MYOCARDIAL STIMULATION BY PANCRURONIUM BROMIDE

R. F. SEED AND J. H. CHAMBERLAIN

SUMMARY

The effect of pancuronium bromide on the canine myocardium was studied by observing several indices of myocardial contractility during i.v. and intracoronary infusion of the drug in an anaesthetized, open-chested dog preparation. Pancuronium produced tachycardia when given for 2 min by i.v. and intracoronary infusion with the heart intact. Following denervation and pacing of the heart the intracoronary infusion of the drug produced increases in maximum acceleration of blood at the aortic root, peak aortic blood flow, maximum dP/dt and (maximum dP/dt)/TP. These changes occurred about 30 s after starting the infusion and returned to control values 5 min after stopping the infusion.

A major problem in the study of drugs with cardiovascular activity is the difficulty of dissociating other factors influencing cardiac or vascular function. Changes in cardiac output and arterial pressure are dependent not only on heart rate and peripheral vascular tone but also on myocardial function, particularly that of the left ventricle. The force developed by the left ventricle depends primarily on three factors: (1) the resting fibre length or the end-diastolic fibre length (pre-load), (2) the out-flow impedance or mean aortic pressure (after-load), (3) myocardial contractility. Experimental studies of this third component should not be influenced by other factors such as heart rate, circulating catecholamines or neural activity. There have been no studies of the effect of pancuronium on left ventricular myocardial function, but Saxena and Bonta (1970) reported increased right ventricular myocardial contractility in dogs using the Walton–Brodie strain-gauge technique. They reported also an increase in ascending aortic blood flow and a decrease in peripheral resistance and in after-load. Duke, Fung and Gartner (1975) stated that pancuronium does not have a direct positive inotropic effect on the myocardium, but their studies on dogs were performed in the presence of halothane, which may modify the response to pancuronium (McDowell and Clarke, 1969; Kölliker, 1972) and the measurements reported were not specific indices of left ventricular myocardial contractility.

This study was designed to elucidate whether or not pancuronium bromide produces a specific positive inotropic effect on left ventricular myocardial contractility.

METHODS

In six unpremedicated dogs anaesthesia was induced with thiopentone 25 mg/kg i.v. The trachea was intubated and ventilation was controlled mechanically using a Cape ventilator to maintain PaCO₂ in the range 4.7–6 kPa.* Anaesthesia was maintained with halothane 0.5% in oxygen 33% in nitrous oxide, suxamethonium 0.02% being infused as a solution during the surgical preparation. The chest was opened by a mid-line sternotomy and an electromagnetic flow probe (S. E. Laboratories) was placed snugly round the root of the aorta. A catheter-tip pressure transducer (Millar Instruments) was placed in the left ventricle and central aortic pressure was measured through a cannula connected to a Bell and Howell pressure transducer. A small branch of the left anterior descending coronary artery was dissected free and cannulated with a thin nylon catheter (0.63 mm o.d.) passed retrogradely so that the tip lay at the origin of the left main coronary artery (fig. 1). Its position was checked at the end of each experiment and if it was not sited correctly the results were discarded.

Recordings of aortic pressure and flow and of left ventricular pressure and their derivatives, maximum dP/dt and maximum dQ/dt, max LV dP/dt divided by the instantaneous total pressure (TP), left ventricular end-diastolic pressure (LVEDP) and peak flow (PF) were made on a multichannel tape-recorder (Precision Instruments) and pen-recorder (Devices M 19). End-tidal carbon dioxide was

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* 1 kPa = 7.5 mm Hg.
monitored and recorded so that analysis could be performed at the same point in the respiratory cycle (Chung, Chamberlain and Seed, 1974). Arterial $P_{O_2}$, $P_{CO_2}$ and pH were measured regularly and maintained within normal limits, while body temperature was held at $37 \pm 1$ °C by warming with a hot-air blower.

