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# Alcuronium pharmacodynamics in dogs: effect-concentration relationships in the diaphragmatic and limb muscles

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Previous studies suggest that the muscles of the diaphragm are less sensitive to neuromuscular blocking agents than the limb muscles. However, this difference has not been characterized directly in terms of relaxant drug plasma concentrations. The pharmacodynamics of the non-depolarizing muscle relaxant alcuronium were therefore investigated in nine dogs using a constant-rate infusion regimen with simultaneous measurement of muscle paralysis in the limb and diaphragm. Maximum paralysis between 95 and 100% was achieved in both muscle groups, within approximately the same time interval. However, during onset of and offset of effect, the pharmacodynamic parameters ECp50 and ECp95 for the limb muscle were lower than in the diaphragm. From a pharmacodynamic effect model it was also predicted that Css(50) and Css(95) for the limb muscles are half those values for the diaphragm. Thus, the diaphragm is less sensitive to the action of alcuronium than are limb muscles. The half-time for equilibration of alcuronium between plasma and the effect site was two-fold lower for the diaphragm, and the rate of recovery from paralysis in diaphragmatic muscles was twice that observed in limb muscles. Collectively, these data suggest that there is a greater margin of safety in the diaphragmatic muscles and that the response of the peripheral limb muscles to nerve stimulation provides only a conservative index of recovery from competitive neuromuscular block in the diaphragmatic muscles.

One major function of neuromuscular blockade during anaesthesia is the relaxation of respiratory musculature, including the diaphragm and the muscles of the abdomen. Clinically, motor nerve stimulation can conveniently be applied to peripheral muscles only. Postoperatively, however, restoration of muscle power in the respiratory muscles, particularly the diaphragm, is of immediate concern since it is necessary to assess conditions for tracheal extubation.

Differential sensitivity of the various muscle groups to non-depolarizing relaxant agents has been reported since the late 1940s. Studies, both in man (Wymore & Eisele 1978; Lee 1976) and in animals (Alderson & Maclagan 1964; Lee et al 1982; Tran et al 1982; Paton & Zamis 1951; Waud & Waud 1972) and in-vitro (Taylor et al 1963; Lu 1970) using isolated muscle preparations have shown that the respiratory muscles are more resistant to blockade by non-depolarizing neuromuscular blocking drugs. Waud & Waud (1972) have shown that this 'sparing' of the respiratory muscles is related to the large 'margin of safety' of neuromuscular transmission. Specifically, in a limb muscle 75–80% of the receptors have to be blocked by curare-like drugs before the most sensitive muscle fibres fail to respond to a single nerve stimuli and 90–95% must be blocked before transmission fails completely. In contrast, the diaphragm needs only 5–10% of receptors to be free to respond normally. Thus, the diaphragm needs only about half as many receptors free as the limbs for a normal twitch response. Those workers also showed in-vitro that the concentration of non-depolarizing neuromuscular blocking drugs needed to block the diaphragm is double that needed to block peripheral muscles (Waud & Waud 1975). Furthermore, it has been shown that the difference in sensitivity is not related to the affinities of the respiratory and limb muscles for the non-depolarizing agents (Lu 1970).

Unfortunately, in the in-vivo studies where the differential sensitivity of the various muscle groups has been studied, relaxant drug plasma concentrations and muscle paralysis have not been determined

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simultaneously, and the difference in response has been interpreted on the basis of drug dosage rather than concentrations. The present study was therefore undertaken to characterize the reported differences in response of the diaphragmatic and peripheral muscles using quantitative assessment of both muscle function and relaxant drug concentration. For ethical and practical reasons it was not possible to conduct such a study in man. Therefore, the study was carried out in dogs using alcuronium as the pharmacological tool since this agent possesses no active metabolites and has a relatively short half-life in dogs, facilitating characterization of onset and offset data in the same subject. By producing progressive paralysis with alcuronium, the relationship between alcuronium concentration and diaphragm and limb muscle paralysis was examined using pharmacodynamic modelling techniques.

