HAEMODYNAMIC EFFECTS OF DILTIAZEM DURING FENTANYL–NITROUS OXIDE ANAESTHESIA†

An In Vivo Study in the Dog

R. M. GRIFFIN, I. DIMICH, R. JURADO AND J. A. KAPLAN

Diltiazem is a calcium channel blocking agent which is used in oral form for the treatment of variant [1] and classic stable angina [2]. Diltiazem is also available in a water soluble, non-light sensitive preparation and may be a useful drug for the management of hypertension, myocardial ischaemia and arrhythmia, in the peri-operative period. Several studies in animals [3–5] have described the use of diltiazem i.v. in association with volatile anaesthetic agents. However, patients with coronary artery disease who may benefit from intraoperative diltiazem therapy are likely to receive fentanyl as part or all of the anaesthetic technique. This study was designed to investigate the cardiovascular effects produced with different plasma concentrations of diltiazem during fentanyl–nitrous oxide anaesthesia.

METHODS

Six unpremedicated mongrel dogs weighing 22.2 ± 0.65 kg (mean ± SEM) were anaesthetized with sodium thiopentone 20 mg kg⁻¹ i.v. The trachea was intubated and ventilation was controlled with a constant volume ventilator using a mixture of 50% nitrous oxide and oxygen. Ventilatory rate and tidal volume were adjusted to maintain an arterial carbon dioxide tension of 4.7–5.3 kPa. An initial bolus of fentanyl 150 μg kg⁻¹ was given followed by a continuous infusion of fentanyl 1.5 μg kg⁻¹ min⁻¹. Pancuronium was given to ensure muscle paralysis. Oesophageal temperature was maintained between 37 and 39 °C with a warming mattress placed under the dog. Normovolaemia was maintained with a continuous infusion of lactated Ringer’s solution 5–10 ml kg⁻¹ h⁻¹ via a femoral vein. Electrocardiographic needle electrodes were placed on the limbs for continuous recording of heart rate and rhythm. Intermittent recording of the ECG at 50 mm s⁻¹ enabled determination of the PR interval. A 14-gauge polyethylene cannula (Intramedic) was threaded into a femoral artery to measure aortic pressure, and to permit intermittent blood sampling for blood-gas analysis (Corning Blood-Gas Analyser Model 165). A 7-French gauge thermodilution catheter was placed, via a femoral vein, in the pulmonary artery.

SUMMARY

The haemodynamic effects of diltiazem were studied in six dogs during fentanyl–nitrous oxide (in oxygen) anaesthesia. A bolus of diltiazem 300 μg kg⁻¹ was given, followed by infusions at 30, 60 and 90 μg kg⁻¹ min⁻¹ which produced plasma diltiazem concentrations of 392 ± 30, 908 ± 54 and 1483 ± 134 ng ml⁻¹, respectively. Diltiazem significantly reduced systemic vascular resistance index, mean arterial pressure, heart rate and PR interval. The decrease in afterload increased cardiac index, since there was little change in myocardial contractility (LV dP/dt). Five dogs developed second degree atrio-ventricular (AV) block in association with the highest dose. Administration of calcium chloride 20 mg kg⁻¹ did not reverse the haemodynamic or electrophysiological effects of diltiazem. Isoprenaline increased heart rate and restored sinus rhythm in four dogs with AV block.
Pulmonary artery pressure was monitored continuously and wedge pressure (PCWP) measured intermittently. Cardiac output was measured in triplicate (thermodilution) using an American Edwards Laboratories cardiac output computer (model 9520A). The heart was exposed through a median sternotomy and a catheter with a microtip pressure sensor (Millar Instruments, Inc., Model PC471), inserted into the left ventricle. Limb lead II of the electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), left ventricular pressure and electrically derived left ventricular contractile force (LV dP/dt) were displayed continuously on a Hewlett-Packard (model 7754B) four-channel oscillograph and recorded on a Hewlett-Packard (model 7755A) polygraph. Cardiac index (CI), stroke volume index (SVI), systemic and pulmonary vascular resistance indices (SVRI, PVRI) and left and right ventricular stroke work indices (LVSWI, RVSWI) were calculated using standard formulae.

