COMPARATIVE HAEMODYNAMIC EFFECTS OF TUBOCURARINE AND METOCURINE IN THE DOG

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SUMMARY

On account of its histamine releasing and ganglion blocking properties tubocurarine is known to have significant haemodynamic effects. Methylation of the compound produces metocurine and should decrease both histamine release and ganglionic blockade. The haemodynamic effects of these two compounds were compared in 10 mongrel dogs anaesthetized with chloralose and morphine. Haemodynamic measurements were made 2 min before and 2, 5, 10 and 20 min after administration of the drugs. Each animal received three doses of each drug with a 2-h rest period between doses: tubocurarine 0.35 (muscle twitch ED$_{95}$), 0.7 and 1.4 mg kg$^{-1}$ and metocurine 0.2 (2 $\times$ ED$_{95}$), 0.4 and 0.8 mg kg$^{-1}$. All doses of tubocurarine produced an increase in heart rate (212, 197 and 212% of control respectively). The mean arterial pressure decreased significantly with 0.7 mg kg$^{-1}$ (48% of control; $P$<0.05). Metocurine produced no significant haemodynamic effects except for the largest dose (8 $\times$ ED$_{95}$). The data suggest that the haemodynamic margin of safety with metocurine in the dog is eight times that of tubocurarine.

In recent years, there has been a renewed interest in the use of dimethyltubocurarine (metocurine) in clinical practice (Savarese, Ali and Antonio, 1977). Structure-activity relationships would predict that the bisquaternary metocurine should produce less histamine release, less profound ganglion blockade and thus lesser haemodynamic side-effects than its monoquaternary analogue tubocurarine. Previous studies have demonstrated that metocurine inhibits neither vagal nor sympathetic activity in cats or monkeys (Hughes and Chappie, 1976a, b) and produces less histamine release (McCullough et al., 1972; Savarese, 1979).

We have compared the haemodynamic effects of metocurine and tubocurarine in dogs.

METHODS

Ten mongrel dogs weighing 17–25 kg were anaesthetized with alpha chloralose 100 mg kg$^{-1}$ and morphine 1 mg kg$^{-1}$ i.v. Arterial pressure was measured in the abdominal aorta via a catheter introduced through the left femoral artery. Central venous, pulmonary artery and pulmonary capillary wedge pressures were recorded via catheters introduced to the right external jugular vein. Heart rate was measured with a tachograph triggered by the arterial pulse wave. Cardiac output was measured by a dye dilution technique using indocyanine green dye and a Beckman recording densitometer. Neuromuscular blockade was measured by the twitch response of the right tibialis anterior muscle stimulated through the peroneal nerve with supramaximal square wave stimuli 0.2 ms in duration at 0.15 Hz. Lung ventilation was controlled to maintain the end-tidal carbon dioxide at 3.5–4.5% recorded by a Beckman LB-1 medical gas analyser.

Following the insertion of the catheters and establishment of a steady state, control measurements were obtained. The animals were then divided arbitrarily into two groups. In group I tubocurarine was given i.v. at three doses—0.35, 0.7 and 1.4 mg kg$^{-1}$ with a 2-h rest period between each dose. Group II received metocurine at doses of 0.2, 0.4 and 0.8 mg kg$^{-1}$ with the same rest period. Following the administration of the drug, haemodynamic measurements were made at 2, 5, 10 and 20 min for each dose in each group.

RESULTS

Haemodynamic data are in tables I and II for group I (tubocurarine) and group II (metocurine) at 2 min. Following the administration of tubocurarine 0.35 mg kg$^{-1}$ there was an increase of 212% from control in heart rate ($P$<0.05). Central venous pressure decreased to 28% of control ($P$<0.05) and mean arterial pressure to 70% of control (n.s.). Similar changes
TABLE I. Haemodynamic effects of tubocurarine. *P < 0.05; **P < 0.01. HR = heart rate; BP = mean arterial pressure; CO = cardiac output; CVP = central venous pressure; PA = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance

<table>
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<tr>
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<th>0.35 mg kg(^{-1})</th>
<th>0.7 mg kg(^{-1})</th>
<th>1.4 mg kg(^{-1})</th>
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<tbody>
<tr>
<td></td>
<td>Control 2 min</td>
<td>Control 2 min</td>
<td>Control 2 min</td>
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<tr>
<td>HR (beat min(^{-1}))</td>
<td>57 ± 6</td>
<td>72 ± 9</td>
<td>70 ± 6</td>
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<tr>
<td>BP (mm Hg)</td>
<td>118 ± 7</td>
<td>117 ± 8</td>
<td>114 ± 9</td>
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<tr>
<td>CO (litre min(^{-1}))</td>
<td>2.48 ± 0.7</td>
<td>2.2 ± 1.3</td>
<td>2.4 ± 1.8</td>
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<tr>
<td>CVP (mm Hg)</td>
<td>4.7 ± 0.3</td>
<td>5 ± 0.7</td>
<td>4.6 ± 0.7</td>
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<tr>
<td>PA (mm Hg)</td>
<td>12 ± 1.1</td>
<td>13 ± 1.6</td>
<td>18 ± 1.8</td>
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<tr>
<td>PCW (mm Hg)</td>
<td>5.5 ± 0.4</td>
<td>6 ± 0.9</td>
<td>5.6 ± 0.7</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>3.1 ± 0.3</td>
<td>3.9 ± 0.6</td>
<td>6.1 ± 1.5</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>0.6 ± 0.3</td>
<td>1 ± 0.1</td>
<td>1.2 ± 0.2</td>
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occurred with 0.7 and 1.4 mg kg\(^{-1}\). There were no significant changes in cardiac output.

In group II, there were no significant changes throughout the study period at doses of 0.2 mg kg\(^{-1}\). With 0.4 mg kg\(^{-1}\) there was a significant increase in heart rate and decrease in systemic vascular resistance. Only at 0.8 mg kg\(^{-1}\) were changes, comparable with those obtained with low-dose tubocurarine, noted.

**DISCUSSION**

The chloralose–morphine anaesthetic technique was chosen to produce a preparation with high autonomic tone and slow baseline heart rate, a vagotonic preparation analogous to the clinical findings in adult man.

The initial dose of tubocurarine (0.35 mg kg\(^{-1}\)) was chosen to represent approximately ED\(_{95}\) for neuromuscular blockade in the dog. Subsequent doses were then two and four times ED\(_{95}\) respectively.
The initial dose of metocurine (0.2 mg kg\(^{-1}\)) represents twice ED\(_{95}\) for this drug in the dog (Mogey and Trevan, 1950; Donlon, Ali and Savarese, 1974) with subsequent doses thus representing four and eight times ED\(_{95}\).

It was apparent that the initial dose of tubocurarine (ED\(_{95}\)) and all subsequent doses produced profound haemodynamic changes within 2 min of administration. Such responses are well documented clinically. It was apparent also that no significant haemodynamic change occurred with metocurine at two or four times ED\(_{95}\). Only at eight times the neuromuscular ED\(_{95}\) did metocurine produce changes similar to those noted for tubocurarine at ED\(_{95}\). These data demonstrate that the safety margin for haemodynamic change after metocurine in the dog is therefore eight times greater than that of tubocurarine.

Although metocurine has been available since its synthesis by King in 1935, it has not been popular in clinical use despite early studies suggesting less histamine release (Wilson, Gordon and Raffan, 1950) and little effect on arterial pressure (Stoelting, Graf and Vieira, 1948). More recent studies have confirmed the absence of significant autonomic effects both in animals (Hughes and Chappie, 1976a; Savarese, Ali and Antonio, 1977; Zaiden et al., 1977). The unpopularity may be in some part the result of difficulty in synthesizing the drug and maintaining batch-to-batch potency (Mogey and Trevan, 1950). This is no longer the case (Savarese, Ali and Antonio, 1977).

While the neuromuscular blocking action of metocurine does not differ substantially from those of other non-depolarizing agents, its cardiovascular effects are different and this may offer a distinct advantage. Metocurine does not block the cardiac muscarinic receptors (Hughes and Chappie, 1976b; Savarese, 1979) and thus does not produce a tachycardia (Stoelting, 1974) unless histamine release occurs. This appears to require significantly greater doses than with tubocurarine. This, and its weaker ganglionic-blocking action, reduces the risk of hypotension.

The wide margin of safety for haemodynamic effects between metocurine and tubocurarine shown in this study suggests that the former may be the relaxant of choice for patients with cardiac disease. Its weak ganglion-blocking and histamine releasing properties and its lack of vagolytic (cardiac muscarinic) blocking action may render it appropriate for patients with coronary artery disease where tachycardia and hypotension may result in myocardial ischaemia.

