The Interaction of Diazepam with Myoneural Blocking Agents

Kenneth Dretchen, M.S., M. M. Ghoneim, M.B., B.Ch., F.F.A.R.C.S.,† J. P. Long, Ph.D.‡*

The interaction of diazepam with neuromuscular blocking agents was studied in patients and in several animal nerve–muscle preparations. This drug did not alter the recovery slope of blockade produced by *d*-tubocurarine, decamethonium, or gallamine. In higher doses diazepam produced a decrease in muscle contractions and blocked the actions of exogenously applied nicotine and acetylcholine in the superfused chick biventer cervicis nerve–muscle preparation. In low doses the commercially available drug given intra-arterially reversed the myoneural blockades produced by both depolarizing and nondepolarizing blockers. However, this property was due to the solvent system of the drug. (Key words: Diazepam; *d*-Tubocurarine; Decamethonium; Neuromuscular blockade.)

THERE SEEMS TO BE considerable controversy concerning the effect of diazepam (Valium) on the action of myoneural blocking agents. Feldman and Crawley [1] reported that the drug increased the magnitude and duration of block produced by gallamine (Flaxedil) and reduced the block of succinylcholine (Anectine). They further observed [2] that diazepam produced persistent postoperative muscle weakness in patients treated with *d*-tubocurarine. Stovner and Endresen [3] found that 8–10 per cent less *d*-tubocurarine was needed during abdominal surgery in patients pretreated with diazepam. Jörgensen [4] found that 10 per cent less succinylcholine was needed when the patients had been pretreated with diazepam. Vergano *et al.*[5] showed that pretreatment with gallamine or *d*-tubocurarine increased the transient blockade produced by diazepam in patients as well as in the frog sciatic nerve–gastrocnemius muscle preparation. On the other hand, Stovner and Endresen [6] later reported that diazepam did not significantly potentiate *d*-tubocurarine or succinylcholine during abdominal operations, and this was later confirmed by Hunter.[7] This study was undertaken to revolve these conflicting observations.

Methods

HUMAN ULNAR NERVE–ADDUCTOR POLLICIS MUSCLE

Fifteen adult patients of both sexes scheduled for surgical operations which did not necessitate profound muscular relaxation were studied. They were in good physical condition without neuromuscular disease and were not receiving any drug known to influence the action of myoneural blocking agents. Preanesthetic medication consisted of morphine sulfate, 6–12 mg, and scopolamine, 0.3–0.4 mg. Three patients also received 25 mg hydroxyzine (Atarax, Vistaril). The drugs were injected intramuscularly an hour before surgery. Induction of anesthesia was achieved with thiopental sodium (Pentothal), 100–250 mg, or nitrous oxide, oxygen and halothane. Three patients received small doses of succinylcholine, 30–40 mg, to facilitate endotracheal intubation. Anesthesia was maintained with nitrous oxide, 3 liters, oxygen, 2 liters, and halothane, 0.5–1 per cent, administered through a semiclosed circuit. Ventilation was assisted or controlled as necessary to provide adequate respiratory exchange as judged clinically. Body temperatures, monitored with a rectal thermistor probe, were maintained between 35 and 37 C.

The thumb of one hand was attached in full abduction to a Statham linear-displacement force transducer. The rest of the fingers were splinted around the handle of the transducer.

* Predoctoral fellow in Pharmacology.
† Assistant Professor of Anesthesia.
‡ Professor of Pharmacology.
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Stimulation of the ulnar nerve was achieved at the wrist with subcutaneous needle electrodes; stimulus current was supplied by a Grass S4 stimulator with a Grass SIU5 stimulus isolation unit. Stimulation conditions were: supramaximal voltage; duration 1.5 msec; frequency 18/min. The evoked responses of the adductor muscles were recorded using a Sanborn recorder.

Following control readings of twitch tension, five patients were given *d*-tubocurarine, 3 mg/sq m; another five were given gallamine, 20 mg/sq m; the other five were given decamethonium, 0.6 mg/sq m; to reduce twitch tension to 50–90 per cent of the control value. If the desired effect had not been achieved two minutes after injection, small increments were added until the desired degree of neuromuscular blockade was reached. In five patients, after stability of the reduced twitch height had been established diazepam, 0.3–0.6 mg/kg, was injected intravenously. In these and in all the others diazepam, 0.3–0.6 mg/kg, was injected while the myoneural junction was recovering. In the patients who received the two doses, total doses varied from 0.8 to 1.2 mg/kg. Control patients were given any of the three blocking agents and saline solution was given instead of diazepam.

