A Comparison of Systemic and Regional Hemodynamic Effects of d-Tubocurarine, Pancuronium, and Vecuronium

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This study was designed to compare the effects of three neuromuscular blocking agents, in a clinically relevant dose range, on the regional distribution of blood flow measured with 15-μm radioactive microspheres in anesthetized, optimally ventilated cats. d-Tubocurarine (400, 800, and 1,600 μg·kg⁻¹) caused hypotension and a decrease in ascending aortic blood flow. Pancuronium (20, 40, and 80 μg·kg⁻¹) only caused a moderate tachycardia, while vecuronium (40, 80, and 160 μg·kg⁻¹) was devoid of any systemic hemodynamic effect. Neither pancuronium nor vecuronium caused major changes in regional blood flows. On the other hand, d-tubocurarine increased blood flow to the stomach but decreased that to the kidneys, liver, skin, spleen, intestine, and adrenal glands. These effects of d-tubocurarine show a striking resemblance to those elicited by the infusion of histamine. Blood flow to the nerve-stimulated tibialis anterior muscle, which was about six times that of the unstimulated muscle, was decreased significantly by all three neuromuscular blockers.

In conclusion, the results clearly show that, while d-tubocurarine produces major cardiovascular disturbances, pancuronium and, in particular, vecuronium do not cause serious changes in systemic and regional hemodynamics in doses that are two to four times the ED₉₀ for neuromuscular blocking action. (Key words: Blood flow: regional. Heart: cardiac output. Neuromuscular relaxants: pancuronium, d-tubocurarine, vecuronium.)

AMONG the nondepolarizing neuromuscular blocking compounds, d-tubocurarine possesses potential marked cardiovascular effects. Upon intravenous administration, it may cause a rapid and severe fall in blood pressure.¹⁻⁴ On the other hand, pancuronium may produce hypotension⁵⁻⁷ with an associated increase in heart rate.⁶ Cardiac output,² and myocardial contractility.⁷ While hypotension following d-tubocurarine is not desirable in critically ill patients, tachycardia induced by pancuronium can elicit signs of myocardial ischemia in patients with coronary artery disease.⁸ To avoid these problems, a monquaternary analogue of pancuronium, vecuronium (Org NC 45), recently has been developed. Indeed, vecuronium seems to be devoid of any systemic hemodynamic effects.⁴ In the present investigation, we have compared the effects of three neuromuscular blocking agents—d-tubocurarine, pancuronium, and vecuronium—in clinically relevant doses on regional distribution of blood flow in cats.

Materials and Methods

Twenty-seven cats of either sex and weighing 3.0 ± 0.1 kg were anesthetized with a mixture of alphachloralose (60 mg·kg⁻¹) and urethane (700 mg·kg⁻¹) injected intraperitoneally. The animals were ventilated artificially via a tracheal cannula using a pediatric respirator (Loosco, Amsterdam). Arterial blood gas values were maintained within the normal range (pH: 7.30–7.45; Po₂: 90–20 mmHg, and PCO₂: 25–35 mmHg). The chest was opened on the left side by an incision between the 3rd and 4th ribs, and a polyvinyl cannula (1.02 mm od) was inserted into the left atrium for the injection of radioactive microspheres. The systemic arterial blood pressure was recorded (Statham P23Ac transducer) from a catheter placed into the aorta via the left common carotid artery. Another catheter was placed into the right brachial artery for the withdrawal of arterial blood samples during microsphere injections. A precalibrated electromagnetic flow probe (6–7 mm id) was placed around the base of the ascending aorta to measure its blood flow. The end diastolic part of the flow signal was regarded as the zero flow line. Heart rate was derived from the aortic flow signals with the help of a tachograph (Grass model PT4). Subsequently, a neuromuscular preparation was set up. The left tibialis anterior muscle was dissected free and its tendon was connected to a Grass FT 10c transducer. The twitch response of the muscle was elicited by a stimulation (supramaximal voltage, 0.2 ms duration, 0.1 Hz frequency) of the peripheral cut end of the common peroneal nerve. All signals were recorded on a model 7 Grass polygraph.