## METHODS

Fasted greyhound dogs of either sex (6 M, 3 F), 20–33 kg, were anaesthetized by an intravenous injection of sodium pentobarbitone 30 mg $kg^{-1}$, into a foreleg vein. Additional amounts were infused at this site when required. The animals were intubated and ventilated mechanically with a mixture of air and oxygen to maintain an end-expired carbon dioxide level at 5%. This was monitored continuously with an Infrared analyzer (Datex, CD-101, Finland) to eliminate the possibility of neuromuscular blockage related to $CO_2$ retention (Baraka 1964; Bridenbaugh et al 1966). A femoral artery was cannulated to monitor blood pressure and blood gases, and for blood sampling. Continuous monitoring of the gas flow in the airway, the electrocardiogram and the arterial blood pressure were performed by means of a multichannel recorder. Dextran (6%) in isotonic saline was infused via the foreleg vein throughout the experiment to help maintain arterial pressure and urinary flow. The temperature of the lower oesophageal and anterior tibialis muscles was maintained between 37 and 39 °C by means of water-circulating heating/cooling blankets.

The degree of neuromuscular blockade was assessed simultaneously in the diaphragmatic and limb muscles. After surgical exposure in the neck and thigh, the phrenic and sciatic nerves were simultaneously stimulated at 10 s intervals (0·1 Hz) with a supramaximal stimulus of 0·1 ms duration. The diaphragmatic electromyogram (EMG) was recorded from insulated wires placed intramuscularly via a small anterolateral thoracotomy while the limb EMG was recorded via needle electrodes placed percutaneously into the small muscles of the hind foot. The intensity of paralysis was assessed from the depression of the EMG amplitude relative to their respective control heights. Neuromuscular blockade was quantified by the degree of paralysis; with zero per cent (the control value) representing no paralysis and 100% representing complete paralysis.

After the control EMG response had stabilized, alcuronium was infused via the foreleg vein at 66·7 μg $min^{-1}$ (mean dose administered was 0·07 ± 0·01 mg $kg^{-1}$), until 95–99% depression of twitch tension occurred in the diaphragm. This infusion rate was chosen after a preliminary study in one dog so that complete paralysis was attained within 30 min.

Blood samples were obtained from iliac artery contralateral to that of the stimulated limb. Samples were withdrawn at 1 min intervals until 10 min post infusion hence at 5–10 min intervals for a further 90 min or until full recovery of the twitch response occurred in the diaphragm.

### *Data analysis*

*Effect-concentration relation.* Plasma concentration-time and paralysis data were available in all dogs during onset and offset of paralysis in the limb and diaphragmatic muscles. Two approaches were used to model the pharmacodynamic data as previously described (Walker et al 1983). Briefly, both the onset and the offset paralysis-concentration data from each set of muscles were fitted to the non-linear form of the Hill equation (Wagner 1968), yielding the pharmacodynamic parameters ECp50, the effective concentration at 50% paralysis, and s, an exponential term describing the sigmoidicity of the effect-concentration relationship. Secondly, plasma concentration-time-paralysis data for each muscle group gathered during onset and offset were fitted simultaneously to a pharmacokinetic and pharmacodynamic effect model (Sheiner et al 1979). The pharmacokinetic parameters were generated using an equation for a constant-rate infusion (Gibaldi & Perrier 1982) and the amount of alcuronium in the effect compartment was determined according to Colburn (1981). This yielded three pharmacodynamic parameters, Css(50) corresponding to 50% paralysis at steady state, s, describing the sigmoidicity at steady state and $k_{eo}$, the rate constant reflecting the equilibrium of alcuronium between plasma and the effect site. Recovery from paralysis in the 20–80% effect range in each muscle group was assessed using linear regression analysis of the paralysis-time data.

*Pharmacokinetic data.* Although the pharmacokinetics of alcuronium in the dog were not the primary concern of this study, some model-independent pharmacokinetic parameters were calculated for comparison with human data. Briefly the total plasma clearance was calculated as dose divided by the total area under the plasma concentration-time curve, which was estimated by the Lagrange method (Yeh & Kwan 1978). The apparent volume of distribution at steady state and the terminal half-life of alcuronium were calculated by moment analysis corrected for input via an infusion (Lee et al 1980) and linear regression of the terminal plasma concentration data, respectively. Statistical analyses were carried out using either the unpaired or paired Student's *t*-test as appropriate for each data set.