Control measurements were taken 30 min after all instrumentation had been completed and repeated every 10 min until stable. An i.v. bolus of diltiazem 300 \( \mu g \) kg\(^{-1}\) was given over 2 min and the infusion of the lowest dose of diltiazem started. Diltiazem was administered at three infusion rates: 30 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) (D1), 60 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) (D2) and 90 \( \mu g \) kg\(^{-1}\) min\(^{-1}\) (D3). Each infusion period lasted for 30 min. Haemodynamic measurements were obtained 2 min after the bolus and, subsequently, at 5, 15 and 30 min during each infusion of diltiazem. Arterial blood samples were taken for the measurement of blood-gas tensions, the serum concentrations of sodium, potassium, total calcium and the haematocrit at the end of each infusion period. Blood for determination of plasma concentration of diltiazem was taken 2 min after the bolus and at the end of each infusion period. Plasma diltiazem and desacetyldiltiazem were measured by high pressure liquid chromatography. After the final infusion of diltiazem (D3), calcium chloride 20 mg kg\(^{-1}\) was given to each dog and measurements repeated 1 min later. Thereafter, each dog received isoprenaline 0.1 mg in 5 \% dextrose 100 ml as a continuous infusion of 5 \( \mu g \) min\(^{-1}\). Haemodynamic measurements were obtained after 5 min.

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<tr>
<th>Time from bolus of diltiazem (min) and stage in study</th>
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<td>0 Control</td>
<td>2</td>
<td>30</td>
<td>60</td>
<td>90</td>
<td>91</td>
<td>96</td>
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<tr>
<td>HR (beat min(^{-1}))</td>
<td>109±6.1</td>
<td>139±14.0</td>
<td>116±11.7</td>
<td>111±10.4</td>
<td>90±13.0*</td>
<td>73±11.8</td>
<td>99±3.34‡</td>
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<tr>
<td>PR (ms)</td>
<td>120±0</td>
<td>130±6</td>
<td>190±26*</td>
<td>213±21*</td>
<td>220±28*</td>
<td>220±22</td>
<td>208±23</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>105±7.3</td>
<td>82±5.5*</td>
<td>91±4.9*</td>
<td>80±3.6*</td>
<td>74±2.53*</td>
<td>75±3.12</td>
<td>72±3.54</td>
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<tr>
<td>PCWP (mm Hg)</td>
<td>11.5±0.76</td>
<td>11.6±0.88</td>
<td>12.8±1.13</td>
<td>14.3±0.80</td>
<td>15.1±1.10</td>
<td>15.2±1.39</td>
<td>15.6±2.29</td>
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<td>MPAP (mm Hg)</td>
<td>16.1±1.32</td>
<td>19.0±2.03</td>
<td>19.5±1.78</td>
<td>21.6±2.07</td>
<td>22.5±2.02</td>
<td>21.6±2.9</td>
<td>22.8±1.39</td>
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<td>RVMP (mm Hg)</td>
<td>9.0±1.23</td>
<td>9.3±1.72</td>
<td>9.6±1.25</td>
<td>10.5±1.52</td>
<td>11.6±1.47</td>
<td>12.6±1.96</td>
<td>11.8±2.0</td>
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<td>CI (litre min(^{-1}) m(^{-2}))</td>
<td>2.40±0.20</td>
<td>3.89±0.88</td>
<td>4.04±0.88*</td>
<td>4.67±0.95*</td>
<td>4.93±0.89*</td>
<td>5.35±1.08</td>
<td>5.52±0.64</td>
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<td>SVI (ml m(^{-2}))</td>
<td>22.6±3.06</td>
<td>27.9±4.82</td>
<td>34.1±4.71</td>
<td>40.6±5.24*</td>
<td>54.5±4.74*</td>
<td>76.9±6.16†</td>
<td>55.4±5.65‡</td>
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<tr>
<td>SVRI (dyn s cm(^{-5}) m(^{-2}))</td>
<td>3249±257</td>
<td>1685±164*</td>
<td>1830±207*</td>
<td>1399±208*</td>
<td>1138±148*</td>
<td>1071±129</td>
<td>906±85</td>
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<td>PVRI (dyn s cm(^{-5}) m(^{-2}))</td>
<td>161±34</td>
<td>170±36</td>
<td>150±29</td>
<td>143±37</td>
<td>125±22</td>
<td>93±17</td>
<td>107±23</td>
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<td>LVSWI (g m m(^{-2}))</td>
<td>29.2±5.27</td>
<td>28.1±6.82</td>
<td>36.9±6.41</td>
<td>37.1±6.1</td>
<td>43.9±4.3</td>
<td>64.9±5.4</td>
<td>43.5±6.3</td>
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<tr>
<td>RVSWI (g m m(^{-2}))</td>
<td>2.19±0.35</td>
<td>4.01±1.27</td>
<td>4.86±1.23</td>
<td>6.76±1.89</td>
<td>8.57±1.91</td>
<td>10.0±3.78</td>
<td>8.7±2.62</td>
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<tr>
<td>LV dP/dt (mm Hg s(^{-1}))</td>
<td>1886±217</td>
<td>1733±256</td>
<td>1800±282</td>
<td>1750±268</td>
<td>1783±175</td>
<td>2940±820</td>
<td>2080±177</td>
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<tr>
<td>Plasma diltiazem (ng ml(^{-1}))</td>
<td>363±73</td>
<td>392±30</td>
<td>908±54</td>
<td>1483±134</td>
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Repeated-measures analysis of variance with Bonferroni's correction was used to search for significant changes for each haemodynamic variable. Variables for which significance was found had subsequent measurements for each time point compared with control values using Fisher's least significant difference procedure. \( P < 0.05 \) was regarded as statistically significant.

