

Durations of Action of *d*-Tubocurarine and Gallamine

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We investigated in man the durations of action of five different single doses of *d*-tubocurarine and three different single doses of gallamine. Duration was estimated by observing the response of the adductor muscles of the thumb to supramaximal ulnar nerve stimulation. Ten per cent recovery time from *d*-tubocurarine was dose-dependent, averaging from 10 to 71 minutes in a dose range from 4 to 16 mg./m.² body surface area (7-28 mg.). Gallamine was studied in both normally-ventilated and hyperventilated patients. In the former, ten per cent recovery averaged from 2.9 minutes to 40 minutes in a dose range from approximately 18 to 72 mg./m.² body surface area (30-130 mg.). In the latter, ten per cent recovery averaged from 6.4 to 64 minutes in a similar dose range. The difference in the durations of action of the two gallamine groups was statistically significant ($P < 0.001$). At equal twitch-suppression doses, recovery from *d*-tubocurarine took 1.5 times longer than recovery from gallamine.

METHODS USED IN THE PAST to determine durations of action of nondepolarizing neuromuscular blockers in anesthetized patients have been unreliable. Recently, the muscular response to nerve stimulation has been used to measure the duration of action of succinylcholine.¹ The same technique has been found suitable for study of *d*-tubocurarine and gallamine.

In a previous investigation, we used a stimulator to determine whether the durations of action of these neuromuscular blockers were influenced by changes in pH that resulted from altered ventilation.² The action of *d*-tubocurarine was not affected significantly by changes in pH within the range from 7.36 to 7.62. On

the other hand, the action of gallamine was extended significantly by production of respiratory alkalosis.

With these findings in mind, we undertook this dose-duration study of five different doses of *d*-tubocurarine and three different doses of gallamine. The latter studies were carried out in two groups of patients so that durations of action during both normal and hyperventilation periods could be determined.

Method

Two hundred forty adult patients, all undergoing general anesthesia for surgical operation, were studied. These patients were in good physical shape, without known or suspected neuromuscular disease, and were not taking medication known to influence the actions of relaxants. Ages ranged from 15 to 78 years, the mean being 40 years. Moderate doses of barbiturates, narcotics and/or an ataractic drug with 0.3-0.4 mg. atropine or scopolamine were given for premedication. Anesthesia was induced with a thiobarbiturate, 300-400 mg., and maintained with nitrous oxide, 2 liters, and oxygen, 2 liters, supplemented with halothane, 0.5 to 1.5 per cent. When tracheal intubation was necessary, succinylcholine, 60 mg., was injected intravenously in some instances. Studies were undertaken when there was no further evidence of succinylcholine action as determined by a nerve stimulator. Saline solution was given at a rate of approximately 400 ml./m.² for the first hour and reduced to 200 ml./m.² in succeeding hours. Although some patients were given blood transfusions, studies usually were completed prior to the use of blood.

One hundred and twenty patients given *d*-tubocurarine, 0.3 per cent, were divided into subgroups of 20 or 40 in order to study the effects of five doses of the drug; 4.0, 5.6, 8.0, 11.2 and 16 mg./m.² body surface area. Ventilation was assisted or controlled as necessary to provide adequate respiratory exchange. Sixty patients given gallamine, 2.0 per cent,

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TABLE 1. Summary of Results of *d*-Tubocurarine Duration Studies

Dose mg./m. ² b.s.a.	No. of Patients	Mean Dose (mg.)	Mean Age (yrs.)	Mean pH	% Mean Twitch Depression	Recovery Time in Minutes					
						10% Recovery		50% Recovery		90% Recovery	
						Mean (S.D.)	Median (Range)*	Mean (S.D.)	Median (Range)*	Mean (S.D.)	Median (Range)*
4.0	40	6.9	42	7.49	67	10.0 (±5.0)	8.4 (6-13)	17.0 (±9.0)	16.3 (10-24)	27.5 (±11.0)	29 (19-36)
5.6	20	10.3	40	7.41	79	14.1 (±7.1)	12.7 (7-20)	24.6 (±13)	24.7 (12-36)	—	32 (21-53)
8.0	20	14.1	43	7.42	92	20.0 (±7.9)	19.5 (13-24)	35 (±14)	33.4 (26-38)	—	46.7 (35-63)
11.2	20	19.0	42	7.43	98	36.7 (±17)	35.0 (24-53)	—	50.5 (40-87)	—	73.5 (57-7)
16.0	20	27.8	49	7.44	99+	71.0 (±24)	71.0 (55-80)	—	109 (79-7)	—	145 (107-7)