## RESULTS

### *Pharmacodynamics of alcuronium*

Maximum paralysis in the limb muscle (98 ± 2%) was similar to that attained in the diaphragm (96 ± 3%) but was achieved in a shorter time (25 ± 5 and 29 ± 6 min, respectively; $P < 0.05$ paired *t*-test). Alcuronium plasma concentrations at onset of peak effect did not differ significantly between the two muscle groups (0·29 ± 0·06 and 0·32 ± 0·07 in the limb and diaphragm, respectively). Fig. 1a shows the

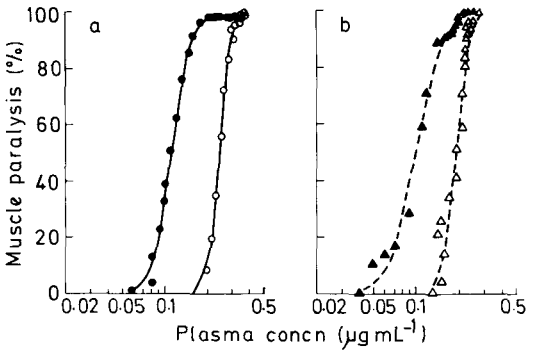


FIG. 1. Relationship between muscle paralysis and alcuronium plasma concentration in (a) the limb and (b) diaphragmatic muscles during onset (open symbols) and offset of (closed symbols) paralysis. The curves were generated using the non-linear form of the Hill equation.

limb muscle paralysis-concentration data in one dog (D9) both during onset and offset of effect, while Fig. 1b shows similar data from the diaphragmatic muscles in another dog (D7). The response-concentration relationship was sigmoid for both muscle groups but the plasma concentration corresponding to a particular degree of paralysis was higher during onset than during offset of effect. Fig. 2a displays the

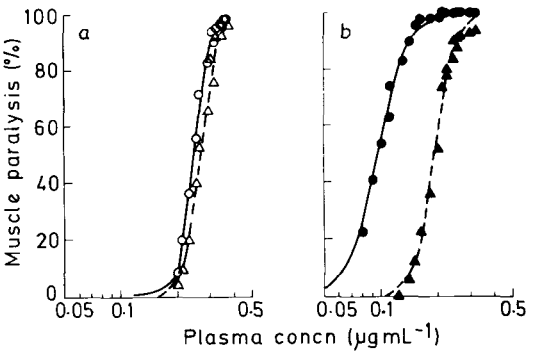


FIG. 2. Relationship between muscle paralysis and alcuronium plasma concentrations during (a) onset and (b) offset of effect in the limb (○, ●) and diaphragmatic (△, ▲) muscles. The curves were generated using the non-linear form of the Hill equation.

onset data for both the limb and diaphragmatic muscles in a single dog (D9). The curves appeared superimposable and this was true for all but two dogs. However, during offset of effect, the effect-concentration curves from the limb and diaphragmatic muscles were not superimposable in any dog. An example of a typical plot during offset in one dog (D8) is shown in Fig. 2b.

Mean effect-concentration data in the limb and diaphragmatic muscles are shown in Fig. 3a (onset) and Fig. 3b (offset). The diaphragm effect-concentration curve is shifted to the right of the limb muscle curve.

The Hill equation parameters, s and ECp50, and the calculated ECp95 value (corresponding to 95% paralysis) obtained during onset and offset of effect,

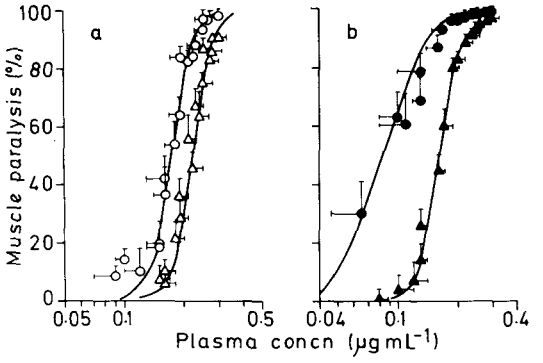


FIG. 3. Effect-concentration relationship for alcuronium during (a) onset and (b) the offset of action in the limb (○, ●) and diaphragmatic (△, ▲) muscles. Each data point represents the mean from nine dogs. The horizontal and vertical bars represent the standard error of the mean plasma concentration and muscle paralysis data points, respectively. The curves were generated using the mean estimates of s and ECp50.

respectively, in both muscle groups are presented in Table 1. When onset and offset data were compared, s, ECp50 and ECp95 were each significantly higher ($P < 0.01$, respectively) during onset of effect in the limb, but only ECp50 and ECp95 were significantly ($P < 0.01$) higher during onset of effect in the diaphragm. The values of the exponent, s, did not differ significantly between the limb and diaphragmatic muscles either during onset or offset of effect. However, both ECp50 and ECp95 were significantly lower in the muscles of the limb relative to the diaphragm during both onset and offset of effect.

