PLASMA CONCENTRATIONS OF PANCURONIUM DURING PREDETERMINED INTENSITIES OF NEUROMUSCULAR BLOCKADE

C. A. SHANKS, A. A. SOMOGYI AND E. J. TRIGGS

SUMMARY

The plasma concentrations of pancuronium were monitored during i.v. infusions of the relaxant in dogs. Pancuronium was administered at rates which maintained the degree of neuromuscular blockade at three predetermined levels. The concentrations of the drug in the blood were consistent for any one animal but showed considerable overlap for the three levels of paralysis between animals. Concentrations obtained during infusion and which maintained the twitch response at 20% and 80% of control were compared, in the same dogs, with concentrations obtained during recovery from a bolus injection of pancuronium. When the infusion maintained the twitch response at 20% of the control value, the mean plasma concentration of pancuronium was 0.152 μg ml⁻¹. That measured after the bolus injection was 0.156 μg ml⁻¹. The concentrations at 80% of control were 0.094 μg ml⁻¹ and 0.083 μg ml⁻¹ respectively. The agreement between these results suggests a relationship between the plasma concentration of the relaxant and its effect during the termination of the action after a large bolus injection of the drug. As this occurs chiefly during the post-distribution equilibrium, the relatively slow decrease in plasma concentration would appear to become the rate-limiting factor in recovery from paralysis.

The relationship between the intensity of neuromuscular blockade produced by a non-depolarizing muscle relaxant and the plasma concentrations of the drug remains enigmatic. Cohen, Paulson and Elert (1957) observed a poor correlation between the blood concentration of tubocurarine (dTC) and the muscular activity of both the intercostal and biceps muscles. Feldman and Tyrell (1970) supported this observation when they proposed their theory of the termination of the action of muscle relaxants. In their isolated arm experiments, release of the tourniquet lowered rapidly the blood concentration of the relaxant, but there was not a concomitant and rapid return toward full neuromuscular transmission. They proposed that the predominant rate-controlling factor for recovery is the rate of disruption of the drug-receptor union rather than the decrease in plasma concentration.

However, Matteo, Spector and Horowitz (1974) reported a highly significant linear correlation between the serum dTC concentration and the twitch tension of the adductor pollicis muscle of the thumb. Feldman (1975) disagreed with their conclusion and suggested that what Matteo's group "...demonstrated was that following injection of dTC, the serum levels of drug in similar individuals fall at approximately the same rate and that the coincident recovery of neuromuscular blockade, following an injection of dTC, also occurs at similar rates in different individuals." Waud (1975) concluded that the two groups of observations were not in disagreement with the conventional views of neuromuscular physiology and pharmacology by calculating the concentrations of dTC at the neuromuscular junction and relating them to the relaxant-receptor dissociation constant and to receptor occupancy.

In defending the apparent correlation between serum dTC concentration and blockade intensity, Matteo (1975) pointed out that there would be a period when dynamic equilibrium exists between dTC concentration in the serum, in the extracellular fluid and at the end-plate. He suggested that the recovery phase following this equilibrium was when the correlation existed.

Diffusion of the muscle relaxant away from the receptor site can be prevented by maintaining a constant plasma concentration by the use of an i.v. infusion of the drug. When examining the early and late relative potencies of pancuronium and dTC in man, Miller and Eger (1976) assumed that a constant concentration of relaxant in the blood would produce both a constant level of paralysis and a constant rate of elimination by the kidney and liver. The subsequent uptake by tissue depots would become negligible with the passage of time as these sites became saturated.
The present studies were designed to examine the constancy of the plasma concentrations of pancuronium during its i.v. infusion at a rate which maintained a constant twitch response. Further studies allowed comparison of the plasma concentrations of the relaxant following its bolus injection with those assayed during continuous infusions of pancuronium in the same animals.