* Semiquartile range.

were divided into subgroups of 20 in order to study the responses to 18, 36 and 72 mg./m.². Ventilation was assisted or controlled to maintain pH and PaCO₂ near normal.

A third group of 60 patients who received the same doses of gallamine differed from the previous group in that they were hyperventilated (minute volume 12-20 liters/minute). Hyperventilation began approximately 15 minutes prior to the injection of gallamine and continued until the experiment was terminated.

Throughout the study, the relaxants generally were given early in the anesthetic course as required for clinical muscular relaxation. Arterial blood was analyzed for pH and PaCO₂. The duration of action of the neuromuscular blocker was evaluated by observing thumb adductor response to supramaximal nerve stimulation, a technique described in detail elsewhere.²

All patients were observed until recovery of 10 per cent twitch force (T10). When the surgical operations were of sufficient length, observations continued until 50 (T50) and 90 (T90) per cent recovery. At the termination of each operation any residual paralysis was reversed with neostigmine. The maximum twitch response after either spontaneous recovery or neostigmine reversal was considered 100 per cent recovery.

Mean duration and standard deviation were calculated for subgroups in which all patients could be followed to spontaneous recovery. Duration of each subgroup was estimated by median and variance estimated by semiquartile range.

The data were also analyzed to determine whether there was any significant correlation between age of patient and duration of neuromuscular block, or if either of the muscle relaxants had a more predictable duration than the other.

Results

The results are summarized in tables 1-3.

GROUP 1—*d*-TUBOCURARINE

Mean duration to 10, 50 and 90 per cent recovery could be obtained for only the lowest dose, 4 mg./m.² At higher doses only mean 10 and 50 per cent recovery times were obtained, and at the largest doses only 10 per cent recovery was determined. These durations were plotted against dose on a log log scale (fig. 1). The 10 per cent recovery curve has two slopes. Below 8 mg./m.² the increase in log time per unit increase in log dose is 1.14 ± 0.19, whereas above 8 mg./m.² the increase is 1.86 ± 1.9.

Median values obtained for 10, 50 and 90 per cent recovery at all doses approximated

the means (fig. 1). Mean twitch suspension ranged from 67 to 99 per cent and was dose-dependent (fig. 4).

GROUP 2—GALLAMINE AND NORMAL VENTILATION

The mean pH of the subgroups ranged from 7.34 to 7.36. Mean 10 per cent recovery times were plotted against dose on a log log scale. These show a near-linear relationship. The slope of the curve is similar to the slope of the *d*-tubocurarine dose-duration curve in the dose range of 8 mg./m.² and above, 1.88 ± 0.12 (fig. 2).

Median values obtained for all levels of recovery and at all doses approximated the means (fig. 2). The mean twitch suppression ranged from 40 to 100 per cent, depending on the dose (fig. 4).

GROUP 3—GALLAMINE WITH HYPERVENTILATION

The pH of the three subgroups ranged from 7.59 to 7.61. Mean durations were significantly longer than those of the previous groups ($P < 0.001$). Plotting the log of duration vs. log dose we again found a linear relationship between the two. The slope of the 10 per cent recovery curves was similar to the slope of the previous gallamine group, 1.70 ± 0.11 (fig. 3).

Median duration to 10, 50 and 90 per cent recovery was obtained in all subgroups; these values approximated the means. Mean twitch suppression ranged from 68 to 90 per cent depending on the dose (fig. 4).