REFERENCES

COMPARAISON DES EFFETS HEMODYNAIQUES DE LA TUBOCURARINE ET DE LA METOCURINE CHEZ LE CHIEN

RESUME
On sait que la tubocurarine produit des effets hemodynamiques significatifs en raison des proprietes qu'elle possede et qui sont a l'origine du degagement d'histamine et du blocage des ganglions. Le traitement au methyle de ce compose produit de la metocurarine et celle-ci devrait permettre de diminuer aussi bien le degagement d'histamine que le blocage des ganglions. On a procede a une comparaison des effets hemodynamiques de ces deux compose sur 10 chiens batars anesthesies a l'aide de chloralose et de morphine. Les mesures hemodynamiques ont ete prises 2 min avant et 2, 5, 10 et 20 min apres l'administration des medicaments. Chaque animal a reçu trois doses de chacun des medicaments, avec une periode de repos de 2 h entre les doses: tubocurarine 0,35 (crispation du muscle ED\(_{95}\)), 0,7 et 1,4 mg kg\(^{-1}\) et metocurine 0,2 (2 x ED\(_{95}\)), 0,4 et 0,8 mg kg\(^{-1}\).
Toutes les doses de tubocurarine ont produit une augmentation de la frequence cardiaque (respectivement 212, 197,
212% des valeurs témoins). La pression artérielle moyenne a diminué d’une manière significative avec 0.7 mg kg\(^{-1}\) (48% de la valeur témoin; \(P<0.05\)). La métocurine n’a produit aucun effet hémodynamique significatif, sauf en ce qui concerne la plus forte dose (8 \(\times\) ED\(_{50}\)). Les données obtenues laissent penser que chez le chien la marge de sécurité hémodynamique de la métocurine est de huit fois celle de la tubocurarine.

**VERGLEICHWEISE HÄMODYNAMISCHE WIRKUNGEN VON TUBOCURARIN UND METOCURIN BEI HUNDEN**

**ZUSAMMENFASSUNG**

Aufgrund seiner Eigenschaften der Freigabe von Histamin und der ganglionischen Blockierung weiss man, dass Tubocurarin wesentliche hämodynamische Wirkungen hat. Methylisierung der Verbindung erzeugt Metocurin, und sollte sowohl die Histamin-Freigabe als auch die ganglionische Blockierung herabsetzen. Die hämodynamischen Wirkungen dieser beiden Verbindungen wurden an zehn Mischrassen-Hunden getestet, die mit Chloralose und Morphium narkotisiert waren. Hämodynamische Messungen wurden 2 min vor und 2, 5, 10 und 20 min nach Verabreichung der Drogen durchgeführt. Jedes Tier erhielt drei Dosen jeder Droge, mit einer zweistündigen Rastperiode zwischen jeder Dosis: 0.35 (Muskelzuckung ED\(_{50}\)), 0.7 und 1.4 mg kg\(^{-1}\) Tubocurarin, und 0.2 (2 \(\times\) ED\(_{50}\)), 0.4 und 0.8 mg kg\(^{-1}\) Metocurin. Alle Dosen von Tubocurarin bewirkten Anstiege des Herzminutenvolumens (212, 197 und 212% des Kontrollwertes), und der mittlere arterielle Druck sank wesentlich mit 0.7 mg kg\(^{-1}\) (48% des Kontrollwertes von \(P<0.05\)). Metocurin bewirkte keine wesentlichen hämodynamischen Effekte, außer in der größten Dosis (8 \(\times\) ED\(_{50}\)). Diese Angaben lassen erkennen, dass die hämodynamische Sicherheitsgrenze von Metocurin bei Hunden achtmal höher liegt wie die von Tubocurarin.

**SUMARIO**

Se sabe que, a raíz de sus propiedades de bloqueo gangliónico y de producción de histamina, la tubocurarina tiene efectos hemodinámicos significativos. La metilación del compuesto produce metocurina y debería reducir tanto la producción de histamina como el bloqueo gangliónico. Se comparon los efectos hemodinámicos de estos dos compuestos en 10 perros cruzados anestesiados con cloralosa y morfina. Se realizaron mediciones hemodinámicas 2 min antes y 2, 5, 10 y 20 min después de la administración de las substancias. Cada animal recibió tres dosis de cada substancia con un periodo de descanso de 2 h entre cada dosis: 0.35 mg (contracción muscular ED\(_{50}\)), 0.7 mg y 1.4 mg kg\(^{-1}\) de tubocurarina y 0.2 mg (2 \(\times\) ED\(_{50}\)), 0.4 mg y 0.8 mg kg\(^{-1}\) de metocurina. Todas las dosis de tubocurarina causaron un aumento del ritmo cardíaco (212, 197, 212% del control, respectivamente). La presión arterial media disminuyó de manera significativa con 0.7 mg kg\(^{-1}\) (48% del control \(P<0.05\)). La metocurina no tuvo ningún efecto hemodinámico significativo, salvo en mayor dosis (8 \(\times\) ED\(_{50}\)). Estos datos sugieren que el margen hemodinámico de seguridad con metocurina en el perro es ocho veces mayor que el de la tubocurarina.