When haemodynamic stability had been established control observations were made. In three dogs an i.v. infusion of pancuronium (0.5 mg/1.5 ml normal saline per min) was given by a constant infusion pump (Braun and Melsungen) for 2 min and recordings made every half-minute, followed by a recovery period of 5 min during which recordings were made every minute. This infusion was repeated in two of the three dogs. After an interval of 45–60 min the same amount of pancuronium was infused similarly into the left ventricle via the coronary catheter in those and three further dogs and the recordings repeated.

Following this intervention both vagus nerves were divided in the neck, both stellate ganglia and the associated ansae subclaviae extirpated and the sympathetic chains stripped out to the levels of T5/6. Heart rate was maintained constant by atrial pacing at a rate just above the intrinsic heart rate (Palmer Stimulator). The intracoronary infusions of pancuronium were repeated in the denervated, paced heart preparation and recordings made as described. Although periodic analysis of all haemodynamic variables was performed throughout, statistical analysis using the paired Student $t$ test was confined to comparison between the control group of data and that obtained at the end of 2 min of infusion of pancuronium.

**RESULTS**

Table I shows the effect on indices of cardiac function produced by pancuronium bromide when given as a constant infusion in a dose of 0.5 mg/1.5 ml normal saline per min for 2 min. When given i.v. to the preparation with an innervated, unpaced heart the only statistically significant change observed was an increase of heart rate of 7 beat/min.

The same dose of pancuronium given by intracoronary infusion into the intact heart produced also a significant increase of heart rate (18 beat/min), a 21% increase in max $dP/dt$ and an 8% increase in peak flow. Following denervation of the heart, which was then paced at a constant rate, the intracoronary infusion of pancuronium produced statistically significant increases in max $dP/dt$ (5%), (max
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean arterial pressure (MAP) (mm Hg)</th>
<th>Stroke volume (SV) (ml)</th>
<th>Left ventric. end-diastolic pressure (LVEDP) (mm Hg)</th>
<th>Max dP/dt (mm Hg/s)</th>
<th>(Max dP/dt)/TP (s⁻¹)</th>
<th>Max dQ/dt (litre/s⁻²)</th>
<th>Peak flow (PF) (ml/s)</th>
<th>Heart rate (HR) (beat/min)</th>
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<tbody>
<tr>
<td>Intravenous</td>
<td>Control Mean ± SD</td>
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<td>130 ± 16</td>
<td>16.2 ± 11.8</td>
<td>8.4 ± 5.6</td>
<td>2201 ± 300</td>
<td>27.6 ± 1.1</td>
<td>6.1 ± 2.5</td>
<td>199 ± 97</td>
<td>197 ± 35</td>
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<tr>
<td>Innervated</td>
<td>Mean ± SD</td>
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<td></td>
<td>131 ± 15</td>
<td>15.0 ± 9.9</td>
<td>8.1 ± 5.4</td>
<td>2190 ± 394</td>
<td>27.8 ± 1.8</td>
<td>6.2 ± 2.5</td>
<td>198 ± 97</td>
<td>204* ± 32</td>
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<td></td>
<td>2 min × 5 in 3 dogs</td>
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<tr>
<td>Intracoronary</td>
<td>Control Mean ± SD</td>
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<td></td>
<td>128 ± 15</td>
<td>10.9 ± 3.5</td>
<td>3.5 ± 3.8</td>
<td>2968 ± 1555</td>
<td>42.3 ± 2.6</td>
<td>5.2 ± 2.6</td>
<td>158 ± 51</td>
<td>180 ± 14</td>
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<tr>
<td>Innervated</td>
<td>Mean ± SD</td>
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<td></td>
<td>131 ± 17</td>
<td>10.2 ± 3.6</td>
<td>3.0 ± 3.4</td>
<td>3579* ± 1644</td>
<td>44.7 ± 2.9</td>
<td>6.2 ± 2.9</td>
<td>171* ± 56</td>
<td>198* ± 16</td>
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<td>2 min × 9 in 6 dogs</td>
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<tr>
<td>Intracoronary</td>
<td>Control Mean ± SD</td>
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<td></td>
<td>120 ± 19</td>
<td>9.1 ± 6.2</td>
<td>5.2 ± 4.1</td>
<td>1652 ± 504</td>
<td>23.1 ± 4.3</td>
<td>3.7 ± 1.8</td>
<td>119 ± 49</td>
<td>Paced</td>
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<tr>
<td>Denervated</td>
<td>Mean ± SD</td>
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<tr>
<td></td>
<td>121 ± 15</td>
<td>9.0 ± 5.7</td>
<td>4.9 ± 3.7</td>
<td>1742* ± 435</td>
<td>25.1* ± 5.0</td>
<td>4.0* ± 2.1</td>
<td>127* ± 57</td>
<td>Paced</td>
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<td>2 min × 11 in 6 dogs</td>
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* P < 0.05.
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D{P/dt}/TP (9%), max dQ/dt (8%) and peak flow (7%). Although these changes related to observations made 2 min after starting the infusion of pancuronium they were noted to be significantly different as early as 30 s after starting the intracoronary infusion. In all experiments the changes were followed at 1-min intervals after stopping the infusion and the percentage changes observed in the denervated, paced heart at each interval shown in figure 2. It can be seen that