We found no significant correlation between patients' ages and the duration of ac-

TABLE 2. Summary of Results of Gallamine Duration Studies in Normal-ventilation Group

Dose mg./m. ² b.s.a.	No. of Patients	Mean Dose (mg.)	Mean Age (yrs.)	Mean pH	% Mean Twitch Depression	Recovery Time in Minutes					
						10% Recovery		50% Recovery		90% Recovery	
						Mean (S.D.)	Median (Range)*	Mean (S.D.)	Median (Range)*	Mean (S.D.)	Median (Range)*
18	20	32.2	34	7.36	40	2.9 (±1.1)	3.2 (2.3-3.7)	4.9 (±1.8)	4.8 (4.2-6)	7.3 (±3.1)	7.2 (6-10)
36	20	56.5	33	7.36	88	11.2 (±4.7)	11.3 (7.4-14)	23.0 (±11)	24.0 (14-33)	—	36.0 (28-57)
72	20	128.0	42	7.34	100	40.0 (±21.)	35.5 (26-48)	—	60.0 (48-?)	—	93.5 (76-?)

* Semi-quartile range.

TABLE 3. Summary of Results of Gallamine Duration Studies in Hyperventilation Group

Dose mg./m. ² b.s.a.	No. of Patients	Mean Dose (mg.)	Mean Age (yrs.)	Mean pH	% Mean Twitch Depression	Recovery Time in Minutes					
						10% Recovery		50% Recovery		90% Recovery	
						Mean (S.D.)	Median (Range)*	Mean (S.D.)	Median (Range)*	Mean (S.D.)	Median (Range)*
18	20	31.3	37	7.61	68	6.4 (±3.8)	4.8 (3.3-8.5)	11.0 (±6.8)	8.5 (5.3-16)	17.0 (±12.0)	17.0 (12-23)
36	20	60.1	38	7.60	99+	22.0 (±10.0)	20.4 (15-26)	38.0 (±17.0)	34.0 (24-52)	—	50.0 (38-2)
72	20	126.5	44	7.59	99+	64.0 (±38.0)	49.0 (38-80)	—	91.0 (68-?)	—	132.0 (93-?)

* Semi-quartile range.

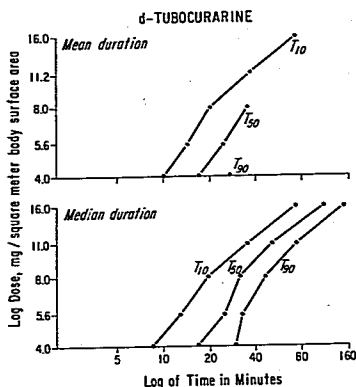


FIG. 1. The log of the dose of *d*-tubocurarine is plotted against the log of duration. At the lowest dose, 4 mg./m.², each point represents pooled results from 40 patients. At all other doses, the points represent pooled results from 20 patients.

tion of either relaxant. The variance in patient response was similar for both *d*-tubocurarine and gallamine.

Discussion

The wide variation in patients' responses to any single dose makes individual predictions unreliable. We attempted to control some of the factors that could increase variation; thus, the same anesthetic technique was used in all cases, fluids were replaced at a prescribed rate and dosage was based on mg./m.² of body surface area rather than weight. That our patients were anesthetized and undergoing surgical operations may have contributed to the variation in response. Undoubtedly circulatory changes occurred in response to changing depths of anesthesia.

The lowest doses of *d*-tubocurarine and gallamine were selected because previous study had showed that they would produce a mean twitch suppression of less than 100 per cent. In addition, the average twitch suppression produced by 4 mg./m.² of *d*-tubocurarine was nearly equal to the average suppression produced by Group 3, gallamine with hyperventilation. Comparing durations of action in these two groups we found that *d*-tubocurarine acted about 1.5 times longer than gallamine.