Fig. 4a displays the concentration-time and limb muscle paralysis data for one dog (D2) using the effect model, while Fig. 4b represents similar data in the same dog obtained from the diaphragm. Inspection of this Figure and that for all other animals revealed excellent agreement between observed and fitted plasma concentration and effect data using the pharmacodynamic effect model.

Computer estimates of $k_{eo}$ s and Css(50) obtained using the effect model and the calculated $t_{\frac{1}{2}}k_{eo}$ (half-time for equilibration between plasma and effect site) and Css(95) values for both the limb and diaphragmatic muscles are presented in Table 2. The

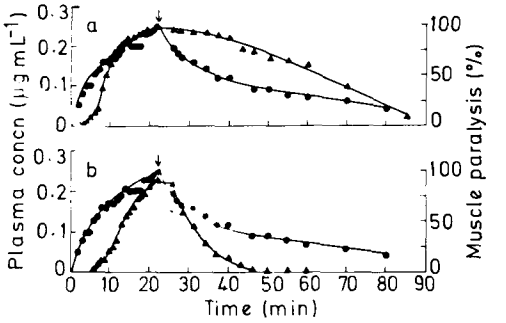


FIG. 4. Relationship between effect-time and alcuronium plasma concentration in a single dog (D2) for (a) the limb and (b) the diaphragmatic muscle. The curves joining the concentration-time data points (●) were generated by the use of a biexponential (two-compartment) model equation, while the curves joining the paralysis time data points (▲) were generated by use of the pharmacodynamic effect model. The arrows indicate the time at which the alcuronium infusion was terminated.

Table 1. Hill equation pharmacodynamic parameter estimates for alcuronium during onset and offset of effect from the canine limb and diaphragmatic muscles.

| | Pharmacodynamic parameters | | | | | |
|---|---|---|---|---|---|---|
| | Limb | | | Diaphragm | | |
| Subject code | s | ECp50 (μg mL$^{-1}$) | ECp95 (μg mL$^{-1}$) | s | ECp50 (μg mL$^{-1}$) | ECp95 (μg mL$^{-1}$) |
| Onset | | | | | | |
| D1 | 9·93 ± 0·70[a] | 0·16 ± 0·001 | 0·22 | 9·44 ± 0·93 | 0·19 ± 0·002 | 0·26 |
| D2 | 5·96 ± 0·84 | 0·11 ± 0·003 | 0·18 | 10·94 ± 1·15 | 0·18 ± 0·002 | 0·24 |
| D3 | 12·00 ± 4·24 | 0·24 ± 0·005 | 0·31 | 8·10 ± 0·84 | 0·31 ± 0·006 | 0·45 |
| D4 | 2·40 ± 0·13 | 0·09 ± 0·003 | 0·31 | 8·56 ± 1·08 | 0·21 ± 0·003 | 0·30 |
| D5 | 12·00 ± 3·40 | 0·25 ± 0·004 | 0·32 | 8·13 ± 1·19 | 0·27 ± 0·005 | 0·39 |
| D6 | 5·00 ± 0·59 | 0·14 ± 0·003 | 0·25 | 6·12 ± 0·64 | 0·16 ± 0·003 | 0·26 |
| D7 | 8·41 ± 1·21 | 0·15 ± 0·003 | 0·21 | 9·30 ± 0·90 | 0·19 ± 0·003 | 0·26 |
| D8 | 11·74 ± 0·90 | 0·16 ± 0·001 | 0·21 | 6·42 ± 0·30 | 0·21 ± 0·002 | 0·33 |
| D9 | 10·46 ± 0·52 | 0·24 ± 0·001 | 0·32 | 9·89 ± 0·77 | 0·26 ± 0·002 | 0·35 |
| Mean ±s.d. | 8·63 ±3·45[c] | 0·17 ±0·06[c,d] | 0·24 ±0·05[c,d] | 8·54 ±1·57 | 0·22 ±0·05[c,d] | 0·32 ±0·07[b,c] |
| Offset | | | | | | |
| D1 | 3·18 ± 0·20 | 0·07 ± 0·001 | 0·18 | 6·94 ± 0·63 | 0·16 ± 0·002 | 0·25 |
| D2 | 2·55 ± 0·13 | 0·05 ± 0·001 | 0·16 | 4·65 ± 0·42 | 0·12 ± 0·003 | 0·23 |
| D3 | 6·52 ± 0·90 | 0·12 ± 0·005 | 0·19 | 6·67 ± 0·65 | 0·25 ± 0·005 | 0·39 |
| D4 | 1·75 ± 0·12 | 0·04 ± 0·003 | 0·22 | 6·49 ± 0·71 | 0·15 ± 0·003 | 0·24 |
| D5 | 11·96 ± 0·74 | 0·16 ± 0·001 | 0·20 | 7·18 ± 0·62 | 0·18 ± 0·003 | 0·27 |
| D6 | 3·44 ± 0·49 | 0·09 ± 0·005 | 0·21 | 12·0 ± 2·74 | 0·13 ± 0·003 | 0·17 |
| D7 | 3·30 ± 0·37 | 0·08 ± 0·004 | 0·20 | 4·71 ± 0·29 | 0·10 ± 0·002 | 0·19 |
| D8 | 5·54 ± 0·31 | 0·10 ± 0·001 | 0·17 | 8·38 ± 0·47 | 0·19 ± 0·002 | 0·27 |
| D9 | 6·34 ± 0·26 | 0·11 ± 0·001 | 0·18 | 12·11 ± 0·67 | 0·17 ± 0·001 | 0·22 |
| Mean ±s.d. | 4·95 ±3·12[c] | 0·09 ±0·04[c,d] | 0·19 ±0·02[b,c] | 7·68 ±2·74 | 0·16 ±0·04[c,d] | 0·25 ±0·06[b,c] |

