CENTRAL EFFECTS OF FIVE MUSCLE RELAXANTS*

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RESEARCH in the past twenty years has contributed significantly to the basic understanding and management of diverse problems in various aspects of clinical medicine. Not the least of these have been advances in anaesthetic techniques, equipment, and available agents which now make possible the contemplation and execution of surgery on "bad risk" patients under such deliberately altered conditions of body economy as hypothermia and extracorporeal circulation. Under such conditions the possibility then arises that the side-effects of a compound or group of compounds may have much more significance than previously.

The introduction of curare into clinical anaesthesia in 1942 by Griffith and Johnson¹ has led to a steadily increasing use of muscle relaxants. A voluminous literature has developed relating to their mode of action both clinically and in the laboratory, and a review of these agents in man has been recently prepared by Foldes.²

It is well accepted that some patients exhibit an abnormal response to relaxant administration, the most vexing and probably the most familiar being that of prolonged hypoventilation or apnoea. Having excluded such causes of respiratory failure as hyperventilation with suppression of the Hering-Breuer reflex, hypocarbia secondary to hyperventilation, gross hypoventilation with carbon dioxide narcosis, respiratory depression secondary to hypnotics, depleted plasma pseudocholinesterase, electrolyte imbalance, and obvious overdosage of relaxant with prolonged myoneural block, there remains a group in which no ready cause is apparent and where a direct central effect of relaxants might be considered.

The purpose of the present study was to assess the central activity of five muscle relaxants in healthy dogs under conditions which excluded all of the abovementioned factors.

METHOD

The investigation of the central action of drugs makes it necessary to separate the central from peripheral effects of the injected agent. To accomplish this, the classical isolated-head technique described by Heymans and Ladon³ and Heymans and Heymans⁴ was used. The method utilizes the cardiovascular system of one

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dog (Donor) to perfuse the head of another (Recipient) which has been separated from its body except for its nervous connections (Fig. 1).

CROSS-CIRCULATION DOGS

FIGURE 1

Healthy dogs of average weights of 15–20 kg. were anaesthetized with intravenous pentobarbital sodium 30 mg./kg. and one femoral artery and vein were cannulated in each dog. The arterial blood pressure of each could then be continuously recorded on a kymograph. Tracheostomy was performed on each animal and a glass T-cannula was inserted into the donor, while in the recipient a special copper tracheal cannula for attachment of a Hall pneumotachygraph was inserted. The carotid arteries and external jugular veins were isolated in both dogs and, after the donor had received 5 mg./kg. Heparin intravenously, vascular anastomoses were established (as shown in Fig. 1) between the two dogs by means of siliconized plastic catheters fitted with capped side tubes for injections. Harvard Model 607 respirators were used when the respiratory rate and/or tidal volume decreased by an arbitrary 50 per cent of control values in either animal. Rectal temperature in each animal was recorded periodically with standard mercury thermometers. The electrocardiograph and electroencephalograph of each animal were recorded on a Grass Model 5 polygraph by means of four-limb subcutaneous plate electrodes and occipital and parietal needle electrodes respectively. The respiratory activity of the recipient, measured by the pneumotachygraph, was also recorded on the Grass polygraph. Then, one sciatic nerve in each animal was isolated and divided for subsequent electrical stimulation with bi-polar electrodes and a Grass square-wave stimulator.

The adequacy of circulatory isolation from the recipient body was checked before injection of the relaxant drugs by intravenous administration of 20–40 μ gm. adrenaline into the femoral vein of the donor dog. A prompt pressor response

in the donor and a reflex bradycardia and hypotension in the recipient was indicative of successful isolation.⁶ A similar injection after the series of relaxant injections was done in most cases to demonstrate the persistence of circulatory isolation during the experiment.

