 ± 301***</td>
<td>2108 ± 575*</td>
</tr>
<tr>
<td>PVR (dyn cm⁻⁵)</td>
<td>96 ± 46</td>
<td>87 ± 41</td>
<td>161 ± 69</td>
<td>110 ± 50***</td>
<td>125 ± 23*</td>
</tr>
<tr>
<td>LVSWI (g m⁻²)</td>
<td>76.3 ± 11.1</td>
<td>67.0 ± 6.7*</td>
<td>61.4 ± 12.2</td>
<td>47.8 ± 11.6**</td>
<td>62.0 ± 10.8</td>
</tr>
<tr>
<td>RVSWI (g m⁻²)</td>
<td>7.7 ± 2.7</td>
<td>8.1 ± 3.5</td>
<td>6.2 ± 2.5</td>
<td>6.0 ± 2.1</td>
<td>5.9 ± 1.5</td>
</tr>
<tr>
<td>RPP</td>
<td>14062 ± 1644</td>
<td>11689 ± 1370*</td>
<td>14914 ± 2074</td>
<td>9912 ± 1966***</td>
<td>14905 ± 2425</td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>
RESULTS
Haemodynamic results are summarized in table I. Nicardipine 0.5 mg decreased SAP by about 17%, and nicardipine 1 and 2 mg decreased SAP and DAP by about 35%: the maximum effects being evident about 2.5 min after administration. The period required for SAP to return to its control value was 7 min following nicardipine 0.5 mg, and 23 min and 19 min for nicardipine 1 and 2 mg, respectively (fig. 1). Severe hypotension was not observed. Nicardipine 1 and 2 mg significantly decreased SVR, PVR, LVSWI and RPP. CI was increased as a result of a significant increase in SVI (fig. 2). Nicardipine 1 and 2 mg did not affect HR, PCWP, MPAP or RAP (fig. 2). Although SAP returned to the control value after nicardipine 1 mg, MAP, DAP, SVR and PVR were significantly less than the control. There were no significant differences between the effects produced by nicardipine 1 or 2 mg. Nicardipine 0.5 mg significantly decreased SVR, LVSWI and RPP. However, these changes were less marked than those obtained following nicardipine 1 or 2 mg.

DISCUSSION
Nicardipine acts on the cardiovascular system by inhibiting the influx of Ca²⁺ (Endoh, Yanagisawa and Taira, 1980; Terai, Takenaka and Maeda, 1981). Other investigators have showed that nicardipine has more effect on the peripheral vessels than on the heart (Seki and Takenaka, 1977).

FIG. 2. Effects of nicardipine on haemodynamic indices (mean ± SD). C = Control; R = recovery of systolic arterial pressure to control value; N1 and N2 = nicardipine hydrochloride 1 and 2 mg, respectively. *P<0.05; **P<0.01; ***P<0.001 compared with control.
Acute hypertension may increase the risk of acute left heart failure and cerebral accident, and the amount of bleeding from suture lines (Estafanous and Tarazi, 1980). Thus, it is necessary to control the systemic arterial pressure promptly and effectively. When used for this purpose, nicardipine decreased SAP and SVR with little influence on left or right ventricular filling pressures, indicating that nicardipine causes dilatation of arterioles with minimal effect on the venules. The onset of its action is rapid and its duration of action fairly short.

It could be expected that the decrease in SAP would induce a reflex increase in heart rate which could be detrimental to patients with coronary artery disease because of the increase in myocardial oxygen consumption. However, heart rate did not increase in this study. Previously, Satoh, Yanagisawa and Taira (1980) demonstrated that nicardipine decreased sinus rate and increased atrio-ventricular conduction time. The present study might also show a negative chronotropic effect of nicardipine.

A decrease in afterload contributed greatly to the increase in cardiac output and stroke volume. Therefore, the inotropic effect of nicardipine hydrochloride could not be evaluated.

Calcium entry blockers decrease increases pulmonary arterial pressures, but not normal pressure (Reves et al., 1982). In this study, nicardipine did not alter pulmonary arterial pressure. However, calculated pulmonary vascular resistance was decreased significantly. Further investigations are necessary to determine whether nicardipine specifically decreases pulmonary vascular resistance in normal lung.

An interaction between nicardipine and other drugs used for anaesthetic management should be considered, since general anaesthetics are usually cardiodепressants and vasodilators. These effects are at least in part related to interference with transmembrane and intracellular movement or translocation of Ca$^{2+}$, or both (Reves et al., 1982). Since halothane may influence the effect of nicardipine on haemodynamics more than fentanyl and diazepam (Reves et al., 1982), different results might be obtained under halothane anaesthesia. It is not clear whether nicardipine interacts with neuromuscular blockers, although there were no effects such as prolonged apnoea in this study.

