USE OF DILTIAZEM TO CONTROL CIRCULATORY FLUCTUATIONS DURING RESECTION OF A PHAEOCHROMOCYTOMA

H. TOKIOKA, T. TAKAHASHI, Y. KOSOGABE, Y. OHTA AND F. KOSAKA

The anaesthetic management of patients undergoing resection of a phaeochromocytoma has been improved by advances in monitoring [1], and by the introduction of new anaesthetic agents such as enflurane [2,3] and isoflurane [4,5]. Preoperative management with the α-blockers, phenoxybenzamine [6] and prazocine [7,8], has also contributed to the safety of anaesthesia. Even now, however, severe hypertension during the manipulation of the tumour and hypotension after its removal are hazardous and, at times, difficult to control.

Diltiazem, a benzothiazepine derivative, is a calcium channel blocking drug which decreases systemic arterial pressure by inducing arterial vasodilatation. In addition, it has an anti-arrhythmic action [9]. It may also interfere with the release of noradrenaline from adrenal medullary tissue [10] and attenuate the increase in arterial pressure in response to exogenous noradrenaline [11].

The purpose of this study was to evaluate the effects of diltiazem on circulatory stability during anaesthesia for the surgical removal of phaeochromocytoma.

PATIENTS AND METHODS

Three male and two female patients (37–66 yr) with a phaeochromocytoma were studied. The procedure was explained in detail and informed consent obtained. The diagnosis of phaeochromocytoma was confirmed by the detection of increased plasma and urinary concentrations of catecholamines. An abdominal computerized axial tomography scan revealed adrenal tumours. Hypertension was paroxysmal in three patients and sustained in two (table I). Phenoxybenzamine was not available in Japan, therefore all of the patients were pretreated with prazocine, labetalol or YM09538 (methylbenzensulphonamide hydrochloride) [12]. Hypertension was well controlled, except in patient No. 5. This patient received prazocine 12 mg and propranolol 30 mg per day although paroxysmal hypertension (systolic arterial pressure greater than 200 mm Hg) occurred at intervals of 1–2 days. The patients were premedicated with diazepam 10–20 mg given by mouth and were well sedated upon arrival at the operating room. The ECG was monitored, and a radial artery was cannulated. A flow-directed pulmonary artery catheter (American Edwards Laboratories) was inserted via the right internal jugular vein. Baseline measurements were made of heart rate (HR), mean arterial pressure (MAP),
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TABLE I. Preoperative data of five patients. NA = noradrenaline; A = adrenaline; YM09538 = methylbenzensulphonamide hydrochloride. Normal values: plasma NA 0.05-0.40 ng ml⁻¹; plasma A < 0.01 ng ml⁻¹; urine NA 10.0-90.0 g day⁻¹; urine A < 10.0 g day⁻¹

<table>
<thead>
<tr>
<th>Age (yr) and sex</th>
<th>Hypertension</th>
<th>Arterial pressure (mm Hg)</th>
<th>Heart rate (beat min⁻¹)</th>
<th>Preoperative medication (mg day⁻¹)</th>
<th>Plasma NA</th>
<th>Plasma A</th>
<th>Urine NA</th>
<th>Urine A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>66 M</td>
<td>Sustained</td>
<td>150-170/130-170</td>
<td>Prazocine 3 Nifedipine 30</td>
<td>0.06</td>
<td>0.01</td>
<td>201.7</td>
<td>30.7</td>
</tr>
<tr>
<td>Patient 2</td>
<td>55 M</td>
<td>Paroxysmal</td>
<td>130-170/80-110</td>
<td>Labetalol 100 Nifedipine 50</td>
<td>0.46</td>
<td>0.23</td>
<td>720.4</td>
<td>128.5</td>
</tr>
<tr>
<td>Patient 3</td>
<td>37 F</td>
<td>Paroxysmal</td>
<td>130-150/70-90</td>
<td>Labetalol 50 YM09538 50</td>
<td>0.53</td>
<td>0.01</td>
<td>1327.1</td>
<td>72.2</td>
</tr>
<tr>
<td>Patient 4</td>
<td>47 F</td>
<td>Paroxysmal</td>
<td>140-150/70-90</td>
<td>YM09538 50 Propranolol 30</td>
<td>0.63</td>
<td>0.05</td>
<td>1741.0</td>
<td>375.3</td>
</tr>
<tr>
<td>Patient 5</td>
<td>55 M</td>
<td>Sustained</td>
<td>160-170/100-110</td>
<td>Prazocine 12 Propranolol 30</td>
<td>—</td>
<td>—</td>
<td>3110.0</td>
<td>25.3</td>
</tr>
</tbody>
</table>