[a] Estimate ±s.d.
[b] $P < 0.05$ limb vs diaphragm.
[c] $P < 0.01$ onset vs offset.
[d] $P < 0.01$ limb vs diaphragm.

Table 2. Pharmacodynamic parameter estimates for alcuronium from the canine peripheral limb and diaphragmatic muscles using simultaneous pharmacokinetic and pharmacodynamic modelling.

| | Pharmacodynamic parameters | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Limb | | | | | Diaphragm | | | | |
| Subject code | $k_{eo}$ ($min^{-1}$) | $t_{\frac{1}{2}}k_{eo}$ (min) | s | Css(50) ($\mu g\ mL^{-1}$) | Css(95) ($\mu g\ mL^{-1}$) | $k_{eo}$ ($min^{-1}$) | $t_{\frac{1}{2}}k_{eo}$ (min) | s | Css(50) ($\mu g\ mL^{-1}$) | Css(95) ($\mu g\ mL^{-1}$) |
| D1 | 0·15[a] ±0·004 | 4·62 | 3·39 ±0·11 | 0·08 ±0·001 | 0·19 | 0·40 ±0·022 | 1·73 | 5·89 ±0·24 | 0·17 ±0·001 | 0·28 |
| D2 | 0·16 ±0·005 | 4·33 | 4·84 ±0·25 | 0·06 ±0·001 | 0·11 | 0·28 ±0·017 | 2·48 | 5·40 ±0·25 | 0·13 ±0·002 | 0·22 |
| D3 | 0·14 ±0·005 | 4·95 | 7·77 ±0·71 | 0·14 ±0·002 | 0·20 | 0·40 ±0·02 | 1·73 | 7·2 ±0·26 | 0·27 ±0·002 | 0·41 |
| D4 | 0·15 ±0·01 | 4·62 | 1·67 ±0·07 | 0·05 ±0·002 | 0·29 | 0·27 ±0·02 | 2·57 | 5·9 ±0·24 | 0·17 ±0·002 | 0·28 |
| D5 | 0·17 ±0·003 | 4·08 | 9·97 ±0·41 | 0·19 ±0·001 | 0·26 | 0·20 ±0·006 | 3·47 | 6·91 ±0·28 | 0·21 ±0·002 | 0·32 |
| D6 | 0·18 ±0·012 | 3·85 | 4·07 ±0·27 | 0·10 ±0·002 | 0·21 | 0·39 ±0·024 | 1·78 | 7·00 ±0·29 | 0·14 ±0·001 | 0·21 |
| D7 | 0·18 ±0·008 | 3·85 | 4·32 ±0·23 | 0·09 ±0·002 | 0·18 | 0·14 ±0·003 | 4·95 | 5·29 ±0·18 | 0·12 ±0·001 | 0·21 |
| D8 | 0·19 ±0·003 | 3·64 | 6·69 ±0·19 | 0·10 ±0·001 | 0·16 | 1·69[b] ±0·24 | 0·41 | 7·21 ±13 | 0·20 ±0·001 | 0·30 |
| D9 | 0·13 ±0·002 | 5·33 | 5·90 ±0·21 | 0·12 ±0·001 | 0·20 | 0·30 ±0·007 | 2·31 | 8·22 ±0·24 | 0·20 ±0·001 | 0·29 |
| Mean ± s.d. | 0·16[b] ±0·02 | 4·36[b] ±0·56 | 5·40 ±2·49 | 0·10[b] ±0·04 | 0·20[b] ±0·05 | 0·45 ±0·47 | 2·38[b] ±1·27 | 6·56 ±0·98 | 0·18[b] ±0·05 | 0·28[b] ±0·06 |