Regional Hemodynamic Variables

Regional blood flow distribution to different organs was measured by using the radioactive microsphere technique.¹³⁻¹⁵ In this study, four different batches of NEN-TRAC® microspheres, labelled with ¹⁴¹Ce, ¹¹⁵Sn, ¹⁰³Ru, or ⁹⁵Nb and having a diameter of 15 ± 2 (SD) μm, were used. To prevent aggregation, the microspheres were ultrasonicated before injecting into the left atrium. Beginning 5–10 s before the injection of microspheres, an arterial blood sample was collected for a period of 60–65 s at a rate of 2 ml·min⁻¹. At the end of the experiment, the animals were killed with an overdose of sodium pentobarbital. All the major organs and
tissues, including the stimulated (left) and nonstimulated (right) tibialis anterior muscle, were dissected out, weighed, and put into plastic vials. The heart was kept for 24 hr in a 10% formalin solution and then was dissected into different parts—atria, right ventricle, septum, and left ventricle. The left ventricle was subdivided further into epicardium, mesocardium, and endocardium. The vials containing tissue and blood samples were put into a Packard gamma scintillation counter (model 5986) equipped with a multichannel analyser (Conrac). The data were analyzed by a set of computer programs\textsuperscript{16} using the following equation for the calculation of tissue blood flow ($\dot{Q}_{\text{tis}}$):

$$\dot{Q}_{\text{tis}} = \dot{Q}_{\text{art}}(I_{\text{tis}}/I_{\text{art}}),$$

where $I_{\text{tis}}$ and $I_{\text{art}}$ represent, respectively, the tissue and arterial blood radioactivities (Counts·min$^{-1}$), and $\dot{Q}_{\text{art}}$ is the rate (ml·min$^{-1}$) of withdrawal of arterial blood. The blood flow was adjusted to 100 g tissue weight. Cardiac output was calculated by summing up ascending aorta blood flow (electromagnetic flowmeter) and myocardial blood flow (microsphere method). Percentage distribution of cardiac output was then calculated by dividing the respective blood flow values by cardiac output and multiplying this fraction by 100. Tissue vascular resistance was determined by dividing mean arterial blood pressure by tissue blood flow.

**Experimental Design**

After obtaining a stable baseline hemodynamic state, usually 30–45 min after the completion of surgery, the first batch of microspheres was injected to measure regional hemodynamic variables. Subsequently, the animals were divided into three groups that received: 1) $d$-tubocurarine chloride (400, 800, and 1,600 $\mu$g·kg$^{-1}$; iv; n = 10), 2) pancuronium bromide (20, 40, and 80 $\mu$g·kg$^{-1}$; iv; n = 7), or 3) vecuronium bromide (40, 80, and 160 $\mu$g·kg$^{-1}$; iv; n = 10). The dosage chosen in each case were such that the first dose caused a near complete blockade of the neuromuscular junction as assessed by the responses of tibialis anterior muscle following peroneal nerve stimulation. The three doses of the neuromuscular blockers, injected every 20 min, were followed 15 min later by a batch of microspheres. The values for heart rate, mean arterial blood pressure, and ascending aorta flow were collected at the baseline and after 1, 5, 10, and 15 min of each dose of the drugs. Arterial blood samples were collected for the analyses of blood gases before and 15 min after the drug administration.

In some of our previous investigations, we have shown that hemodynamic measurements made with different batches of radioactive microspheres infused after 0.9% NaCl\textsuperscript{17} or 25% propylene glycol\textsuperscript{18} (used as vehicle for the drugs investigated) did not substantially differ from the measurements performed at the baseline with the first batch of the microspheres. It is for this reason we have not used a control series again in this investigation.

**Statistical Evaluation**

All values, unless otherwise stated, are presented as mean ± SEM. The effects of the neuromuscular blocking agent are shown as percentage change from the baseline value. The significance of the changes has been evaluated by Wilcoxon matched pair signed rank test, considering a $P$ value of 0.05 or less as statistically significant.

**Results**

**Arterial Blood Gases**

The baseline values of arterial blood gases in the 27 cats were: pH, 7.34 ± 0.01; $P_{\text{CO}_2}$, 28 ± 1 mmHg; $P_{\text{O}_2}$, 115 ± 5 mmHg, and $O_2$-saturation, 96.4 ± 0.7%. None of these values were modified significantly by the neuromuscular blocking agents, except that $P_{\text{O}_2}$ was decreased moderately following the highest dose of $d$-tubocurarine (−24 ± 6%) and pancuronium (−8 ± 4%).

**Systemic Hemodynamic Variables**

The baseline values (n = 27) of heart rate, mean arterial blood pressure, and ascending aortic blood flow were 167 ± 6 beats·min$^{-1}$, 90 ± 4 mmHg, and 271 ± 14 ml·min$^{-1}$, respectively. The changes elicited by the three neuromuscular blockers are shown in figure 1. The administration of $d$-tubocurarine caused hypotension, while the ascending aortic blood flow decreased following a transient increase. Pancuronium increased the heart rate, but in these experiments it did not significantly modify arterial blood pressure or ascending aortic blood flow. Vecuronium caused no systemic hemodynamic change in the doses used.