The relaxant drug was injected into one carotid-artery cross-over tube so that it went directly into the cerebral circulation of the recipient dog. The dose of relaxant was doubled at intervals of five minutes and continuous recordings of the arterial blood pressure, EEG, EKG, and respiratory activity were made. Interrupted shocks of 40 volts and 5-msec. duration were applied to the distal end of the sectioned sciatic nerve before and two minutes after each injection of relaxant to ascertain the presence or absence of myoneural block; this response was observed visually. A total of approximately ten times the myoneural blocking dose in the donor was given and effects on the abovementioned parameters were noted in the recipient. In three experiments arterial and venous blood samples were obtained from the cross-over tubing for oxygen determinations by the Roughton-Scholander method.⁵

The following relaxants were used, one agent being used in each experiment: succinylcholine chloride (Anectine®, Burroughs Wellcome); d-tubocurare chloride (Tubarine®, B.W.); decamethonium (Syncurine®, B.W.); gallamine tri-ethiodide (Flaxedil®, Poulenc); 1,6-hexamethylene-bis-carbaminoylcholine (Imbretil®, B.W.)

RESULTS

The present experiments revealed that, collectively, as indicated in Table I, electrocardiograph activity was unimpaired in the absence of hypoxia. Arterial blood pressure in both donor and recipient was well maintained in every experiment at all the dosage levels employed, except for the d-tubocurare group. In the d-tubocurare group, a significant hypotension was observed in each experiment and intravenous methoxamine or metamphetamine was given via the donor femoral vein to maintain perfusing pressures.

Two principal positive findings resulted from these experiments. First, in the experiments with decamethonium, curare, and hexamethylene bis-carbaminoylcholine (HMCC), signs of cerebral stimulation were elicited. With decamethonium both EEG and clinical evidence of convulsions following intra-arterial doses of 0.32 and 0.64 mg./kg. were noted (Fig. 2) in two of the three experiments with this agent. In one experiment with curare, although no clinical evidence of convulsions was observed, there was questionable EEG evidence of cerebral stimulation. Finally, in one of the four HMCC experiments there was EEG and clinical evidence of convulsive activity. In all of these experiments oxygenation and cerebral perfusion was felt to be adequate and in the HMCC experiment the arterial oxygen content at the time of convulsions was 17.6 volumes per cent. This finding excluded the possibility that hypoxia was the cause of deranged cerebral activity.

Secondly, respiratory depression was significant and marked in all experiments. This depression was shown to be independent of myoneural block. In each case there was respiratory depression of over 50 per cent in the recipient in the presence

TABLE I
SUMMARY OF EFFECTS OF RELAXANTS

		Doses required for (mg./kg.)				Coincident effects on			
		myoneural junction block		tidal volume reduced 50 per cent		art. press (mm. Hg)	EEG	EKG	Notes
		donor	recip.	donor	recip.				
Succinylcholine	1	0.4	*	0.4	0.2	100	level 1-2	unchanged	corneal reflex present. #1 not on artif. vent.
	2	0.4	*	0.4	0.2	90	level 1-2	unchanged	Hypoxic EKG and EEG changes after 0.8 mg./kg.
	3	0.4	*	0.4	0.2	100	level 1-2	unchanged	
	5	0.8	*	0.8	0.2	80	level 1-2	unchanged	
ClO	6	0.16	*	0.16	0.16	120	level 1-2	unchanged	corneal reflex present. EEG
	7	0.32	*	not reduced	50%	120	0.32 mg./kg.-EEG convulsive activity	S-T seg. after 0.64 mg./kg.	convulsive activity in 7 and 8 after 0.32 mg./kg.
	8	>0.64	*	>0.64	0.16	90	0.32 mg./kg. EEG convulsive activity	unchanged	
Curarine	9	0.8	*	0.8	1.6	70	? convulsion after 1.6 mg./kg.	unchanged	corneal reflex present
	10	0.4	*	0.4	0.2	80	level 2	unchanged	vasopressor support in all experiments
	11	0.4	*	0.4	0.4	70	level 2	unchanged	
Gallamine	12	1.6	*	1.6	1.6	90	level 2	unchanged	corneal reflex present
HMCC†	13	*	0.32 (weak)	*	0.32	110	level 1-2 with 13, 15, 16	unchanged	corneal reflex present
	14	0.32	0.32	0.32	0.04	120	convulsive activity post 0.02, 0.04, 0.08 mg./kg. in 14	unchanged	
	15	0.32	0.16	0.32	0.08	100		unchanged	
	16	0.32	0.16	0.32	0.04	110		unchanged	