[a] Estimate (±s.d.).
[b] $P < 0·01$ limb vs diaphragm.

estimate of $k_{eo}$ was significantly lower using data obtained from the limb muscles, and thus the $t_{\frac{1}{2}}k_{eo}$ was longer than that obtained with the diaphragm data. Estimates of the exponent, s, did not differ significantly for the two muscle groups but both the Css(50) and the Css(95) values were significantly higher in the diaphragm.

Rate of recovery from paralysis in the linear 20–80% effect range in the diaphragmatic muscles (3·80 ± 1·16% $min^{-1}$) was approximately twice that in the limb muscle (1·58 ± 0·42% $min^{-1}$, $P < 0·01$ paired *t*-test).

*Pharmacokinetics of alcuronium*

The pharmacokinetic parameters for alcuronium in dogs are different from those obtained in normal surgical patients. Alcuronium half-life in dogs was approximately five times shorter than in man (Walker et al 1980) (38 ± 21 and 200 ± 76 min, respectively) and the plasma clearance was substantially greater (5·70 ± 1·12 and 1·32 ± 0·32 mL $min^{-1}$ $kg^{-1}$, respectively). Although the volume of distribution was three-fold lower in dogs than in man in absolute terms (6·8 ± 1·7 vs 20·9 ± 7 L), this difference could be accounted for by differences in body weight (254 ± 43 vs 316 ± 94 mL $kg^{-1}$).

## DISCUSSION

To achieve maximal paralysis in the limb and diaphragm muscles over a short time a relatively fast constant-rate infusion of alcuronium was administered to dogs. This regimen was successful in providing effect-concentration-time data both during onset and offset of effect, in all animals studied.

For both muscle groups it was possible to characterize accurately the relationship between plasma concentration and effect during onset and offset of action using the non-linear form of the Hill equation. However, ECp50 and hence ECp95 estimates obtained during onset were substantially higher than those obtained during offset of effect, for both muscle groups. This discrepancy arises because the Hill equation does not account for the fact that onset data are gathered during a relatively rapid infusion when plasma concentration and effect are maximally out of phase (Sheiner et al 1979), whereas, offset data are gathered when disequilibrium between concentration and effect is minimal. However, using a pharmacodynamic effect model the discrepancy between the onset and offset effect-concentration data may be reconciled and an estimate obtained of the steady-state effect-concentration relationship for both muscle groups.

The time to peak effect was significantly shorter

and the maximum effect higher in the peripheral muscle than in the diaphragm during onset. However, these differences were small and corresponding plasma alcuronium concentrations did not differ significantly. The similar plasma concentrations probably reflect the relatively rapid infusion of alcuronium used in this study which would have obscured any possible differences in response between the limb and diaphragmatic muscles. However, the ECp50 (and ECp95) estimate for alcuronium during onset of effect in the diaphragm was approximately 30% higher than in the limb muscle.

The offset data in each dog clearly showed that the effect-concentration curves for the diaphragm muscles was shifted to the right of those for the limb muscles. Thus ECp50 and ECp95 during offset of effect were higher in the diaphragm than in the peripheral limb. Similarly the Css(50) and Css(95) were approximately two-fold higher in the diaphragm than in the limb muscles. These results imply that canine diaphragmatic muscle is less sensitive to the action of alcuronium than are limb muscles.