Cat Sciatic Nerve–Gastrocnemius Muscle Preparations

Cats were anesthetized with pentobarbital sodium, 30 mg/kg, administered intrathoracically. The jugular vein was cannulated for drug administration and the carotid artery was cannulated for monitoring of blood pressure. The sciatic nerve was ligated and a shielded electrode was placed on the peripheral portion of the nerve. The gastrocnemius muscle was freed from the surrounding muscles and a thread was attached to the tendon of the muscle. Stimulation conditions were: supramaximal voltage, 10 v; pulse duration 1 msec; frequency of 10/min. Contractions of the muscle were measured with a Grass force-displacement transducer and recorded on an Offner Dynograph recorder.

After the twitch had stabilized, blockade was produced with *d*-tubocurarine, 100 μg/kg, gallamine, 100 μg/kg, or decamethonium, 10 μg/kg. During the recovery phase of the blockade, diazepam, 1 mg/kg, was given intravenously. In another series of experiments, 20 cats were pretreated with saline solution or diazepam, 1 mg/kg, and the durations of blockades produced by *d*-tubocurarine and decamethonium were measured.

Chick Biventer Cervicis Nerve–Muscle Preparation

The superfused chick biventer cervicis nerve–muscle preparation was prepared according to the method of Chiou and Long.[8] Stimulation conditions were: supramaximal voltage, 100 v; pulse duration 1 msec; frequency 10/min.

After stabilization, *d*-tubocurarine, 2 μg/ml, or decamethonium, 0.5 μg/ml, was used as the superfusate. When blockade had been

Table 1. Effects of Diazepam on Neuromuscular Blockades Produced by *d*-Tubocurarine, Gallamine and Decamethonium

Test Preparation	Agent	Normal Recovery Slope	Recovery Slope after Diazepam	Significance at $P \leq 0.05$
Human ulnar nerve–adductor pollicis muscle	*d*-Tubocurarine	0.04 ± 0.00*	0.04 ± 0.00	NS†
	Decamethonium	0.11 ± 0.03	0.11 ± 0.00	NS
	Gallamine	0.09 ± 0.00	0.09 ± 0.00	NS
Cat sciatic nerve–gastrocnemius muscle	*d*-Tubocurarine	0.25 ± 0.03	0.27 ± 0.02	NS
	Decamethonium	0.26 ± 0.04	0.28 ± 0.04	NS
Chick biventer cervicis nerve–muscle preparation	*d*-Tubocurarine	0.24 ± 0.07	0.19 ± 0.06	NS
	Decamethonium	0.18 ± 0.03	0.20 ± 0.02	NS

* Values are means ± SE, n = 5.
† Comparisons made by use of Student's *t* test.

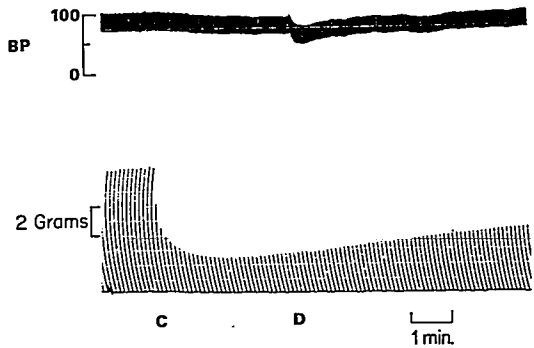

FIG. 1. Effect of diazepam, 1 mg/kg, administered intravenously, on the recovery slope of neuromuscular blockade produced by *d*-tubocurarine in the cat sciatic nerve–gastrocnemius muscle preparation. C = *d*-tubocurarine; D = diazepam.

achieved, normal Tyrode's solution replaced the former solution and the muscle twitch began to return to normal. During the recovery phase, diazepam, 0.5 μg/ml, was added to the Tyrode's solution. In ten animals the contractions produced by nicotine, 1 and 2 mg, and acetylcholine, 50, 100, and 200 μg, were measured in normal Tyrode's solution and solution containing diazepam, 0.5 μg/ml. Responses to the drug were also measured in Tyrode's solution containing the solvent system, 1 ml/liter.

In another series of experiments, the effect of diazepam, 0.6 μg/ml to 40 μg/ml, and the solvent system, 5 ml/liter, on control twitch height was studied.

Dog Blood-Perfused Anterior Tibialis Muscle

Ten mongrel dogs were anesthetized with pentobarbital sodium, 30 mg/kg, administered intravenously. The femoral vein was cannulated for drug administration. The sciatic nerve was ligated and a shielded electrode was placed on the peripheral portion of the nerve. The tendon of the anterior tibialis muscle was dissected free and the blood supply to the muscle isolated by the method of Brown.[9] Constant perfusion of the muscle with blood from the carotid artery was attained by the use of a Sigmamotor pump after ligation of the femoral artery. Perfusion pressure was monitored by a Statham pressure transducer connected by a T tube between the pump and the muscle. With flow remaining constant, any change in pressure would reflect a change in vascular resistance. Each dog was given heparin, 5 mg/kg, before the blood flow to the muscle was isolated. Stimulation conditions were: supramaximal voltage, 10 v; pulse duration 1 msec; frequency 10/min. Contractions of the muscle were measured with a Grass force-displacement transducer and recorded on an Offner Dynograph recorder.