*Not blocked

†1,6-Hexamethylene-bis-carbaminoylcholine

FIGURE 2 Decamethonium—convulsions Panel 1 pre convulsions Panel 2 convulsive activity in R post 0.32 mg/kg intracarotid injection Panel 3 30 sec post convulsion noting some flattening and increased slow wave activity 10 mm/sec (D donor R recipient)

of an intact myoneural junction. These effects and the doses required to produce them are summarized in Table II. A typical tracing of respiratory depression is shown in Fig. 3.

TABLE II
RELATING MYONEURAL BLOCK TO RESPIRATORY DEPRESSION OF GREATER THAN 50 PER CENT

		mg/kg intra arterial to recipient							
		0.04	0.08	0.1	0.2	0.3	0.4	0.6	1.2 and over
Curarine (10)									
Myoneural junction									
donor				+	+	+	○	○	○
recipient				+	+	+	+	+	+
Respiration									
recipient		+	+	○	○	○	○	○	○
Succinylcholine (3)									
Myoneural junction									
donor				+	+	+	○	○	○
recipient				+	+	+	+	+	+
Respiration									
recipient				+	○	○	○	○	○
Decamethonium (8)									
Myoneural junction									
donor				+	+	+	+	○	○
recipient				+	+	+	+	+	+
Respiration									
recipient				○	○	○	○	○	○
Gallamine (12)									
Myoneural junction									
donor					+	+	+	+	○
recipient					+	+	+	+	+
Respiration									
recipient					+	+	+	+	○

+ no blocked ○ blocked

FIGURE 3 Decamethonium Panel 1 pre injection 25 mm/sec Panel 2 pre injection 10 mm/sec Panel 3 post 0.16 mg/kg intracarotid injection showing decline in R respiration Panel 4 post 0.64 mg/kg intracarotid injection at 10 mm/sec and 25 mm/sec showing lack of EKG and EEG effects (D donor R recipient)

The four experiments with the new agent 1.6 Hexamethylene bis carbamoyl choline (HMCC) deserve special mention in respect to both central effects on respiration and myoneural block. There was a constant and very marked decrease in both tidal volume and respiratory rate following 0.04 mg/kg in three experiments and following 0.32 mg/kg in the fourth (Table I). There was no evidence of myoneural block in the donor dog until after 0.32 mg/kg in three experiments and a block was never obtained in the donor in the fourth. In each of the HMCC experiments however evidence of myoneural block was demonstrated in the recipient dog with the dosages shown in Table I. This did not occur in any experiments with any of the other agents although they were conducted under the same conditions. Table III which relates myoneural block to respiratory depression in a typical HMCC experiment can be compared with Table II in which this same relationship is expressed with the four commonly used relaxants. To investigate further the myoneural blocking effect of HMCC the classic experiment of Claude Bernard utilizing the frog sciatic nerve gastrocnemius preparation was performed on four different frogs using control frogs with d tubocurarine. Doses of 0.025, 0.12 and 0.14 mg/gm HMCC were injected into the dorsal lymph sac but no myoneural block was ever obtained. The control frogs received 0.15 and 0.32 mg/gm d tubocurarine which elicited a myoneural

TABLE III
RELATING MYONEURAL BLOCK TO RESPIRATORY DEPRESSION WITH HMCC* (16)

	mg /kg intra arterial to recipient									
	0 01	0 02	0 04	0 08	0 1	0 2	0 3	0 4	0 6	1 2
<i>Myoneural junction</i>										
donor	+	+	+	+	+	+	○	○	○	
recipient	+	+	+	+	○	○	○	○	○	
<i>Respiration</i>										
recipient	+	+	○	○	○	○	○	○	○	