The onset of action was similar to that with other calcium blockers (Stone et al., 1980). Nifedipine effects mainly arterioles, while the major effect of verapamil is on atrio-ventricular conduction (Reves et al., 1982). Nicardipine seems to have an effect intermediate between those of nifedipine and verapamil.

Nicardipine 10 and 20 µg kg$^{-1}$ administered i.v. produced a dose-dependent decrease in arterial pressure without depressing cardiac function in healthy awake volunteers (Seki and Takenaka, 1977). Therefore, we used 0.5 mg to examine the haemodynamic effects in anaesthetized patients. Nicardipine 1 mg decreased arterial pressure by 34%, which was sufficient to return arterial pressure to the preoperative value. Haemodynamic effects of 1 and 2 mg were almost identical. This suggests that there might be an element of tachyphylaxis.

REFERENCES


EFFETS HEMODYNAMIQUES DU CHLORHYDRATE DE NICARDIPINE
Etudes faites lors de son utilisation pour contrôler les accès hypertensifs chez les patients anesthésiés

RESUME
Quatorze patients vasculopathes ont été étudiés dans le but d'évaluer l'efficacité du chlorhydrate de nicardipine comme agent hypotenseur dans le traitement des accès hypertensifs per-opératoires. Cinq patients ont reçu une injection rapide de 0,5 mg de chlorhydrate de nicardipine. Neuf autres patients ont reçu des injections rapides de 1-2 mg de nicardipine. La dose de 0,5 mg de nicardipine diminuait significativement la pression artérielle systémique (d'environ 24%), les résistances vasculaires systémiques (RVS), l'index de travail systolique de ventricule gauche (ITTSVG) et le produit pression-fréquence (PPF). Les doses de 1 ou 2 mg de nicardipine diminuaient la pression artérielle deux fois plus que la dose de 0,5 mg sans modifier significativement la fréquence cardiaque, ni les pressions de remplissage des ventricules droit et gauche. L'index cardiaque et l'index d'éjection systolique augmentaient alors que les RVS, les résistances vasculaires pulmonaires, l'ITTSVG et le PPF diminuaient significativement.

HÄMODYNAMISCHE WIRKUNGEN VON NICARDIPIN-HYDROCHLORID
Studien während der Anwendung des Präparats zur Kontrolle akuter Hypertension bei narkotisierten Patienten

ZUSAMMENFASSUNG
Bei vierzehn gefäßerkrankten Patienten wurde die Wirksamkeit von Nicardipin-Hydrochlorid als hypotensaiver Wirkstoff bei der Behandlung akuter Hypertension während Narkosen untersucht. Fünf Patienten erhielten eine Bolusinjektion von 0,5 mg der Substanz, neun Patienten 1 und 2 mg. Die 0,5-mg Dosis führte zu einer signifikanten Abnahme von arteriellem Systemdruck (um etwa 24%), systemischem Gefäßwiderstand, linksventrikulärem stroke work index (LVSWI) und Frequenz–Druck-Produkt (RPP). Die 1- oder 2-mg Dosen senkten den arteriellen Druck etwa doppelt so stark wie die niedrigere Dosis, ohne signifikante Veränderung von Herzfrequenz oder der rechts- oder linksventrikulären Füllungsdrucks. Der Herzindex und der Schlagvolumenindex stiegen an, der systemische Gefäßwiderstand, der Lungengefäßeindex, LVSWI und RPP sanken signifikant ab.

EFECTOS HEMODINAMICOS DEL HIDROCLORURO DE NICARDIPINA
Estudios durante el uso para controlar la hipertensión en pacientes anestesiados

SUMARIO
Se hizo un estudio en catorce pacientes que padecían de enfermedad vascular con el objeto de evaluar la eficacia del hidrocloruro de nicardipina como agente hipotenso en el tratamiento de la hipertensión aguda que ocurre durante la anestesia. Se administró a cinco pacientes una inyección de bolo de 0,5 mg de hidrocloruro de nicardipina. Otros nueve pacientes recibieron inyecciones de bolo de 1 y 2 mg de nicardipina. Los 0,5 mg de nicardipina hicieron bajar de manera significante la presión arterial sistémica (de un 24% aproximadamente), la resistencia vascular sistémica (SVR), el índice del movimiento sistólico ventricular izquierdo (LVSWI) y el producto presión-rítmico (RPP). Las dosis de 1 ó 2 mg de nicardipina tuvieron un efecto doble del de las dosis de 0,5 mg al hacer bajar la presión arterial, pero sin provocar un cambio significativo en el ritmo cardíaco ni tampoco en las presiones de relleno de los ventrículos derecho e izquierdo. El índice cardíaco y el índice del volumen sistólico aumentaron, mientras que la SVR, la resistencia vascular pulmonar, el LVSWI y el RPP disminuyeron sensiblemente.