After stabilization of the muscle, *d*-tubocurarine, 10 μg, or decamethonium, 1 μg, was given intra-arterially to produce 70–90 per cent muscle blockade. During recovery from the blockade, diazepam, 10 μg, or the solvent system, 0.2 ml, was given intra-arterially and the slope measured.

Five additional dogs were pretreated with phentolamine (Regitine), 2 mg/kg, or methysergide (Samsert), 0.5 mg/kg, intravenously before the blocking agent and the solvent were administered.

Statistics

For most comparisons Student's *t* test (Steele and Torrie[10]) was used. In experiments using constant blood perfusion, analysis of variance and comparison of the means by Duncan's New Multiple Range test were used (Steele and Torrie[10]). In all cases the level of probability was $P \leq 0.05$.

Results

In human subjects, diazepam did not alter the recovery rate of any of the three neuromuscular blocking agents (table 1). There were similar absences of effect in the cat neuromuscular preparation (fig. 1) and in the chick biventer cervicis preparations.

TABLE 2. Effects of Diazepam on Times for 80 Per Cent Recovery from Neuromuscular Blockade in the Cat Sciatic Nerve-Gastrocnemius Muscle Preparation

	Control Recovery (Min)	Recovery after Diazepam (Min)	Significance at $P \leq 0.05$
d-Tubocurarine	7.5 ± 0.7*	7.5 ± 1.4	NS†
Decamethonium	10.7 ± 0.5	11.2 ± 0.4	NS

* Values are means ± SE, n = 5.
† Comparisons of means by Student's *t* test.

Diazepam did not alter the duration of blockade produced by the neuromuscular blocking agents. Cats treated with diazepam had the same time course of blockade as control animals (table 2).

The drug when given alone did block the contractions of the isolated chick biventer cervicis preparation, and the block was dose-related (fig. 2). The actions of exogenously-applied acetylcholine and nicotine were blocked by diazepam. The solvent system for diazepam (40 per cent propylene glycol, 10 per cent ethyl alcohol, 5 per cent sodium benzoate and benzoic acid, 1.5 per cent benzyl alcohol in sterile water) did not affect the twitch height or the actions of exogenously-applied drugs. The drug given intra-arterially in doses of 5 mg also blocked contractions of dog and cat anterior tibialis muscle.

When the commercially available drug preparation was given intra-arterially in the dog, the blockades produced by decamethonium and *d*-tubocurarine were dramatically reversed (fig. 3). However, the solvent system for diazepam also reversed the actions of these blocking agents (table 3). Intra-arterial injection of diazepam in its solvent resulted in a small transient increase in the peripheral resistance of the muscle vascular bed, followed by a slight decrease. Administration of phentolamine and methysergide did not alter this reversing action.

Discussion

The benzodiazepines are considered to have muscle relaxant properties and have been used to control muscle rigidity and spasms in patients with tetanus and cerebral palsy and in the treatment of trismus.[11] The probable site of action is central, on supraspinal structures such as the reticular facilitatory system and on the polysynaptic pathways within the spinal cord.[12] Doses in excess of the therapeutic range depress the skeletal muscle contractions of the isolated preparations of the chick. Very high concentrations, 5 mg, injected intra-arterially block neuromuscular transmission in both cat and dog sciatic nerve–anterior tibialis muscle preparations. Thus, diazepam also has an action at the neuromuscular synapse which may involve direct muscle depression. It is evident, however, that this is not the main site of action of the drug. Diazepam, 1 mg/kg, injected intravenously does not depress the evoked contractions of the indirectly stimulated muscle, and in doses as high as 1.2 mg/kg it does not interact with either depolarizing or nondepolarizing neuromuscular blockers.

The action of the solvent in reversing myoneural blockades produced by *d*-tubocurarine and decamethonium could not be due to a blood-flow effect, since intra-arterial injection of the solvent resulted in an increase rather than a decrease in peripheral vascular resist-

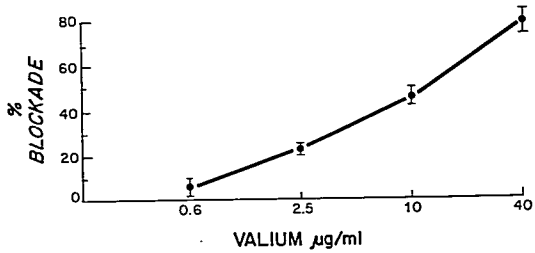

FIG. 2. Effects of various concentrations of diazepam on blockade of the chick biventer cervicis nerve–muscle preparation.