*1 6 hexamethylene bis carbaminoylcholine

+ not blocked ○ blocked

block in the leg with intact blood supply, as might be expected. On the other hand, in dogs the Claude Bernard experiment revealed that in the leg with occluded blood supply no block occurred, whereas in the limb with intact circulation a block occurred. This block occurred at the myoneural junction because it was shown that direct stimulation of the muscle elicited a response, and stimulation of the central end of the cut sciatic nerve produced a pressor response showing that the nerve could still conduct impulses. Later studies demonstrated that intrathecal injections of Imbretil were capable of producing myoneural block in the perfused leg but again occlusion prevented its action in the other leg. Further experimental work is in progress to elucidate this block.

DISCUSSION

The present study indicates that with each of the agents a very definite respiratory depressant effect can be elicited which is independent of peripheral myoneural block. The findings of Harmel *et al*⁷ in cross-circulation experiments also showed a central respiratory depression. Cardiovascular effects were minimal except with d tubocurarine which consistently caused hypotension with larger doses.

Previous work on the central effects of relaxants following the introduction of curare into clinical anaesthesia in 1942 has been largely inconclusive. McIntyre *et al*⁸ and Ellis *et al*⁹ in experiments with cats and dogs noted central depression following intravenous curare as evidenced by the EEG and by respiratory arrest. Anoxic phenomena were not ruled out and Everett,¹⁰ in experiments on cats, rabbits and rats felt that d tubocurarine had little central effect *per se*, but that if anoxia developed then convulsions occurred. Salama and Wright¹¹ demonstrated that direct application of curare to the exposed cortex or via subarachnoid injection resulted in stimulation of vasomotor, respiratory, cardiac, and other autonomic centres, but again the adequacy of cerebral oxygenation was not clarified. McIntyre *et al*¹ concluded that the conflicting results were due in part to dosage and mode of application. The evidence to that time suggested that d tubocurarine was capable of modifying central nervous system activity independent of secondary anoxic effects.^{11 12 13} It does not follow that non-curarizing dosages are devoid of all central action and the present experiments with d tubocurarine indicate a definite central effect: respiratory depression or apnoea was

produced repeatedly in the presence of an intact myoneural junction in the recipient animal.

Haber *et al.*¹⁵ in their investigation of the site of the inspiratory and expiratory centres in the medulla using microelectrodes found no evidence of central depression of respiratory discharges following succinylcholine up to fifty times the paralyzing dose, or with d-tubocurare and decamethonium. Similarly, Paton and Zaimis¹⁶ found no change in phrenic-nerve action potentials following d-tubocurare and decamethonium in paralyzing doses until asphyxia supervened, at which time discharges were intensified. These findings are at variance with the results of our study and with those of Harmel *et al.*⁷

In the present experiments it appears that the muscle relaxant agents are indeed able to depress respiratory activity when injected directly into the cerebral circulation. This has been shown with each experiment, when respiratory activity was depressed significantly in the presence of an intact myoneural junction. We believe, also, that these experiments indicate that decamethonium in particular and, to a lesser extent, curare and HMCC are able to evoke cerebral stimulation when injected under the previously described conditions.

The manner in which the agent in question reaches its target—in this case the central nervous system—inevitably evokes the blood-brain or blood-tissue barrier. By intra-arterial injections the cerebral circulation could be selectively perfused with the agent unaltered by metabolic processes.

In view of the apparent central effects discussed, the factors which are thought to influence blood-brain or blood-tissue permeability must be briefly considered. Paton¹⁷ says the literature relevant to clinical work is unsatisfactory. Several workers—Paton,¹⁷ Foster,¹⁸ and Hunter¹⁹—cite electrolyte derangements, particularly decreased potassium ion concentration, as contributing to increased permeability of the blood-brain barrier and consequent abnormal effects following administration of relaxants.