METHODS

Anaesthesia was induced in adult greyhounds (19-36 kg; n = 12) with an injection of sodium pentobarbitone into a foreleg vein. Further pentobarbitone was infused at this site as required, the rate being just sufficient to prevent movement. A cuffed tube was placed in the trachea, and a mixture of 40% oxygen (in air) was used to ventilate the animal with a minute volume sufficient to keep the end-tidal carbon dioxide concentration at 5%. The lower oesophageal and anterior tibialis muscle temperatures were maintained at 38 ± 1 °C. Pressures in the iliac artery and inferior vena cava were monitored via catheters inserted through the femoral vessels. The venous catheter was double-lumen, the second line being reserved for infusion of pancuronium from a McGaw volumetric infusion pump.

The sciatic nerve was isolated in the opposite thigh and transsected. It was stimulated distally via insulated hooked needles, using a 25-V stimulus of 0.2 ms duration at a rate of 0.1 Hz. In the first group of dogs recordings of the electromyograms (e.m.g.) were obtained from insulated hooked needles inserted into the soleus muscle and adjusted for the most monophasic signal. The amplitude of the first major deflection of the e.m.g., as displayed on the storage oscilloscope, was used as the index of neuromuscular transmission. In the second group of dogs the intensity of neuromuscular blockade was measured by two techniques simultaneously. In addition to the e.m.g., the evoked mechanical twitch response was recorded, using the transsected soleus tendon. A stable control twitch height was maintained for not less than 45 min before the administration of pancuronium.

During the infusion of pancuronium, arterial samples were drawn at intervals of 30-60 min after attainment of a constant e.m.g. response. Plasma was separated and the concentrations of pancuronium determined by the spectrofluorimetric method of Kersten, Meijer and Agoston (1973) using a Perkin-Elmer model 204 fluorimeter.

The first group of greyhounds (n = 4) had their e.m.g. twitch responses maintained at 50% of the control value by the infusion of pancuronium for 2, 3, 5 and 5 h respectively.

After the establishment of control values, the second group of greyhounds (n = 8) received a bolus injection of pancuronium via the foreleg infusion line, at a dose of 0.1 mg per kg body weight. Arterial samples were drawn when the e.m.g. response had recovered to 20% and 80% of the control value. Following this, an infusion of pancuronium (40 μg ml⁻¹) was administered via the inferior vena cava. The infusion was adjusted to maintain a predetermined depression of the twitch response usually for 2-3 h. The chosen levels of paralysis at 20% and 80% were allocated randomly so that four of the eight dogs were held at 20% paralysis in the first infusion period and at 80% in the second. When the infusion was discontinued after the period with the response held at 20% of the control value, the time was noted for the recovery of the response to 80% of control. This allowed comparison with the time for the same degree of change in response following the i.v. bolus dose.

RESULTS

Following the infusion of pancuronium in the first group of dogs (e.m.g. response held at 50% of the control value), the average plasma pancuronium concentrations were 0.082, 0.101, 0.111 and 0.097 μg ml⁻¹ respectively, giving an overall mean of 0.098 (SD 0.012) μg ml⁻¹. Details of dog C are shown in figure 1.
Details of the results obtained in the second group of dogs are shown in table I. The mean plasma concentration of pancuronium after an i.v. bolus of 0.1 mg kg\(^{-1}\) was 0.156 (SD 0.037) μg ml\(^{-1}\) at an e.m.g. twitch response of 20% of control, and 0.083 ± 0.030 μg ml\(^{-1}\) at the 80% twitch response level (table IA). The corresponding values during the infusion mean gave a paired t test on the difference between the bolus and infusion plasma concentrations shown in table I would support Matteo (1975) in his concept of the period of relationship after dynamic equilibrium. This does not refute the observations made in the isolated arm experiments, where the release of the tourniquet was not accompanied by a precipitate decrease in recovery from neuromuscular blockade (Feldman and Tyrell, 1970). However, such a precipitate decrease in the plasma concentration would be rare clinically.

After a bolus injection of muscle relaxant, the plasma concentrations show a steep initial decrease, followed by a slower rate of decline. With low doses of relaxant, the attainment of effective plasma concentrations is short-lived, as this initial steep decrease will decrease the blood concentration rapidly. If a large dose of relaxant is used, as recommended by Feldman (1973), then recovery from paralysis will occur entirely during the terminal phase.