**Regional Hemodynamic Variables**

*Baseline values.* In figure 2 are shown the baseline distribution of cardiac output and the regional blood flows to the major organs of the cat. Though the actual baseline values slightly differ from those reported earlier from this laboratory in the cats,\textsuperscript{17,18} the precision of the radioactive microsphere technique as used by us is still indicated by the following: 1) the blood flows (ml·min$^{-1}$·100 g$^{-1}$) to symmetrical organs, such as left (216
FIG. 1. Effect of three neuromuscular blocking agents, d-tubocurarine (400, 800, and 1,600 μg · kg⁻¹), pancuronium (20, 40, and 80 μg · kg⁻¹) and vecuronium (40, 80, and 160 μg · kg⁻¹) on mean arterial blood pressure, heart rate, and aortic blood flow. D₁, D₂, and D₃ denote, respectively, the first, second, and third dose of the drugs.

* Significant change from the respective baseline value (P < 0.05).

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Cardiac output are shown in figure 3. While pancuronium and vecuronium caused only minimal changes (a decrease in splenic fraction by the first dose of pancuronium and an increase in cerebral fraction by the highest dose of vecuronium), d-tubocurarine produced pronounced effects. The fraction of cardiac output distributed to skin, hepatic artery, spleen, small intestine, and adrenals was reduced, while that to the stomach was increased (fig. 3). There were no statistically significant changes in brain, kidneys, and large intestines, and in other organs (lungs, mesentery plus pancreas, heart, and the unstimulated skeletal muscle) not shown in fig. 3.

Regional blood flow. In figure 4 are depicted the effects of d-tubocurarine, pancuronium, and vecuronium on the regional blood flow. Administration of d-tubocurarine was associated with a decrease in renal, dermal, hepatic arterial, splenic, intestinal, and adrenal blood flow; only blood flow to stomach tended to increase, and no changes were elicited in brain, mesentery, plus pancreas and heart. The other two drugs, pancuronium and vecuronium, did not cause any appreciable change in regional blood flow.

Blood flow to stimulated and unstimulated tibialis anterior muscle. As expected, the baseline blood flow to the stimulated tibialis anterior muscle (10.0 ± 0.8 ml · min⁻¹ · 100 g⁻¹) was about six times that of the unstimulated tibialis anterior muscle (1.7 ± 0.2 ml · min⁻¹ · 100 g⁻¹). As shown in figure 5, the three neuromuscular blocking agents did not affect the blood flow to the unstimulated muscle, but there was a marked reduction in the flow to the stimulated muscle. Both d-tubocurarine and pancuronium decreased the flow to values (1.0 ± 0.3 and 1.5 ± 0.3 ml · min⁻¹ · 100 g⁻¹, respectively, after the highest dose of the two drugs) comparable to that for the unstimulated muscle. However, vecuronium caused only a partial blockade; blood flow to the stimulated muscle after the highest dose was 3.9 ± 1.3 ml · min⁻¹ · 100 g⁻¹.

Regional vascular resistance. As shown in table 1, d-tubocurarine decreased the tissue vascular resistance in stomach, brain, and large intestines, while that in liver (hepatic artery) and spleen was increased. Pancuronium had no effect, whereas vecuronium caused a moderate decrease with its highest dose in the vascular resistance in brain, kidneys, skin, liver, and intestines.

Discussion

The effects of neuromuscular blocking agents on systemic hemodynamic variables—arterial blood pressure, heart rate, and, sometimes, cardiac output—have been described by a large number of investigators. However, little or no attention has yet been paid toward regional...
Fig. 2. Distribution of cardiac output and regional blood flow to major organs in 27 cats at baseline. The liver represents hepatic artery flow and lungs denote bronchial artery plus arteriovenous anastomotic flow. * Only a part of the tissue was dissected out from the body, hence percentage of cardiac output distributed to the whole tissue was not calculated. Mes. + Panc. = Mesentery plus pancreas.

Blood flow (ml.min⁻¹ 100g⁻¹)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Blood Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>328 ± 33</td>
</tr>
<tr>
<td>Stomach</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>Mes. + Panc.</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Brain</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Heart</td>
<td>107 ± 9</td>
</tr>
<tr>
<td>La. Intestine</td>
<td>57 ± 8</td>
</tr>
<tr>
<td>Spleen</td>
<td>122 ± 12</td>
</tr>
<tr>
<td>Sm. Intestine</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Liver</td>
<td>51 ± 6</td>
</tr>
<tr>
<td>Lungs</td>
<td>178 ± 17</td>
</tr>
<tr>
<td>Kidneys</td>
<td>218 ± 9</td>
</tr>
<tr>
<td>Skin*</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Muscles*</td>
<td>1.7 ± 0.2</td>
</tr>
</tbody>
</table>

% Cardiac output

Fig. 3. Effect of d-tubocurarine (400, 800, and 1,600 µg·kg⁻¹), pancuronium (20, 40, and 80 µg·kg⁻¹) and vecuronium (40, 80, and 160 µg·kg⁻¹) on the distribution of cardiac output to some tissues. D₁, D₂, and D₃ represent, respectively, the first, second, and third dose of the drugs. * Significant change from the respective baseline value (P < 0.05).