Cole²⁰ and Comroe and Dripps²¹ mention histamine release which is manifested in man by skin flushing (vasodilatation), hypotension, and bronchospasm, and in dogs by gastrointestinal haemorrhages. It is interesting to speculate whether widespread changes in tissue permeability, including the blood-brain barrier, may follow vascular injections of relaxants—all of which have been shown to exhibit histamine-releasing activity²²—although in one study Paton and Zaimis¹⁶ found no evidence of histamine release following curare injection. Payne²³ cites cases of transient gallamine-induced hypotension of 20–100 mm. mercury following non-myoneural blocking doses and, noting that the hypotension was relieved by atropine, concluded that the mechanism was not central. Biological variation and the stimuli required to provoke histamine release from the perivascular or skin mast cells²⁴ are obviously significant.

Besides the mechanisms of electrolyte imbalance and histamine as they affect tissue permeability in general and the blood-brain barrier in particular, there are two other factors which have been considered. The first is the effect of elevated carbon dioxide levels which was found in a study by Payne²⁵ to oppose the action of succinylcholine, decamethonium, and gallamine, and to enhance the action of d-tubocurare. Concomitant studies of plasma potassium ion concentration and

blood pH showed no direct relationship between plasma potassium and relaxant action. Payne suggests that changes in the degree of ionization and protein binding are responsible for changes in the permeability of the blood-brain barrier rather than hypercarbia *per se*. It is to be noted that in the present study hypoventilation and hypercarbia were avoided. The second factor is that of muscle temperature as it affects muscle relaxant activity. Bigland *et al.*²⁶ reported that decreased muscle temperature increased the magnitude of the effect of depolarizing agents and prolonged their action, whereas cooling reduced the magnitude and duration of non-depolarization block. The effects of total body cooling have quite recently become of much greater clinical significance with the increased scope and extent of cardiovascular and neurosurgery and with wider use of the extracorporeal circulation.

Another variable in studies of this kind is that of species resistance; the classical experiment by Smith *et al.*²⁷ is an example. The author himself was the experimental subject and received up to two and one-half times the paralyzing dose of d-tubocurare with no demonstrable central effects.

The new agent, Imbretil, was found to exhibit some interesting features in the experimental animal not found with the other agents. The observation that a peripheral block occurred in the limbs of the recipient despite the demonstration of circulatory isolation between the donor and the recipient's body was puzzling. Possibly there is a very marked permeability of the blood-brain barrier induced by hexamethylene carbaminoylcholine (HMCC)—to such an extent that in the recipient a significant amount reaches the isolated body via drainage from the spinal veins and causes a myoneural block without causing a similar block in the donor. The classical Claude Bernard experiment on dogs discussed earlier demonstrates the effect to be at the myoneural junction; it was also found that blockade could be induced by intrathecal injection of the Imbretil without any being administered directly into the circulation. There have been a number of clinical reports on the use of HMCC (Imbretil), the consensus being that a "dual block" was involved—with an initial depolarizing type being followed by a longer-acting non-depolarizing block which could be antagonized by neostigmine.^{28,29,30} Reis³¹ observed that ganglionic blocking agents tended to potentiate the myoneural block. Dripps³² remarked on the variable and unpredictable duration of respiratory depression and the lack of a reliable antagonist to this depression. These clinical studies on the unpredictability of blockade together with the excellent abdominal relaxation "almost equivalent to that obtained with spinal anaesthesia"³² taken with the results of the present study would tend to support the concept of a high degree of permeability of the central nervous system to this agent and a not insignificant central effect *per se*. Certainly, further work is indicated in this field and further experimental investigation is contemplated.

SUMMARY

Fifteen experiments utilizing cross-circulated healthy dogs were performed to investigate the purely central action of succinylcholine chloride, decamethonium, d-tubocurarine chloride, gallamine tri-ethiodide, and 1,6-hexamethylene-bis-carbaminoylcholine bromide.

The experiments were conducted under conditions of normothermia and controlled oxygenation and perfusion pressure to reduce the variables influencing the central nervous system.

All the relaxant drugs used were considered to exhibit central activity, apart from their well-known activity at the myoneural junction. Hexamethylene carbaminoylcholine, in particular, appeared to exert a marked central action because of its ability to permeate the blood-brain barrier with relative ease.

