CARDIAC CONDUCTION INTERACTIONS OF PROPRANOLOL AND VERAPAMIL WITH HALOTHANE IN PENTOBARBITONE-ANAESTHETIZED DOGS

A. P. HART, R. L. ROYSTER AND W. E. JOHNSTON

The inhalation anaesthetic agents halothane and enflurane prolong AV nodal conduction [1,2], and in some circumstances (hypertension, hypercapnia and administration of adrenaline, they induce arrhythmias [3,4]. The beta-adrenoceptor antagonist, propranolol, and the calcium entry blocker, verapamil, are used frequently to treat arrhythmias caused by the depressant effect of inhalation anaesthetics on cardiac conduction [5-7]. I.v. propranolol or verapamil, alone or in combination, may be required during inhalation anaesthesia to treat supraventricular arrhythmias in patients with a history of arrhythmias or cardiac disease for which they are receiving calcium or beta-antagonists by mouth. This study has examined the effects of verapamil and propranolol on cardiac conduction and refractoriness in dogs anaesthetized with pentobarbitone and halothane.

MATERIALS AND METHODS

Twenty-one mongrel dogs (13.5-28.5 kg) of both sexes were anaesthetized with pentobarbitone 30 mg kg⁻¹ i.v., the trachea was intubated after suxamethonium 80 mg i.m. and the lungs ventilated using a Harvard 607 (TM) ventilator. Anaesthesia was maintained with an i.v. infusion of pentobarbitone 0.5-1.0 mg min⁻¹ throughout the experiment. This low-dose continuous infusion is used commonly to provide a stable model in animals for the study of effects of drugs on cardiac electrophysiology [8,9]. The right external jugular vein was cannulated and a 7.5-French gauge pulmonary artery catheter inserted. A catheter was placed in the right femoral artery for measurement of arterial pressure and a 6-French gauge quadripolar His bundle catheter (USCI) in the left femoral artery. The quadripolar catheter was passed retrogradely into the ascending aorta under continuous electrographic monitoring with an ECG–His amplifier on a Gould ES 1000 (TM) monitored recorder until a stable His bundle

SUMMARY

We have studied the effects of propranolol 0.25 mg kg⁻¹ and verapamil 0.075 mg kg⁻¹ on cardiac conduction and refactoriness in 21 dogs anaesthetized with pentobarbitone 30 mg kg⁻¹ using His bundle electrocardiography and programmed stimulation. After baseline studies under pentobarbitone and halothane (1.3 MAC) anaesthesia, the dogs were allocated randomly to two groups: group 1 received verapamil followed by propranolol; group 2 received propranolol followed by verapamil; the drugs were given in a continuous infusion over 10 min. The atrial–His (AH) interval, the atrioventricular node effective (AVERP), and functional (AVFRP) refractory periods, were prolonged by verapamil in both groups, but not the His–ventricle (HV) interval or the ventricular effective refractory period (VERP). AVFRP and VERP were prolonged by propranolol in both groups. Corrected sinus node recovery times were normal after each drug. Heart rate and the rate required to produce Wenckebach were decreased by each drug. The combination of verapamil and propranolol during halothane anaesthesia in dogs has significant cardiac conduction effects; however, no spontaneous AV block occurred during the study.
recording was obtained. Standard ECG recordings were obtained with cutaneous electrodes. Through a right thoracotomy, epicardial pacing wires were sutured on the right atrial appendage and anterior–medial surface of the right ventricle. A Medtronic 5325 (TM) programmable stimulator delivering square wave impulses at 1.8 ms duration at twice diastolic threshold was used to pace the heart, and data were recorded on a Gould ES 1000 (TM) eight-channel recorder at a paper speed of 250 mm s⁻¹.