We were interested in determining whether the same relationship of duration between these drugs held at other equally twitch-suppressing doses. Although there were no other subgroups from which direct comparisons could be made, an indirect comparison was made by interpolation of our findings. Gallamine 36 mg./m.² in Group 2 produced 88 per cent suppression (table 2). We estimated that 7.1 mg. of *d*-tubocurarine would produce a similar degree of suppression (fig. 4) and would require 18 minutes for 10 per cent recovery and 32 minutes for 50 per cent recovery (fig. 1). Compared with the mean recovery times from Group 2 gallamine (11.2 and 23 minutes), the duration of action of curare was again about 1.5 times longer at equal twitch-suppressing doses.

As the dose of curare was increased from 4 to 8 mg./m.² there was a proportionate increase in duration to mean 10 per cent recovery from 10 to 20 minutes. A further increase above 8 mg./m.² resulted in a disproportionate prolongation of duration. Thus, the dose 11.2 mg./m.² resulted in a mean 10 per cent recovery time of 36 minutes, and 16 mg./m.² extended mean recovery to 71 minutes. This resulted in a flattening of the slope of 10 per cent recovery time above the 8 mg./m.² dose

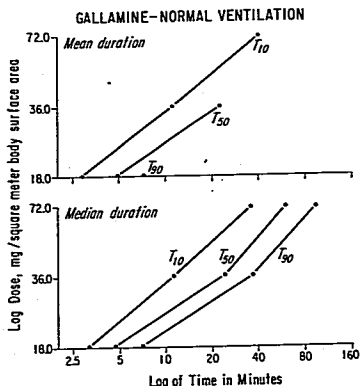


FIG. 2. The log of the dose of gallamine is plotted against the log of duration. The patients in this group were ventilated to keep pH and P_{CO_2} near normal. Each point represents pooled results from 20 patients.

in figure 1. The nonlinear response can be explained by the inability of the body mechanisms responsible for removing the drug from the plasma to operate with equal efficiency at the higher dose range.

Kalow has postulated that the reduction in plasma *d*-tubocurarine concentration occurs in three phases.³ In the first, the most important mechanisms are the distribution of the drug throughout the extra-cellular fluid compartment and binding to the plasma proteins. The half-life for this phase is 5.7 minutes; it is nearly complete in 10–20 minutes. In the second phase, plasma *d*-tubocurarine concentration is further reduced as the molecules are redistributed to nonspecific *d*-tubocurarine acceptor sites throughout the body. In addition, significant urinary excretion of the drug takes place. The half-life of phase 2 is about 45 minutes; this phase predominates for about two–three hours. In phase 3, drug metabolism plays the dominant role in removing *d*-tubocurarine from the plasma. The half-life of this period is about 3.5 hours.

Cohen has determined tissue *d*-tubocurarine concentrations in dogs after both small and large doses of the drug.⁴ Following the injection of *d*-tubocurarine, 0.3 mg./kg., muscle tissue held up to 35 per cent of the injected dose. The peak concentration was found in about 20 minutes, and the concentration fell to zero in three hours. When dogs were given a larger dose (1 mg./kg.) striking changes were found in the distribution. Muscle held as much as 60 per cent for the entire three hours of the experiment. Cohen, noting the consistency of the high concentration of *d*-tubocurarine in muscle, suggested that saturation of this tissue had occurred. The net effect on the plasma *d*-tubocurarine concentration was to lessen the fall-off after about one hour of the experiment.

This finding parallels our own regarding the disproportionate increase in duration of action of *d*-tubocurarine when larger doses were used. The increased duration may be the result of saturation of the nonspecific tissue acceptors and the elimination of one of the normal mechanisms by which plasma *d*-tubocurarine concentration can be reduced.