TABLE II. Haemodynamic data (means±SD). HR = heart rate (beat min⁻¹); MAP = mean arterial pressure (mm Hg); PAP = mean pulmonary artery pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); CI = cardiac index (litre min⁻¹ m⁻²); SVR = systemic vascular resistance (dyn s cm⁻⁵). *P < 0.05, baseline v. diltiazem

<table>
<thead>
<tr>
<th>HR</th>
<th>MAP</th>
<th>PAP</th>
<th>PCWP</th>
<th>CI</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>75 ± 8</td>
<td>111 ± 12</td>
<td>15 ± 3</td>
<td>10 ± 3</td>
<td>3.41 ± 0.80</td>
</tr>
<tr>
<td>Before anaesthesia with diltiazem</td>
<td>72 ± 6</td>
<td>96 ± 4</td>
<td>16 ± 4</td>
<td>8 ± 5</td>
<td>3.32 ± 0.55</td>
</tr>
<tr>
<td>After intubation</td>
<td>69 ± 5</td>
<td>74 ± 12</td>
<td>16 ± 4</td>
<td>10 ± 4</td>
<td>2.60 ± 0.39</td>
</tr>
<tr>
<td>After incision</td>
<td>73 ± 8</td>
<td>84 ± 15</td>
<td>20 ± 4</td>
<td>12 ± 4</td>
<td>2.41 ± 0.40</td>
</tr>
<tr>
<td>Tumour manipulation</td>
<td>79 ± 8</td>
<td>114 ± 25</td>
<td>23 ± 4</td>
<td>15 ± 4</td>
<td>2.92 ± 0.88</td>
</tr>
<tr>
<td>Tumour removal</td>
<td>74 ± 13</td>
<td>72 ± 12</td>
<td>15 ± 5</td>
<td>9 ± 4</td>
<td>2.17 ± 0.43</td>
</tr>
<tr>
<td>After anaesthesia</td>
<td>81 ± 13</td>
<td>106 ± 26</td>
<td>19 ± 3</td>
<td>11 ± 3</td>
<td>2.90 ± 0.95</td>
</tr>
</tbody>
</table>

mean pulmonary artery pressure (PAP), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP). Cardiac output was measured using the thermodilution technique. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated using standard formulae.

Diltiazem was administered i.v. at a rate of 3 μg kg⁻¹ min⁻¹. The PCWP was maintained at the baseline value by infusion of lactated Ringer's solution. When MAP was greater than 100 mm Hg, or SVR was greater than 1500 dyn s cm⁻⁵ 30 min after the start of diltiazem, the rate of infusion of diltiazem was increased to 6 μg kg⁻¹ min⁻¹. Once the circulation became stable, haemodynamic measurements were performed.