The results of the present study confirm previous findings which indicate that there are differences in sensitivity between the limb and diaphragmatic muscles. For example, Wymore & Eisele (1978) found that the sensitivity to (+)-tubocurarine, of human peripheral musculature was about twice that in diaphragmatic muscles, while Taylor et al (1963) showed in-vitro that guinea-pig peripheral muscles are more sensitive than the diaphragm to (+)-tubocurarine. The data we obtained with alcuronium are also consistent with the classical in-vitro findings of Waud & Waud (1972) which showed that the concentration of (+)-tubocurarine required to block nerve transmission in the diaphragm was double that needed to block the peripheral musculature (Waud 1977).

In addition to being less sensitive to alcuronium, the diphragmatic muscles in the dog also recovered from neuromuscular paralysis at a rate double that in peripheral muscles. Previous work in man (Johansen et al 1964; Lee 1976; Wymore & Eisele 1978) and animals (Waud & Waud 1972; Tran et al 1982) have also shown that recovery in the diaphragm precedes that in the peripheral muscles.

The observed differences in sensitivity of the limb and diaphragmatic muscles to curare-like drugs may result from a number of possible factors including differences in receptor affinity, muscle temperature, blood flow and diffusional characteristics. The first possibility seems unlikely since the affinities of (+)-tubocurarine and other non-depolarizing blocking agents to the neuromuscular junction receptors of the limb and diaphragm are similar (Lu 1970). That temperature affects the action of non-depolarizing relaxant drugs is well recognized. Alderson & Maclagan (1964) observed that the temperature of the limb muscles of cats was always about 2–3 °C lower than the respiratory muscles. They attributed their finding of a difference in sensitivity to (+)-tubocurarine to a difference in muscle temperature. When the temperature of the two muscles was brought to the same level, the magnitude of the block produced was similar. However, they did note that the difference in sensitivity between the soleus muscle on the one hand and the tibialis and respiratory muscles on the other hand was a true difference and not the result of a temperature gradient. Despite attempts to control temperature in the present study, the limb muscle temperature was 2–3 °C lower than the oesophageal temperature. Similarly, Waud & Waud (1972) concluded that temperature differences between the limb and respiratory muscles in the cat were not responsible for differences in sensitivity to (+)-tubocurarine. Their conclusions are supported by the in-vitro experiments of Taylor et al (1963) showing differences in muscle sensitivity at controlled temperatures.

Theoretically, muscle blood flow may also play a role in the difference in sensitivity of the limb and diaphragmatic muscles. However, the time for alcuronium plasma concentration to equilibrate with the effect site was shorter in the diaphragm than in the limb muscles ($t_{\frac{1}{2}}k_{eo}$; 2 and 4 min, respectively) and muscle perfusion is one of the major determinants of $k_{eo}$ and $t_{\frac{1}{2}}k_{eo}$ (Sheiner et al 1979). Thus our results imply that muscle blood flow may not be important since the diaphragmatic muscles are better perfused yet are more resistant to blockade than are the limb muscles. In addition, differences in transport and distribution cannot solely explain the results since such barriers are minimal in in-vitro preparations where similar differences in sensitivity have been observed (Waud & Waud 1975).

Although the exact reason for the differences in sensitivity to alcuronium between the limb and diaphragmatic muscles cannot be established from the present work, the experimental results clearly demonstrate that a higher plasma concentration of alcuronium is needed to elicit the same response in the diaphragm as in the limb, which, together with the fact that Waud & Waud (1975) also found this to be true in their in-vitro preparation, suggests that a

pharmacodynamic rather than a pharmacokinetic (distribution and elimination) mechanism is likely. Thus, the present data also support the conclusions of Waud & Waud (1975) that, in order to exhibit a normal twitch response, the diaphragm needs a smaller fraction of free cholinergic receptors than the limb. Furthermore, recovery of the diaphragmatic musculature precedes that in the limb and occurs at double the rate.

Although the pharmacokinetics of alcuronium was not a major concern in this study, the pharmacokinetic parameter estimates indicate that the disposition of alcuronium in dogs is quantitatively different from that in man. Furthermore, effective concentrations in dogs are approximately five times less than in man (Css(95), man vs dogs; 0·91 vs 0·20 $\mu g\ mL^{-1}$).

In summary, the findings with alcuronium demonstrate that in the dog the muscles of the diaphragm are more resistant to blockade than the limb muscles and that they recover faster from the neuromuscular paralysis. Thus, the response of the peripheral muscles to nerve stimulation provides only a conservative index of recovery from competitive neuromuscular block in the diaphragmatic muscles.

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