After baseline data were recorded, halothane was administered from a Fluotec Mark III (TM) vaporizer to maintain an end-tidal concentration of 1.13 (0.08)% (1.3 MAC) (as determined by mass spectrometry). Repeat data were recorded. The dogs were subsequently allocated randomly to two groups: group 1 (n = 10) received verapamil 0.075 mg kg⁻¹ i.v. over 10 min and data were collected, then propranolol 0.25 mg kg⁻¹ was given i.v. over 10 min and data were recorded; group 2 (n = 11) received propranolol initially, followed by verapamil.

At each data collection, the following variables were measured: the atrial–His (AH) interval (a measurement of atrioventricular node conduction time), the His–ventricle (HV) interval (a measurement of ventricular bundle branch and Purkinje fibre conduction time), the atrioventricular node effective (AVERP) and functional (AVFRP) refractory periods (measurements of AV node repolarization or recovery time), the ventricular effective refractory period (VERP) (a measurement of ventricular recovery time), sinus node recovery times, the heart rate producing Mobitz type I atrioventricular nodal block (Wenckebach) (an indirect measurement of AV node conduction time), and the spontaneous heart rate. The AH interval was measured from the beginning of atrial activity in the intra-aortic electrogram to the beginning of the His potential. The HV interval was measured from the beginning of the His potential to the earliest point of ventricular activity on the electrocardiogram or intra-aortic electrogram. The Q–T interval at constant pacing (pQT) was measured before and after administration of halothane.

The basic cycle length for atrial and ventricular pacing was shorter than the spontaneous cycle length (to achieve stable capture) and was maintained during the study. Determination of refractory period was by using stimuli at increasingly premature intervals until failure of conduction occurred in the tissue studied. As defined by Josephson and Seides [10], the AVERP represents the longest interval between the paced atrial impulse (A₁) and the premature atrial impulse (A₂) that failed to conduct to the His bundle (fig. 1). The AVFRP is the shortest A₁A₂ interval between the paced His impulse (H₁) and the premature His impulse (H₂) that conducted to the ventricle (fig. 1). The VERP corresponds to the longest interval between the paced ventricular impulse and the premature ventricular impulse that failed to capture the ventricle. Sinus node recovery times were measured at paced intervals of 353, 333, 316, and 300 ms. Sinus node recovery times were corrected for heart rate.

At each data collection, spontaneous heart rate, arterial pressure, cardiac output (in triplicate), central venous pressure, pulmonary artery pressure, pulmonary wedge pressure, serum potassium concentration, temperature, and arterial blood-gas tensions were recorded. Throughout
TABLE I. Electrophysiological data (mean (SEM)) before and after administration of halothane 1.3 MAC (n = 21). AH = atrial-His interval; HV = His-ventricular interval; AVERP = AV nodal effective refractory period; AVFRP = AV nodal functional refractory period; VERP = retrograde ventricular effective refractory period; pQT = QT interval paced at constant rate. *P < 0.05 compared with baseline

<table>
<thead>
<tr>
<th>Interval</th>
<th>Baseline (ms)</th>
<th>After halothane (ms)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH</td>
<td>59 (2.7)</td>
<td>68 (1.9)*</td>
<td>+15</td>
</tr>
<tr>
<td>HV</td>
<td>29 (1.0)</td>
<td>29 (1.1)</td>
<td>—</td>
</tr>
<tr>
<td>AVERP</td>
<td>125 (10)</td>
<td>151 (8.1)*</td>
<td>+20</td>
</tr>
<tr>
<td>AVFRP</td>
<td>200 (7.3)</td>
<td>223 (6.7)*</td>
<td>+12</td>
</tr>
<tr>
<td>VERP</td>
<td>141 (2.4)</td>
<td>165 (2.7)*</td>
<td>+17</td>
</tr>
<tr>
<td>pQT</td>
<td>380 (10)</td>
<td>410 (10)*</td>
<td>+8</td>
</tr>
</tbody>
</table>

the experiment, systolic arterial pressure was maintained at a value greater than 100 mm Hg with i.v. crystalloid fluid and phenylephrine as required. Ventilation and administration of sodium bicarbonate were adjusted to maintain mean $P_{aCO_2}$ at 4.7 (SEM 0.6) kPa and pH at 7.40 (0.1). Supplementary oxygen and positive end-expiratory pressure were used to maintain $P_{aO_2}$ greater than 8 kPa. Serum potassium concentration was maintained at 3.5-5.0 mmol litre$^{-1}$.