\[
\begin{align*}
\text{FIG. 2. Diagram illustrating percentage changes from} \\
\text{control (100), in steps of 5%, of indices of myocardial} \\
\text{function during intracoronary infusion of pancuronium} \\
\text{bromide for 2 min, followed by recovery for 5 min.}
\end{align*}
\]

5 min after stopping the infusion of pancuronium all the indices of cardiac function had returned to control values and this occurred also when the drug was given i.v. or by intracoronary infusion to the intact heart.

\[
\begin{align*}
\text{DISCUSSION}
\end{align*}
\]

Clinically it is observed often that the administration of pancuronium results in transient tachycardia and hypertension. An increase in cardiac output (Loh, 1970; Smith, Proctor and Spence, 1970; Kelman and Kennedy, 1971; Coleman et al., 1972; Gertel et al., 1972; Stoelting, 1972), has been reported also although Brown, Smiler and Plaza (1973) were not able to demonstrate such changes. It has been suggested that the increase in arterial pressure is more a reaction to inadequate levels of anaesthesia than a direct sympathetic stimulation (Sellick, 1968) and that these responses may be modified in the presence of halothane (McDowell and Clarke, 1969; Kölliker, 1972) although Miller and others (1975) found no correlation between heart rate and arterial pressure changes and the alveolar concentration of halothane or the dose of pancuronium. The results reported here indicate that pancuronium bromide has a direct stimulating effect on the canine heart, producing both an increase in heart rate and, quite separately, an increase in myocardial contractility. This is shown during the studies, at a constant heart rate, by the increase in max dP/dt, (max dP/dt)/TP, max dQ/dt and peak flow and the absence of any significant changes in LVEDP.

The tachycardia produced by pancuronium has been examined by Bonta, Goorissen and Derickx (1968) who demonstrated in a cat preparation that pancuronium possessed a cardiac vagolytic action similar to that of tubocurarine and gallamine. In 1971 Saxena and Bonta demonstrated in dogs that, while the vascular depressor effect of the cholinergic drugs acetylcholine, carbachol and methacholine was reduced only slightly, their negative chronotropic and inotropic actions were blocked completely by pancuronium, suggesting that pancuronium could block specifically the muscarinic cholinergic receptors of the heart. Similar results were obtained also in the guineapig heart preparation, in which pancuronium antagonized the negative inotropic and chronotropic action more selectively than the coronary-dilating effect of the cholinergic drugs. Since the response to potassium chloride on the heart was not affected by pancuronium it must be assumed that the compound paralysed the myocardial muscarinic receptors. These observations were confirmed in man by Kelman and Kennedy (1971), Miller and colleagues (1975) and Coleman and colleagues (1972), who found that the prior administration of atropine modified the cardiovascular changes produced by pancuronium. This type of competitive antagonism between
acetylcholine and pancuronium at cholinergic receptor sites has been reported by Goat and Feldman (1972), Duke, Fung and Gartner (1975) and also by Baden (1976) who demonstrated similar responses with two other steroid non-depolarizing muscle relaxants, Organon 6368 and dacruronium. It has been shown by Stovner, Ofstedal and Holmboe (1975) that pancuronium causes a powerful and highly selective inhibition of human serum cholinesterase and they suggested that the tachycardia produced by pancuronium may be related to this inhibition.