**RESULTS**

The haemodynamic results and plasma concentrations of diltiazem are summarized in table I. MAP and SVRI were significantly reduced 2 min following the bolus injection of diltiazem (fig. 1). With increasing doses of diltiazem, SVRI was progressively reduced, reaching 35% of the control value at the end of D3. CI showed a progressive increase with the infusion of diltiazem, which became significant at the end of D1. Minimal depression of myocardial contractility (LV \( \frac{dP}{dt} \)) was observed. PCWP and LVSWI showed moderate increases with each infusion of diltiazem. HR increased following the bolus of diltiazem, but then decreased gradually to be significantly less than the control value during D3 (fig. 2). PR was significantly prolonged 5 min after the administration of diltiazem (fig. 2).

Five dogs developed first degree atrioventricular (AV) block, three of these during D1. All five dogs subsequently became established in second degree AV block, one during D1, two during D2 and two during D3. In addition, two dogs had episodes of slow junctional rhythm. Figure 3 shows the development of all these arrhythmias in one dog, in association with the increasing plasma concentrations of diltiazem. Calcium chloride significantly increased SVI,
but had no effect on the other measured or derived haemodynamic variables (figs 1, 2).

Calcium chloride had no effect on the conduction block produced by diltiazem. However, the infusion of isoprenaline increased HR significantly and restored sinus rhythm in four out of the five dogs with AV block.

DISCUSSION

The net haemodynamic effects of calcium channel blockade in the intact animal are determined by the balance between the direct pharmacodynamic actions on the heart and peripheral circulation, their interaction and the degree of reflex sympathetic response which these elicit [6]. In the present study, the predominant haemodynamic effect of diltiazem during fentanyl–nitrous oxide (in oxygen) anaesthesia was a profound reduction in peripheral vascular resistance. The increase in cardiac output and the systemic hypotension were related to the decrease in afterload rather than any direct myocardial depression, since LV $dP/dt$ was unaffected. The increase in heart rate seen after the bolus of diltiazem was indicative of an initial reflex sympathetic response to the acute reduction in peripheral resistance. However, as the dose increased, the direct negative chronotropic effect of diltiazem overcame this and produced a progressive decrease in heart rate.