Anaesthesia was induced with 3–5% enfurane and nitrous oxide in oxygen (1:1) during the continuous infusion of diltiazem. Orotracheal intubation was facilitated with vecuronium (patients Nos 1 to 4) or pancuronium (patient No. 5). (Vecuronium is not commercially available in Japan.) Anaesthesia was maintained with 1–3% enfurane and 50% nitrous oxide in oxygen. Ventilation was controlled, and vecuronium or pancuronium given to provide continued neuromuscular blockade. Hypertension during the exploration of the abdomen was controlled by increasing the inspired concentration of enfurane or by increasing the infusion rate of diltiazem to 10 μg kg⁻¹ min⁻¹. If systolic arterial pressure remained greater than 200 mm Hg in spite of this treatment, phentolamine was administered. Propranolol was given if a tachyarrhythmia was noted. The infusion of diltiazem was continued until the draining vein from the tumour had been ligated. Hypotension, after removal of the tumour, was treated by the rapid infusion of fluid. At the end of surgery, neuromuscular block was antagonized with neostigmine 1.0 mg (and atropine
Haemodynamic measurements were performed before the infusion of diltiazem, during the infusion of diltiazem before anaesthesia, after intubation and before surgical incision, during exploration of the abdomen, during tumour manipulation, after removal of the tumour and once anaesthesia had been terminated.

All data are presented as the mean and standard deviation. Comparisons between baseline values and values during infusion of diltiazem were performed with the paired Student's t test. A P value of less than 0.05 was considered significant.

**RESULTS**

Haemodynamic data for the duration of the study are presented in table II, and details of observations during anaesthesia in table III.

Heart rate remained stable and was between 69 ± 5 and 79 ± 8 beat min⁻¹ during anaesthesia. There was no ventricular tachycardia. Propranolol was used only in patient No. 4, to treat ventricular premature beats.

Average MAP (fig. 1) decreased significantly from 111 ± 12 to 96 ± 4 mm Hg with diltiazem and increased to 114 ± 25 mm Hg during manipulation of the tumour (event 5). Peak systolic arterial pressures were 204 mm Hg, and 222 mm Hg (patients Nos 2 and 4, respectively), although they returned to less than 200 mm Hg within 1 min.

Total dose of phentolamine was 2 mg in patient No. 2, and 22 mg in patient No. 4. In the other three patients, peak systolic arterial pressure was below 200 mm Hg and phentolamine was not required. Average MAP decreased to 72 ± 12 mm Hg. The trachea was extubated and the patient transferred to the recovery room.
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Hg after removal of the tumour; no vasoconstrictive drugs or inotropic agents were required to treat the decrease in arterial pressure.

PAP and PCWP were stable during the infusion of diltiazem. Both values increased during manipulation of the tumour but returned to their baseline values after the removal of the tumour. Cardiac index did not change when diltiazem was administered initially, but decreased after the induction of anaesthesia with enflurane; it decreased further after the removal of the tumour before returning partially towards baseline once anaesthesia was discontinued.

Mean SVR (fig. 1) decreased significantly from 1674 ±304 to 1341 ±315 dyn s cm$^{-5}$ with diltiazem, increased after incision, reached 1831 ±437 dyn s cm$^{-5}$ during tumour manipulation and decreased after removal of the tumour.

All of the patients had an uneventful postoperative course.

DISCUSSION

The principal finding of this study was that diltiazem effectively minimized the changes in arterial pressure and heart rate. Arterial pressure was easy to control, and heart rate was remarkably stable. There were no serious ventricular premature beats.

The anaesthetic management during the removal of a phaeochromocytoma is sometimes difficult because of the fluctuations in arterial pressure and tachyarrhythmia. Increased secretion of catecholamines by the tumour results in vasoconstriction and a reduction in the circulating blood volume. Preoperative expansion of the plasma volume using an $\alpha$-blocker is the key to safe anaesthesia. Phenoxybenzamine has been the most useful drug and prazocine is now accepted in clinical use [7, 8]. We evaluated the preoperative haemodynamic state and tried to estimate the degree of vasoconstriction. In spite of the preoperative administration of an $\alpha$-blocker, SVR was increased. Therefore, we gave diltiazem at a rate of 3–6 $\mu$g kg$^{-1}$ min$^{-1}$ to reduce SVR. SVR decreased by 20%, to less than 1500 dyn s cm$^{-5}$ in four of the five patients. This expansion of the plasma volume decreased the cardiovascular changes evident during anaesthesia. Vasodilators given during surgery have also been recommended for the control of arterial pressure. Phentolamine is commonly used for the treatment of hypertensive episodes [3, 13]; however, it results in tachycardia and tachyphylaxis. Sodium nitroprusside [3-5], nitroglycerin [14], prostaglandin E$_1$ [15] and nicardipine [13] have also been used to control hypertension. However, the clinical efficacy of these drugs has not been systematically evaluated.