Results were analysed using the SAS statistical program and a VAX 730 computer. Measurements of AH, HV, AVERP, AVFRP and VERP were analysed using a Wilcoxon sign rank test. All other data were analysed using parametric $t$ tests.

RESULTS

Halothane prolonged significantly AH, AVERP, AVFRP, VERP and the pQT compared with baseline (table I; fig. 1). Halothane did not change the HV interval. The paced rate to induce Wenckeback periodicity varied from 280 (7.6) ms at baseline to 241 (6.3) ms after halothane.

Verapamil prolonged significantly AH, AVERP, and AVFRP when given after either halothane or halothane-propranolol (tables II, III). The paced rate to induce Wenckeback periodicity varied from 231 (7.1) ms after halothane to 199 (6.5) ms after verapamil (group 1) and from 224 (8.6) ms after halothane-propranolol to 194 (11) ms after verapamil (group 2). Verapamil did not effect HV or VERP in either group.

Propranolol significantly prolonged the VERP after either halothane or halothane-verapamil (tables II, III). Propranolol prolonged the HV interval significantly only after halothane in combination with verapamil. It had no significant effect on the AH interval after halothane with verapamil. Propranolol prolonged significantly the AVFRP (both groups) and the AVERP after halothane-verapamil only. The paced rate to induce Wenckeback periodicity varied from 249 (9.7) ms after halothane to 224 (8.6) ms after propranolol (group 2) and from 199 (6.5) ms after halothane-verapamil to 180 (5.2) ms after propranolol (group 1).

AV nodal block did not occur during the study, despite significant effects on AV conduction data. Corrected sinus node recovery times did not change significantly after halothane, verapamil or propranolol.

There were significant reductions in spontaneous heart rate and cardiac output after halothane and after group 1 and group 2 drugs (table IV). After the administration of the second drug (propranolol in group 1; verapamil in group 2), one dog in group 1 and four dogs in group 2 died as a result of severe hypotension and myocardial depression. In all animals, severe hypotension occurred before any electro-

TABLE II. Cardiac electrophysiological data (mean (SEM)) before and after halothane, verapamil and propranolol (group 1, n = 10). *P < 0.05 compared with preceding value. Abbreviations as in table I

<table>
<thead>
<tr>
<th>Interval</th>
<th>Baseline (ms)</th>
<th>After halothane (ms)</th>
<th>After verapamil (ms)</th>
<th>After propranolol (n = 9) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH</td>
<td>60 (3.3)</td>
<td>72 (4.7)*</td>
<td>102 (12)*</td>
<td>120 (7.0)</td>
</tr>
<tr>
<td>HV</td>
<td>30 (1.3)</td>
<td>30 (1.6)</td>
<td>30 (1.7)</td>
<td>33 (1.7)*</td>
</tr>
<tr>
<td>AVERP</td>
<td>127 (16)</td>
<td>158 (13)*</td>
<td>206 (17)*</td>
<td>244 (23)*</td>
</tr>
<tr>
<td>AVFRP</td>
<td>210 (10)</td>
<td>237 (8.0)*</td>
<td>271 (9.6)*</td>
<td>302 (16)*</td>
</tr>
<tr>
<td>VERP</td>
<td>140 (3.5)</td>
<td>164 (4.1)*</td>
<td>170 (4.2)</td>
<td>185 (4.6)*</td>
</tr>
</tbody>
</table>
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Table III. Cardiac electrophysiological data (mean (SEM)) before and after halothane, propranolol and verapamil (group 2, n = 11). * P < 0.05 compared with preceding values. Abbreviations as in table I