Previous animal studies have found that the relative preponderance of haemodynamic and electrophysiological effects of diltiazem are dependent upon the plasma concentration. In dogs under barbiturate anaesthesia, solely electrophysiological effects were produced at low serum concentrations of 100–300 ng ml$^{-1}$, whereas much higher values (800–1800 ng ml$^{-1}$) were required to produce haemodynamic effects [7]. In a comparative study of calcium channel blockers in pigs anaesthetized with 1 MAC halothane [4], diltiazem was given until the mean arterial pressure had decreased 25–30% from control values. The mean diltiazem plasma concentration measured at this point was 1650 ng ml$^{-1}$. Hypotension was secondary to a reduction in myocardial contractility, since systemic vascular resistance was unaffected, although LV $dP/dt$ and cardiac index were reduced by 50% and 42%, respectively. In dogs anaesthetized with 1.5% end-tidal isoflurane and given diltiazem [5], the only significant haemodynamic changes observed were depression of LV $dP/dt$ and increases in left and right filling pressures. The lower plasma diltiazem concentrations (50–400 ng ml$^{-1}$) were insufficient to produce any changes in MAP. In accordance with the study of Kates and colleagues [4], there was no decrease in SVR with diltiazem. The use of a vasodilating anaesthetic may explain the lack of further vasodilatation produced by diltiazem, in comparison with the greater effect of diltiazem on SVRI and MAP during fentanyl–nitrous oxide anaesthesia. In the present study, plasma diltiazem concentrations of 300–400 ng ml$^{-1}$ produced significant hypotension without any evidence of myocardial depression. In contrast, significant myocardial depression has been observed when diltiazem was administered during inhalation anaesthesia in animals. Therefore, in dogs, the mechanism of diltiazem-induced hypotension during fentanyl–nitrous oxide anaes-
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AV sequential pacing for severe impairment of AV conduction, secondary to calcium channel blockade. However, a pharmacological approach for the correction of conduction block may be simpler and equally effective. Isoprenaline, a beta-agonist, was successful in re-establishing normal conduction in the majority of these dogs. To the extent that this animal study is relevant to clinical anaesthetic practice, isoprenaline should be considered as the drug of choice for the treatment of severe conduction defects produced by diltiazem during fentanyl–nitrous oxide anaesthesia.

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REFERENCES


The potential use of diltiazem in clinical anaesthesia may be limited by adverse electrophysiological effects, which occur at plasma concentrations necessary to achieve haemodynamic changes. Second degree AV block and junctional escape rhythm at plasma concentrations of less than 30 ng ml⁻¹ have been reported during enfurane [8] and isoflurane [5] anaesthesia in dogs. In the present study, during fentanyl–nitrous oxide anaesthesia, second degree AV block was not observed consistently until relatively high plasma diltiazem concentrations were achieved (greater than 400 ng ml⁻¹). By this time, there were significant effects on SVRI and, consequently, MAP. Further investigation of lower plasma diltiazem concentrations in combination with fentanyl-based anaesthesia may be warranted to determine the optimum plasma concentration with which to achieve the desired haemodynamic effect, with minimal changes in intracardiac conduction time.

In animals, calcium chloride has been shown to counteract the haemodynamic, but not the electrophysiological, effects of calcium channel blockade with verapamil [9]. Calcium chloride was given to reverse the haemodynamic changes produced by diltiazem. Although myocardial contractility was increased, the systemic arterial vasodilatation and hypotension induced by diltiazem were not antagonized by calcium chloride. This is in agreement with the findings of Kates and colleagues [4] who observed a slight decrease in SVR after the administration of calcium chloride to pigs given diltiazem during halothane anaesthesia. An alpha-adrenergic agonist drug such as phenylephrine may be more effective for correction of the peripheral vasodilator effects of prolonged administration of calcium channel blockers.

No effect of calcium chloride was observed on the prolonged AV conduction produced by diltiazem, confirming the results of previous studies [4,9]. Reves [10] has proposed the use of AV sequential pacing for severe impairment of heart rate.

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