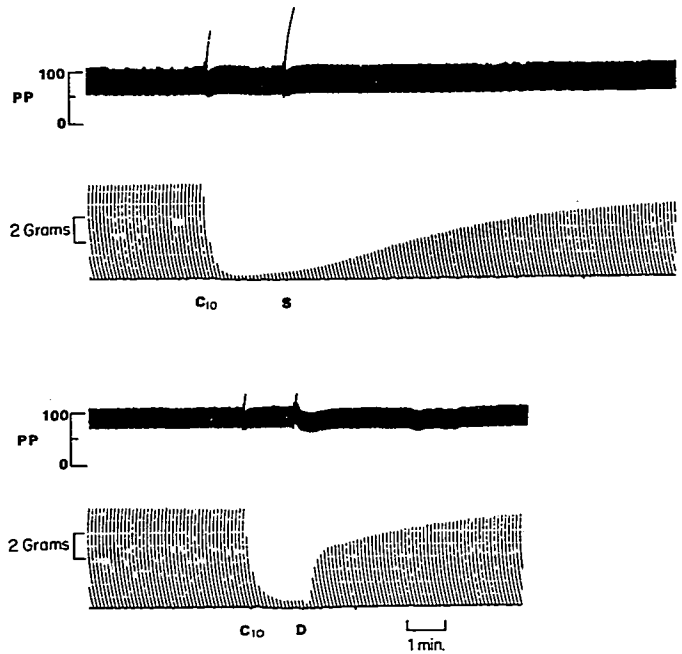

FIG. 3. Effect of diazepam, 0.5 mg, injected intra-arterially, on decamethonium blockade in the constantly perfused anterior tibialis muscle of the dog. C_{10} = decamethonium; S = saline solution; D = diazepam.

ance of the muscle bed. Another possibility is that one of the solvent chemicals could be irritating the vessel wall. This irritating action might release catecholamines or serotonin from the arterial wall and could antagonize at least the nondepolarizing blockade.[13, 14] However, pretreatment of the animals with both an alpha-adrenergic blocking agent and a serotonin antagonist did not negate the myoneural reversal. The latter action seems to correspond to an initial potentiation of the muscle twitch of the isolated phrenic nerve–diaphragm preparation before the muscle was blocked, observed by Hamilton.[15] However, we were not able to reproduce this transient facilitation in the isolated chick preparation. Since both depolarizing and nondepolarizing blockers are antogonized, it can be assumed that the drug acts directly on the muscle fiber.

The results of Feldman and Crawley,[1] who found potentiation of nondepolarizing blockers and antagonism of depolarizing blockers, may

TABLE 3. Effects of Intra-arterially-administered Diazepam and Solvent on Recovery from Neuromuscular Blockade in the Blood-perfused Dog Anterior Tibialis Muscle

	Normal Recovery Slope	Recovery Slope after Diazepam	Recovery Slope after Solvent
d-Tubocurarine	0.52 ± 0.14*	1.42 ± 0.19†	1.28 ± 0.23
Decamethonium	0.60 ± 0.14	2.46 ± 0.46	2.32 ± 0.46

* Values are means ± SE, n = 5, $P \leq 0.05$.
† Means were compared by Duncan's New Multiple Range test. Those means underlined by the same line are not significantly different from each other; those means not underlined by the same line are significantly different from each other.

be explained by the design of their experiment. The control measurements were made and experiments done on the same subject. The results could represent potentiation of a second dose of *d*-tubocurarine or gallamine given with diazepam and tachyphylaxis to succinylcholine given with diazepam. In our study control values and experimental values were determined in different animals and no differences in the magnitude or duration of myoneural blockade were evident. The results of Vergano *et al.*[5] can also be criticized on the basis that control measurements were made and experiments done on the same animal.

Feldman and Crawley[2] reported that two patients who received diazepam before the *d*-tubocurarine during anesthetization had persistent muscle weakness and respiratory depression for three and four hours after the operation. The muscle weakness did not respond to neostigmine. Doughty[16] reported a patient who received 10 mg of diazepam intravenously while recovering from an overdosage of methaqualone diphenhydramine (Mandrax) and developed apnea with muscular relaxation for two hours. Buskop, Price, and Molner[17] reported that an 81-year-old man under extradural anesthesia became apneic following 10 mg of diazepam intravenously and had to be artificially ventilated for three to four hours. It is difficult in these cases to separate the central respiratory depressant action[18] from hypotonia of the muscles and from a possible peripheral myoneural depressant action. However, it is possible that in certain pathologic conditions the depressant action of diazepam may be manifested at the myoneural junction in response to ordinary therapeutic doses.

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