<table>
<thead>
<tr>
<th>Interval</th>
<th>Baseline (ms)</th>
<th>After halothane (ms)</th>
<th>After verapamil (ms)</th>
<th>After propranolol (n = 7) (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AH</td>
<td>60 (4.6)</td>
<td>65 (3.6)*</td>
<td>73 (2.4)*</td>
<td>101 (9.6)*</td>
</tr>
<tr>
<td>HV</td>
<td>29 (1.5)</td>
<td>28 (1.5)</td>
<td>28 (1.3)</td>
<td>29 (1.5)</td>
</tr>
<tr>
<td>AVERP</td>
<td>123 (13)</td>
<td>145 (10)*</td>
<td>159 (13)</td>
<td>229 (23)*</td>
</tr>
<tr>
<td>AVFRP</td>
<td>191 (9.9)</td>
<td>211 (9.3)*</td>
<td>236 (8.2)*</td>
<td>290 (15)*</td>
</tr>
<tr>
<td>VERP</td>
<td>142 (3.5)</td>
<td>166 (3.7)*</td>
<td>183 (7.7)*</td>
<td>191 (11)</td>
</tr>
</tbody>
</table>

Table IV. Haemodynamic data (mean (SEM)) at baseline and after halothane, group 1 and group 2 drugs. HR = spontaneous heart rate (beat min⁻¹); CO = cardiac output (litre min⁻¹); MAP = mean arterial pressure (mm Hg); PAWP = pulmonary artery wedge pressure (mm Hg); V = verapamil; P = propranolol. * P < 0.05 compared with preceding value

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline (n = 21)</th>
<th>After halothane (n = 21)</th>
<th>V (n = 10)</th>
<th>P (n = 9)</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>148 (3.5)</td>
<td>126 (2.2)*</td>
<td>112 (3.6)*</td>
<td>104 (5.1)*</td>
<td>115 (2.9)*</td>
<td>107 (5.9)*</td>
</tr>
<tr>
<td>CO</td>
<td>3.6 (0.3)</td>
<td>2.9 (0.3)*</td>
<td>2.5 (0.3)*</td>
<td>1.5 (0.1)*</td>
<td>1.8 (0.2)*</td>
<td>1.3 (0.5)*</td>
</tr>
<tr>
<td>MAP</td>
<td>138 (10)</td>
<td>106 (6.0)*</td>
<td>102 (1.6)</td>
<td>98 (9)</td>
<td>93 (3.0)*</td>
<td>91 (3.6)</td>
</tr>
<tr>
<td>PAWP</td>
<td>12 (1.2)</td>
<td>17 (1.9)*</td>
<td>18 (2.5)</td>
<td>18 (3.8)</td>
<td>18 (3.5)</td>
<td>18 (3.9)</td>
</tr>
</tbody>
</table>

Physiological abnormalities, and AV nodal block per se was not observed. However, this was not significant between groups (Fisher exact test).

**DISCUSSION**

Verapamil blocks calcium channels and causes reduced entry of calcium into cardiac cells, which leads to decreased inotropy and chronotropy [11]. Peripheral smooth muscle relaxation produced by verapamil produces reflex increase in sympathetic stimulation which tends to attenuate hypotension partially [11]. Propranolol, a beta-adrenoceptor antagonist, inhibits calcium entry by blocking receptors controlling calcium channels [12]. This results also in negative inotropic and chronotropic responses. Verapamil and propranolol may interact, through different mechanisms inhibiting calcium entry, to produce additive or synergistic adverse haemodynamic or electrophysiological effects. In addition, by reducing the normal reflex sympathetic response to calcium entry blockers, propranolol may produce significant hypotension.