In 1973 Nana, Cardan and Domokos reported that 5 min after injection of pancuronium i.v. there were statistically significant increases in the concentration of catecholamines in the blood, particularly of nor-adrenaline, suggesting that an increased sympathetic nervous activity may be the explanation of the slight increase in arterial pressure and heart rate noted after administration of the drug. In contrast with this report, Zsigmond and colleagues (1974) were unable to demonstrate any changes in plasma catecholamines when pancuronium was given to patients after induction with thiamylal. These differing reports may be a result of the different methods used to estimate catecholamines in plasma although Zsigmond and others studied only eight patients, compared with 30 studied by Nana, Cardan and Domokos (1973) (of whom six demonstrated a decrease in total blood catecholamines after pancuronium). Gertel and others (1972) suggested that the effect of the drug may be related to the prevailing sympathetic tone as set by the arterial carbon dioxide tension (P_{acO2}) as this greatly influences sympathetic reactivity which secondarily affects cardiac output (Prys-Roberts and Kelman, 1966; Theye, Milde and Michenfelder, 1966; Hewitt, Chamberlain and Seed, 1973). However, it should be noted that Nana's patients were ventilated mechanically to maintain P_{acO2} in the range 4.1–5.9 kPa. Stoelting (1972) reported premature ventricular contractions in two of four patients receiving pancuronium, which may have been a result of a change in the ratio of parasympathetic to sympathetic tone secondary to the cardiac vagolytic action of pancuronium, resulting in increased sympathetic activity and subsequent ventricular irritability. Although the six groups of patients of Miller and others (1975) were maintained at P_{acO2} values of 4.5–5.2 kPa three developed either ventricular extrasystoles or A–V dissociation and they suggested that ventricular arrhythmia from pancuronium is more likely during halothane than during nitrous oxide/thiopentone anaesthesia.

In the present study the changes in the indices of myocardial contractility were not large but they indicate that pancuronium has a positive inotropic effect on the left ventricle which is independent of an increase in heart rate. With no change in LVEDP there was an increase of 9% in (max dP/dt)/TP, which we have shown previously to be independent of loading changes of the heart (Chung, Chamberlain and Seed, 1973). However, the dose that was given may be larger than the left ventricle would receive from its coronary blood supply after a normal i.v. dose of 0.07–0.1 mg/kg. Presently available evidence indicates that the concentration of pancuronium in venous blood in man, a few minutes after injection of 4–8 mg, varies between 0.6 and 15 μg/ml (Baird, 1970; Agoston, Kersten and Meijer, 1973; Agoston et al., 1973; Buzello, 1975; McLeod, Watson and Rawlins, 1976). There is no information presently available on peak arterial blood concentrations of pancuronium, which may presumably be higher immediately after i.v. injection and before redistribution occurs. We have measured left coronary blood flow in the type of preparation described here on different occasions, both by the Xe133 washout technique and also using an electromagnetic flow probe. Left ventricular blood flow using these methods was found to be 96 ± 13 ml/100 g.min⁻¹. Thus the intracoronary concentrations of pancuronium in these studies would have been of the order of 5 μg/ml. Although the results which have been presented indicate significant changes after 2 min of infusion (after 1 mg had been given) the indices of contractility as expressed by max dP/dt, (max dP/dt)/TP, max dQ/dt, LVEDP, peak flow and stroke volume were already changed significantly as early as 30 s after starting the infusion (after 250 μg had been given).