% Change from baseline

- Stomach
- Brain
- Kidneys
- Skin
- Liver
- Spleen
- Small intestines
- Large intestines
- Adrenals
blood flows that substantially may change without any alterations in the systemic hemodynamics. Because the neuromuscular blocking agents are not being used only in complicated surgical operations but also as an adjunct to optimal ventilatory support in critically ill patients, we thought it important to compare the regional hemodynamic effects induced by \(d\)-tubocurarine, pancuronium, and, its recently discovered monoquaternary analogue, vecuronium. The three drugs were investigated using clinically relevant doses, because the ED90 values for neuromuscular blockade in the cat is: \(d\)-tubocurarine, 0.2–0.34 mg·kg\(^{-1}\); pancuro-

### Table 1. Effect of Neuromuscular Blocking Agents on Regional Vascular Resistance

<table>
<thead>
<tr>
<th></th>
<th>Percentage Change from Baseline Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>d-Tubocurarine (µg·kg(^{-1}))</strong></td>
<td>400</td>
</tr>
<tr>
<td>Stomach</td>
<td>-1±13</td>
</tr>
<tr>
<td>Brain</td>
<td>-17±8*</td>
</tr>
<tr>
<td>Kidneys</td>
<td>-5±5</td>
</tr>
<tr>
<td>Skin</td>
<td>3±15</td>
</tr>
<tr>
<td>Liver</td>
<td>19±10*</td>
</tr>
<tr>
<td>Spleen</td>
<td>4±16</td>
</tr>
<tr>
<td>Small intestines</td>
<td>5±8</td>
</tr>
<tr>
<td>Large intestines</td>
<td>-3±12</td>
</tr>
<tr>
<td>Adrenals</td>
<td>2±9</td>
</tr>
<tr>
<td>Heart</td>
<td>15±18</td>
</tr>
</tbody>
</table>

* Significant change from baseline values (\(P < 0.05\).
The systemic hemodynamic effects of d-tubocurarine consisted of a marked hypotension and a decrease, preceded by a transient increase, in the ascending aortic blood flow. Pancuronium caused a moderate tachycardia but vecuronium was devoid of any systemic hemodynamic activity. Such results are in agreement with several previous investigations dealing with the cardiovascular effects of these drugs. In particular, we confirm that pancuronium, which antagonizes cardiac muscarinic receptors, causes tachycardia, but vecuronium, which has no antimuscarinic activity, does not. The hypotension produced by d-tubocurarine has been reported to result from a combination of autonomic ganglion blockade, direct myocardial depression, and a release of histamine. Indeed, even in humans, d-tubocurarine (0.25–0.75 mg·kg⁻¹) has been shown to cause a dose-related increase in plasma histamine concentration that significantly correlated with hypotension elicited by the drug. In our experiments also, the release of histamine by d-tubocurarine seems likely because there is a striking resemblance between the regional circulatory effects of d-tubocurarine and histamine. This neuromuscular blocker, like histamine in cats, caused an increase in blood flow to stomach and a decrease in that to kidneys, liver, skin, adrenal glands, and spleen. Tissue vascular resistance in stomach and large intestines was reduced, while that in spleen and skin was enhanced by both drugs. Neither pancuronium nor vecuronium produced any major regional hemodynamic changes, other than a moderate vasodilatation in some organs following the largest dose of the monoquaternary agent (table 1). It is known that these drugs do not release endogenous histamine.  

The baseline blood flow, as can be expected because of increased metabolic demand, was about six times higher in the working (stimulated) than in the non-working (unstimulated) tibialis anterior muscle. All three drugs reduced the blood flow to the stimulated muscle perhaps because of a reduction of metabolic activity following neuromuscular blockade. However, d-tubocurarine and pancuronium more effectively reduced the blood flow to the stimulated muscle than did vecuronium. This more potent effect of the first two agents either may result from a prejunctional action
reducing the release of acetylcholine,29 which, in addition to enhanced metabolic activity, is responsible for the vasodilation in skeletal muscles. Alternatively, the preferential anticholinergic autonomic blockade by \( d \)-tubocurarine and pancuronium\(^9,12,29\) also may play a role. Vecuronium practically seems to be devoid of any autonomic activity.\(^9,12\)

In conclusion, our experiments show that, while \( d \)-tubocurarine possesses marked systemic and regional hemodynamic effects that could be dangerous in critically ill patients, pancuronium and, more particularly, vecuronium are devoid of deleterious cardiovascular actions.

This study was financed partly by the Dutch Heart Foundation.

References