Gallamine curves were nearly linear in the dose range studied. As mentioned, the slopes

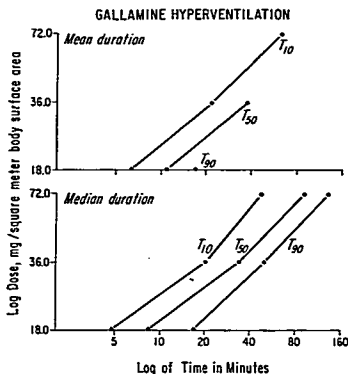


FIG. 3. The log of the dose of gallamine is plotted against the log of duration. Patients in this group were hyperventilated. Each point represents pooled results from 20 patients.

were similar to the *d*-tubocurarine slope in the higher dose range. Gallamine, a less potent muscle-blocking drug than *d*-tubocurarine, must be given in a higher dose to be clinically effective. Although studies of tissue concentrations of gallamine have not yet been carried out, it is probable that with the lowest dose studied, 18 mg./m.², nonspecific drug acceptor sites already had been saturated.

That the *d*-tubocurarine and gallamine recovery curves do not parallel each other throughout the dose range studied has clinical significance. We have demonstrated that *d*-tubocurarine has a longer duration of action than gallamine. However, the increased duration must be interpreted in the light of equal twitch-suppressing doses. When we compared 4 mg./m.² *d*-tubocurarine with 18 mg./m.² gallamine plus hyperventilation, we were comparing two drugs of equal pharmacologic potency. If, however, both doses were doubled, we no longer deal with drugs of equal strength. Gallamine 36 mg./m.² produced a mean twitch depression of 99+ per cent, whereas the mean twitch suppression of 8 mg./m.² *d*-tubocurarine was only 92 per cent. The duration of action of these two groups were nearly equal. When dealing with still larger doses, doses which usually produce 100 per cent twitch depression, it is not possible

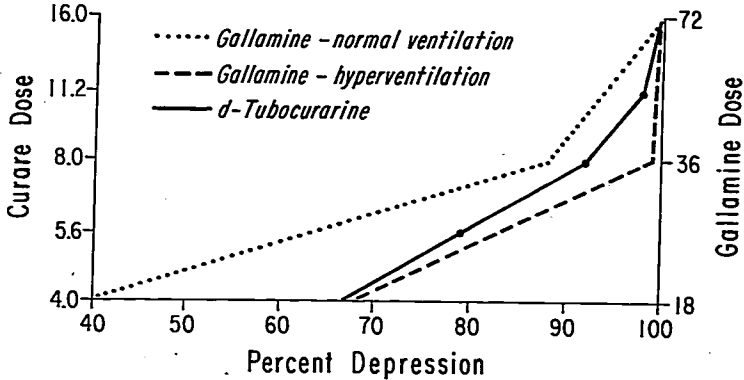
DOSE DEPRESSION CURVES FOR
d-TUBOCURARINE AND GALLAMINE

FIG. 4. The logs of the doses of *d*-tubocurarine and gallamine have been plotted against mean per cent twitch suppression.

by presently-available means to determine equally potent doses of these drugs. Under these circumstances gallamine may not be a shorter-acting muscle relaxant.

Summary

The durations of action of *d*-tubocurarine and gallamine were estimated by observing thumb adduction in response to supramaximal ulnar nerve stimulation. Two hundred and forty patients were divided into groups of 20 or 40 to study multiple drug doses and, in the case of gallamine, to study duration of action at two levels of pH.

The duration of action of *d*-tubocurarine was dose-dependent, with the time to 10 per cent recovery averaging 10-71 minutes in a dose range of 7-28 mg.

The duration of action of gallamine was also dose-dependent, and showed a linear relationship between log dose and log time. In the patients managed with near-normal ventilation, 10 per cent recovery averaged from 3 to 40 minutes in the dose range of approximately 30 to 130 mg. In hyperventilated patients, 10 per cent recovery averaged from 6.4 to 64 minutes in a similar dose range. The duration

of action of gallamine in the hyperventilated patients was significantly longer than that in normally-ventilated patients. The duration of *d*-tubocurarine averaged 1.5 times longer than that of gallamine at equal twitch-suppressing doses. Responses to the relaxants by individual patients were unpredictable. There was no significant correlation between age of patient and duration of action of either muscle relaxant.

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