In man the terminal phase for pancuronium has a half-life in the region of 90–160 min (Agoston et al., 1973; Somogyi, Shanks and Triggs, 1976). Both these studies used a 6-mg bolus injection of pancuronium and Somogyi and others reported also that the initial recovery from the blockade occurred before the onset of the terminal phase. However, at this point.

### Table I. Group 2 Plasma Concentrations of Pancuronium

<table>
<thead>
<tr>
<th>Dog</th>
<th>Plasma Conc (μg ml(^{-1})) at twitch response (%) Control</th>
<th>Recovery Interval between 20% and 80% Response Concentrations (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.213</td>
<td>0.090</td>
</tr>
<tr>
<td>2</td>
<td>0.170</td>
<td>0.107</td>
</tr>
<tr>
<td>3</td>
<td>0.143</td>
<td>0.058</td>
</tr>
<tr>
<td>4</td>
<td>0.194</td>
<td>0.138</td>
</tr>
<tr>
<td>5</td>
<td>0.100</td>
<td>0.055</td>
</tr>
<tr>
<td>6</td>
<td>0.164</td>
<td>0.084</td>
</tr>
<tr>
<td>7</td>
<td>0.140</td>
<td>0.078</td>
</tr>
<tr>
<td>8</td>
<td>0.120</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Mean* 0.156 ± 0.083

SD 0.037

### Table II: During i.v. Infusion of 40 μg ml\(^{-1}\)

<table>
<thead>
<tr>
<th>Dog</th>
<th>Plasma Conc (μg ml(^{-1})) at twitch response (%) Control</th>
<th>Recovery Interval between 20% and 80% Response Concentrations (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.154</td>
<td>0.071</td>
</tr>
<tr>
<td>2</td>
<td>0.144</td>
<td>0.082</td>
</tr>
<tr>
<td>3</td>
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<td>0.090</td>
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<tr>
<td>4</td>
<td>0.194</td>
<td>0.146</td>
</tr>
<tr>
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<td>0.093</td>
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<tr>
<td>6</td>
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<td>0.106</td>
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<tr>
<td>7</td>
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<td>0.071</td>
</tr>
<tr>
<td>8</td>
<td>0.125</td>
<td>0.093</td>
</tr>
</tbody>
</table>

Mean† 0.152 ± 0.094

SD 0.024

* A paired t test on the difference between the bolus and infusion means gave P values between 0.25 and 0.50.
† Infusion period to produce 20% twitch height preceded that for 80%.
‡ Technical infusion problems precluded completion of this period.

The results in table I for the dogs in group 2 suggest that the plasma concentrations of pancuronium at 20% and 80% paralysis following an i.v. bolus dose of pancuronium are similar to the concentrations obtained during infusion. The results for any one level of twitch response show a range of plasma concentrations, with some overlap between the 20% and 80% response concentrations. In an attempt to produce internally consistent e.m.g. responses, each animal was used as its own control, as the degree of paralysis observed may be valid only for the muscle site examined. The comparability of the bolus and infusion plasma concentrations shown in table I would support Matteo (1975) in his concept of the period of relationship after dynamic equilibrium. This does not refute the observations made in the isolated arm experiments, where the release of the tourniquet was not accompanied by a similar rapid change in recovery from neuromuscular blockade (Feldman and Tyrell, 1970). However, such a precipitate decrease in the plasma concentration would be rare clinically.

The maintenance of predetermined responses during the i.v. infusion of a drug should provide information on the therapeutic concentrations of the drug as they plateau in body fluids. The results obtained for pancuronium from the dogs in group 1 (for example fig. 1) suggested that a reasonably steady e.m.g. response and plasma concentration could be expected within 2 h of attaining the selected level of paralysis. As the dogs in group 2 had their infusions commenced after an i.v. bolus of pancuronium had been administered, a shorter time for the attainment of relatively constant plasma concentrations could be anticipated.