By far the most significant central effect was on the respiratory centre, causing depression and apnoea in the isolated recipient body. The dosage required to produce central respiratory arrest or depression was found to approximate closely that required to produce a peripheral myoneural block in the donor body.

Significant tachyphylaxis was observed only with decamethonium, where it was difficult to effect myoneural block and long-lasting central respiratory depression.

Vasomotor effects were not noted except with d-tubocurarine: increasing doses resulted in increasing hypotension.

Cerebral stimulation was elicited in two of the three decamethonium experiments, one of three curare experiments, and one of four hexamethylene carbaminoylcholine experiments.

No cardiac effects attributable to these agents were noted. A hypothesis for the possible action of hexamethylene carbaminoylcholine is suggested in the light of the results obtained in these experiments and from other published clinical reports. Further work in this field is indicated.

The increasing significance of altered body economy and the increased scope and extent of surgery in the presence of such conditions suggest to us that the side-effects of muscle relaxants may come to assume a more significant role than previously.

Species variation in the effects of myoneural blocking agents undoubtedly occurs, but it is felt that the present study, combined with the clinical appraisals, leads to the belief that central activity can indeed be significant in certain cases.

The nebulous blood-brain barrier offers a wide field for further investigation of drug action.

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RÉSUMÉ

Nous avons fait quinze expériences en employant des chiens en bonne santé en circulation croisée, pour étudier exclusivement l'action centrale du chlorure du succinylcholine, du décaméthonium, du chlorure de d-tubocurarine, du tri-

iodure de gallamine et du bromure 1, 6-hexaméthylène-biscarbaminoyl-cholines.

Ces expériences ont été faites en maintenant la température normale mais en contrôlant l'oxygénation et la pression de perfusion dans le but de diminuer le nombre de facteurs susceptibles d'influencer le système nerveux central.

Tous les médicaments myorésolutifs nous ont semblé produire une activité centrale en plus de leur action bien connue à la jonction myoneurale. L'hexaméthylène carbominoylcholine en particulier a semblé produire une action centrale marquée à cause de sa facilité à traverser la barrière sang-cerveau.

L'action, de beaucoup la plus marquée sur le système nerveux central, s'est manifestée sur le centre respiratoire en provoquant une dépression et une apnée sur le récepteur isolé. La dose nécessaire pour provoquer un arrêt respiratoire central ou une dépression semble être voisine de la dose requise pour produire un blocage myoneural périphérique chez le donneur.

Une tachyphylaxie importante a été observée seulement avec le décaméthonium avec lequel il a été difficile de produire un blocage myoneural et une dépression respiratoire centrale d'une certaine durée.

Nous n'avons pas observé d'effets vaso-moteurs si ce n'est avec le d-tubo dont des doses croissantes ont provoqué une hypotension proportionnelle.

Une stimulation cérébrale a été manifeste au cours de deux des trois expériences avec le décaméthonium au cours d'une des trois expériences avec le curare, et au cours d'une des quatre expériences avec l'hexaméthylène carbominoylcholine.

Nous n'avons observé aucun effet de ces médicaments sur le cœur. A la suite des travaux publiés sur ce sujet et des renseignements recueillis au cours de ces expériences, nous émettons l'hypothèse d'une action possible sur le cœur de l'hexaméthylène carbominoylcholine. Il s'impose de continuer la recherche dans ce domaine.

L'importance croissante que prennent les perturbations organiques et l'extension progressive de la chirurgie dans ces circonstances nous portent à croire que les effets secondaires des myorésolutifs peuvent venir à jouer un rôle plus important qu'ils ne l'ont fait antérieurement.

Sans doute, il existe des variantes dues à l'espèce dans les effets du blocage myoneural, mais nous avons l'impression que l'étude actuelle, en plus de l'évaluation clinique, conduit à la conclusion que l'activité centrale, en certains cas, peut être assez marquée.

Cette vague barrière sang-cerveau ouvre un champ considérable de recherches sur l'action des médicaments.

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