Diltiazem is a calcium channel blocker with an antihypertensive effect and an antiarrhythmic action. The hypotensive effect of diltiazem can be attributed not only to direct vasodilatation, but also to attenuation of the pressor effect of the catecholamines [11]. The hypotensive effect of the drug is noticeable within 1 min. When the infusion is stopped, recovery from the effects of diltiazem occurs in a few minutes. This rapid but reversible action is beneficial in the treatment of hypertensive crises.

It has also been demonstrated that the reflex tachycardia usually associated with a decrease in arterial pressure does not develop with diltiazem [9, 16]. In our patients heart rate decreased slightly with diltiazem. This stabilization of heart rate is important because patients with phaeochromocytoma readily become ischaemic, as a result of longstanding hypertension and catecholamine-induced cardiomyopathy [17].

The antiarrhythmic action is another benefit of diltiazem. Although concentrations of the catecholamines were not measured during surgery in our patients, they could, theoretically, have been 10 to 50 times greater than preoperative values [1, 3, 15]. Increases in adrenaline concentration can result in dangerous arrhythmias. However, propranolol was required, in only small doses, in one of the five patients. Many investigators have reported that diltiazem was effective as an antihypertensive or antiarrhythmic agent, although there have been no reports that diltiazem was administered to control the haemodynamics of patients with phaeochromocytoma.

Recently, several investigators reported a relationship between calcium channel blockers and catecholamine secretion from adrenal medullary tissue. Pinto and colleagues [18] reported that the calcium channel blocker methoxyverapamil inhibited the release of catecholamines from the adrenal medulla perfused in vitro. Serfas and co-workers [19] demonstrated that another calcium channel blocker, nifedipine, suppressed noradrenaline secretion by a phaeochromocytoma. On the other hand, Lenders and associates [20] and Favre and colleagues [21] reported that
nifedipine did not have a direct influence on catecholamine release from the tumour—although it might interfere with the action of catecholamines in patients with phaeochromocytoma. Hypertensive crises during surgery occur when catecholamines are suddenly released from the tumour in response to manipulation. Therefore, the interaction between calcium channel blockers and catecholamines may be beneficial in the treatment of hypertension.

Another problem is severe hypotension which may follow the removal of the tumour. This problem may result from the reduced circulating blood volume consequent upon the intense vasoconstriction and sudden vasodilatation following removal of the tumour and the resultant decrease in catecholamine concentration. Catecholamine-induced cardiomyopathy may induce further deterioration. In our patients, MAP decreased to 72 ± 12 mm Hg after removal of the tumour, but no positive inotropic agents or vasoconstrictive drugs were required. Our findings suggest that diltiazem produced enough vasodilatation to expand the circulating blood volume and attenuate the cardiovascular changes.

No side effects of diltiazem were observed in our study. However, diltiazem has a weak negative inotropic action and inhibitory effects on the atrioventricular node and the sinus node. Therefore, it may have adverse interactions with the β-adrenergic blocker, propranolol. Diltiazem should be given cautiously in the presence of pre-existing β-adrenergic blockade.

In conclusion, the continuous infusion of diltiazem, given before and during anaesthesia, attenuated the cardiovascular changes during surgery and appeared to play a useful role in the control of haemodynamic status in patients with a phaeochromocytoma.

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