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In man the terminal phase for pancuronium has a half-life in the region of 90–160 min (Agoston et al., 1973; Somogyi, Shanks and Triggs, 1976). Both these studies used a 6-mg bolus injection of pancuronium and Somogyi and others reported also that the initial recovery from the blockade occurred before the onset of the terminal phase. However, at this point.
time distribution was largely completed, and a major part of the recovery from paralysis occurred in the terminal phase. The mean value of the plasma concentrations of pancuronium when human patients had recovered to 20% of control was 0.169 μg ml\(^{-1}\) (Somogyi, Shanks and Triggs, 1976), and this compares to the 0.156 μg ml\(^{-1}\) in the dog (table I).

Several groups of workers have examined the pharmacodynamics of pancuronium and demonstrated the terminal phase (Agoston et al., 1973; McLeod, Watson and Rawlins, 1976; Somogyi, Shanks and Triggs, 1976). All interpreted their data according to a multicompartment open model. McLeod, Watson and Rawlins (1976) showed that the elimination of pancuronium in this terminal phase was diminished markedly in patients with poor renal function. Presumably, a prolonged increase of the plasma pancuronium concentrations explains the increased duration of its activity observed in patients with renal failure (Miller, Stevens and Way, 1973).

Goat and others (1976) examined, in the dog, the effects of alterations in the circulation on the blockade produced by gallamine triethiodide, using a roller pump and aorto-femoral shunt to change limb blood flow. They did not find a correlation between the rate of recovery from paralysis and the blood flow to the muscle, although the onset and depth of paralysis were related directly. Unfortunately, their study did not include measurement of plasma concentrations of gallamine. As their dogs received a preliminary dose of gallamine, it is unlikely that the plasma concentrations of relaxant in these studies would have decreased at rates comparable to those expected in the isolated arm experiments of Feldman and Tyrell (1970).

Goat and colleagues (1976) used the time from 75% to 25% paralysis for their recovery index, which for their dogs lay between 5 and 30 min. Thus, the recovery index for gallamine in dogs appears to be of duration comparable to that following a bolus injection of pancuronium (table I). During the subsequent infusion studies, only one of our dogs recovered more slowly than within 15 min, suggesting a similarity in the termination of action following both techniques of pancuronium administration. In conclusion, it would appear that there are two mechanisms which can function as the rate-controlling factor in the termination of action of a non-depolarizing muscle relaxant. When the decrease in its plasma concentration is precipitate, then the rate of disruption of the drug–receptor union is the predominant factor (Feldman and Tyrell, 1970). However, when the decrease in circulating relaxant concentrations occurs more slowly, particularly when renal failure or other disease states slow the rate of elimination, the rate of decrease in the plasma concentrations becomes predominant.

ACKNOWLEDGEMENTS

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REFERENCES


CONCENTRATIONS DE PANCURONIUM DANS LE PLASMA PENDANT LE BLOCAGE NEUROMUSCULAIRE A DES INTENSITES PREDETERMINNEES

RESUME

On a surveillé les concentrations de pancuronium dans le plasma pendant l'infusion intra-veineuse de cet agent
relaxant à des chiens. Le pancuronium a été administré à des taux permettant de maintenir le degré de blocage neuromusculaire à trois niveaux prédéterminés. Les concentrations de cet agent dans le sang ont été constantes, pour n'importe quel animal, mais elles ont accusé des chevauchements considérables entre les animaux, pour les trois degrés de paralysie. Les concentrations obtenues pendant l'infusion, et qui ont maintenu la réaction à la contraction à 20% et à 80% des valeurs témoins, ont été comparées sur les mêmes chiens aux concentrations obtenues pendant la récupération suivant l'injection d'un bol de pancuronium. Lorsque l'infusion a maintenu la réaction à la contraction à 20% de la valeur témoin, la concentration moyenne de pancuronium dans le plasma a été de 0,152 μg ml⁻¹. Celle mesurée après l'injection du bol a été de 0,156 μg ml⁻¹. Les concentrations à 80% de la valeur témoin ont été respectivement de 0,094 μg ml⁻¹ et de 0,083 μg ml⁻¹. La concordance entre ces résultats laisse penser qu'il existe une relation entre la concentration d'agent relaxant dans le plasma et son effet, lorsque l'action qui se produit après la forte injection d'un bol de cet agent, est sur le point de prendre fin. Comme cela se produit essentiellement pendant l'équilibre qui suit la diffusion, la diminution relativement lente de la concentration dans le plasma semble devenir le facteur limitateur du taux pendant la récupération de la paralysie.