The exact mechanism of this effect of pancuronium on myocardial contractility is not known. The stimulation could be mediated either via autonomic nerve endings in the heart or through a direct effect of the drug on cross-bridge formation between the actin and myosin filaments in the cardiac muscle cell, perhaps as a result of changes in the local biochemical environment such as the supply of high energy phosphates or calcium ion exchange. Pancuronium may act like digitalis which has a steroid-like structure also and which inhibits adenosine triphosphatase.

Whatever the mechanism, there can be no doubt that pancuronium has a direct stimulating effect on the canine heart, to increase both its rate and its force of contraction. If such a response does occur in the human heart it may enhance myocardial metabolic
demands, which may be a disadvantage in patients with ischaemic heart disease. On the other hand, the absence of hypotension as a result of any cardiac component may be of benefit to certain patients. However, the effect of pancuronium on the heart is relatively transient and related to the short time during which peak blood concentrations of the drug occur following i.v. injection and redistribution. It is probable that any continuing cardiovascular stimulation following the administration of pancuronium would be a result of some other cause, such as light anaesthesia or catecholamine release.

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REFERENCES


STIMULATION DU MYOCARDE PAR LE BROMURE DE PANCURONIUM

RÉSUMÉ

L'effet du bromure de pancuronium sur le myocarde des chiens a été étudié en observant plusieurs indices de contractilité du myocarde pendant l'infusion intraveineuse et intracoronaire du médicament sur un chien anesthésié ayant la poitrine ouverte. Le pancuronium a provoqué une tachycardie lorsqu'il a été administré pendant 2 min par infusion intraveineuse et intracoronaire, lorsque le cœur...
etait intact. Après dénervation et régularisation du cœur, l'infusion intracoronaire du médicament a produit des augmentations dans l'accélération maximale du sang à la racine aortique, un débit sanguin aortique de pointe, une \(\frac{dP}{dt}\) maximale et une \(\frac{(dP/\text{dt maximal})}{\text{TP}}\). Ces changements se sont produits environ 30 s après le commencement de l'infusion et tout est retourné aux valeurs témoins 5 min après l'arrêt de l'infusion.

**MYOKARDAL-STIMULIERUNG DURCH PANCURONIUM BROMID**

**ZUSAMMENFASSUNG**

Die Wirkung von Pancuronium auf das Myokardium des Hundes wurde studiert durch Beobachtung mehrerer Indizes der myokardialen Kontraktilität während i.v. und intrakoronarer Verabreichung der Droge bei narkotisierten Hunden mit geöffnetem Brustraum. Pancuronium rief eine Tachykardie hervor, wenn es 2 min lang i.v. und intrakoronar bei intaktem Herzen verabreicht wurde. Nach Denervierung und Herzregulierung bewirkte die Droge Erhöhungen in der maximalen Blutbeschleunigung an der Aortawurzel, Spitzenwerte im Aortabstrom, Maximum \(\frac{dP}{\text{dt}}\) und \(\frac{(\text{Maximum } dP/\text{dt maximal})}{\text{TP}}\). Diese Veränderungen erfolgte etwa 30 s nach Infusionsbeginn, und 5 min nach Beendigung der Infusion waren die Kontrollwerte wieder erreicht.

**ESTIMULACION DEL MIOCARDIO MEDIANTE BROMURO DE PANCURONIO**

**SUMARIO**

El efecto del bromuro de pancuronio sobre el miocardio canino fue estudiado observando diversos índices de contractilidad miocárdica durante infusión intracoronaria e i.v. del fármaco en un perro anestesiado con preparación a tórax abierto. El pancuronio produjo una taquicardia cuando se dio durante 2 min por i.v. e infusión intracoronaria con el corazón intacto. Tras desnervación y marcación cardiaca la infusión intracoronaria del fármaco produjo aumentos en la aceleración máxima de la sangre en la raíz aórtica, flujo máximo hemático aórtico, máxima \(\frac{dP}{\text{dt}}\) y \(\frac{(\text{máxima } dP/\text{dt maximal})}{\text{TP}}\). Estos cambios se produjeron a unos 30 s tras iniciada la infusión y volvieron a los valores testigos 5 min después de detener la infusión.