Propranolol decreases hepatic blood flow and reduces clearance of verapamil [13]. As both drugs are metabolized by the liver, competitive metabolic inhibition may reduce elimination, thereby increasing plasma concentrations of both drugs. Verapamil administered to animals receiving propranolol decreased myocardial contractility and prolonged atrioventricular conduction time [14-16]. The combination of infusions of verapamil and propranolol in thiopentone-anaesthetized dogs caused severe haemodynamic alterations and increases in plasma concentrations of both drugs [13]. However, in patients with good left ventricular function who were receiving propranolol by mouth, the addition of i.v. or oral verapamil resulted in some reduction in cardiac output and hypotension which was not clinically significant [17-18]. No significant disturbance occurred in sinus node or AV node conduction. Studying the combination of i.v. verapamil and propranolol in patients with paroxysmal supraventricular tachycardia, Yee, Gula-husein and Klein [19] demonstrated additive effects on AVFRP and noted no significant hypotensive problems or AV nodal block.

Halothane also has calcium entry blocking effects which produce negative inotropy and chronotropy [20]. Halothane prolongs AV nodal conduction time and prolongs HV conduction.
time [1,21—23]. Administration of combinations of verapamil and propranolol during halothane anaesthesia may cause additive or synergistic effects as all three drugs influence calcium conductance. Inhalation anaesthetics increase plasma concentrations of verapamil by decreasing the steady state volume of distribution and reducing total clearance [24]. Significant depression of contractility occurs after verapamil in dogs during anaesthesia with halothane and enflurane, but is absent during isoflurane anaesthesia [25]. Halothane also reduces liver blood flow, decreases the metabolism of propranolol and increases plasma concentrations of propranolol in dogs [26]. Kapur and Flacke [24] studied the effects of i.v. verapamil 0.2 mg kg\(^{-1}\) during 1.1 MAC halothane anaesthesia in dogs anaesthetized initially with thiopentone. Significant reductions in mean arterial pressure and left ventricular contractility occurred with prolongation of the PR interval and episodes of second degree and third degree heart block.

The doses of propranolol (0.25 mg kg\(^{-1}\)) and verapamil (0.075 mg kg\(^{-1}\)) we have used were shown in previous canine studies to achieve adequate plasma concentrations and significant electrophysiological changes [27—28]. Although we have not measured plasma concentrations, our results suggest that significant concentrations of each drug were reached, and our data were obtained immediately after discontinuing the infusions of verapamil and propranolol.

Our study has demonstrated that halothane prolonged significantly AV node conduction time and refractoriness, in addition to ventricular refractoriness. Our observations that halothane has no effect on HV conduction time differ from those of others [1,21], although Morrow, Logic and Haley [29] noted no change in HV intervals during halothane administration under pentobarbitone anaesthesia. Verapamil maintained electrophysiological and haemodynamic effects after halothane and halothane—propranolol. These effects appeared to be additive; however, the death of four dogs in group 2, compared with one death in group 1, suggests a more significant haemodynamic interaction when verapamil is administered after propranolol during halothane anaesthesia. This could result from a greater reduction in calcium entry or an increase in plasma concentrations of verapamil or propranolol, or both, because of metabolic inhibition by competition between the drugs or by halothane. However, we cannot exclude an effect of pentobarbitone, which could contribute especially to the severe haemodynamic depression. Although propranolol alone depresses only AV conduction and refractoriness [5], it had significant effects on VERP after halothane and halothane—verapamil in the present study. In addition, the AH interval was not changed significantly when propranolol was administered after halothane—verapamil, demonstrating attenuation by prior administration of verapamil. Pentobarbitone may have attenuated AV node depression by increasing sympathetic tone, especially after the initial bolus. However, the low doses of the continuous infusion during which our data were collected should have limited this effect.

In summary, we have demonstrated that halothane significantly prolonged AV nodal conduction time, AV nodal refractoriness, ventricular refractoriness and the paced QT interval. AV nodal depression produced by verapamil was additive to that from halothane and halothane—propranolol. The effects of propranolol were additive also, but varied, with unexpected significant prolongation of the VERP occurring after halothane and halothane—verapamil. The administration of i.v. verapamil and propranolol in any order during halothane anaesthesia has profound additive effects on cardiac electrophysiology.

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