**SUMMARY**

**PLASMA PANCURONIUM DURING NEUROMUSCULAR BLOCKADE**

**ZUSAMMENFASSUNG**

Die Plasmakonzentrationen von Pancuronium wurden bei Hunden während intravenöser Infusion des Entspannungsmittels gemessen. Das Pancuronium wurde in Abständen verabreicht, die den Intensitätsgrad der neuromuskulären Blockierung auf drei vorausbestimmten Ebenen bewahrte. Die Drogenkonzentrationen im Blut waren bei den einzelnen Tieren jeweils gleich, unterschieden sich jedoch wesentlich untereinander im Bezug auf die drei Ebenen der Lähmung. Die während der Infusion erzielten Konzentrationen, die die Zuckreaktionen auf 20% und 80% des Kontrollwertes bewahrten, wurden bei denselben Hunden mit den Konzentrationen verglichen, die während der Erholung von einer Bolusinjektion von Pancuronium erzielt wurden. Wenn die Infusion die Zuckreaktion auf 20% des Kontrollwertes bewahrte, betrug die Plasmakonzentration von Pancuronium 0,152 μg ml⁻¹. Die nach der Bolusinjektion gemessene Konzentration betrug 0,156 μg ml⁻¹. Die Konzentrationen bei 80% des Kontrollwertes betrugen 0,094 μg ml⁻¹, bzw. 0,083 μg ml⁻¹. Die Übereinstimmung zwischen diesen Resultaten lässt eine Beziehung zwischen den Plasmakonzentrationen der Droge und ihren Wirkungen während der Beendigung der Drogeneinwirkung nach einer grossen Bolusinjektion von Pancuronium erkennen. Das die hauptsächlich während des Äquilibriums nach Verteilung der Droge geschieht, scheint das relativ langsames Absinken der Plasmakonzentration der Faktor zu sein, durch den das Tempo der Erholung von der Lähmung eingeschränkt wird.

**CONCENTRACIONES DE PLASMA DE PANCURONIO DURANTE INTENSIDADES PREDETERMINADAS DE BLOQUEO NEUROMUSCULAR**

Se observaron las concentraciones de plasma de pancuronio durante infusiones intravenosas del relajante en perros. El pancuronio fue administrado en cantidades que mantuvieron el grado de bloqueo neuromuscular a tres niveles preterminados. Las concentraciones de la droga en la sangre resultaron consistentes para cualquiera de los animales pero acusó un considerable desborde entre los tres niveles de parálisis entre animales. Se compararon las concentraciones obtenidas durante la infusión y que mantuvieron la respuesta de sacudida muscular a 20% y 80% de control, en los mismos perros, con concentraciones obtenidas durante la recuperación mediante una inyección de bolo de pancuronio. Cuando la infusión mantuvo la respuesta de sacudida muscular a 20% del valor de control, la concentración media de plasma de pancuronio fue de 0,152 μg ml⁻¹. Aquella medida después de la inyección de bolo fue de 0,156 μg ml⁻¹. Las concentraciones a 80% de control fueron de 0,094 μg ml⁻¹ y 0,083 μg ml⁻¹ respectivamente. El acuerdo entre estos resultados sugiere una relación entre la concentración de plasma del relajante y su efecto durante la terminación de la acción después de una gran inyección de bolo de la droga. Como esto ocurre principalmente durante el equilibrio post-distributivo, la disminución relativamente lenta en la concentración de plasma parece convertirse en el factor limitador del tiempo de recuperación del parálisis.