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Pancuronium, Gallamine, and d-Tubocurarine Compared: Is Speed of Onset Inversely Related to Drug Potency?

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The relative potency and speed of onset of action of pancuronium, gallamine, and d-tubocurarine was studied in 55 adult female patients receiving nitrous oxide/oxygen–narcotic anesthesia. The integrated electromyogram of the adductor pollicis muscle was monitored using a cumulative dose-response technique; train-of-four stimuli were administered at 0.05 Hz. The measured ED_{95} values for pancuronium and gallamine were 0.069 and 2.38 mg/kg, respectively. In three separate groups, pancuronium 0.07 mg/kg, gallamine 2.4 mg/kg, or d-tubocurarine 0.45 mg/kg were given as a single bolus and the speed of onset and time to maximum effect determined. Peak twitch depression was essentially identical in all groups (92.7 ± 1.4 [SE] *vs.* 93.3 ± 1.1 *vs.* 93.7 ± 1.1%, respectively). The rate of onset of neuromuscular blockade in these three groups was, however, quite different. After administration of pancuronium (n = 10) the times to 5%, 20%, 50%, and 80% twitch depression were 68 ± 5, 97 ± 6, 141 ± 8, and 222 ± 18 s. The comparable times following gallamine (n = 10) were 29 ± 2, 42 ± 3, 66 ± 5, and 136 ± 14 s; d-tubocurarine (n = 10) was intermediate in speed with onset times of 40 ± 4, 63 ± 6, 99 ± 11, and 178 ± 25 s. It appears that the onset times of different nondepolarizing blocking agents (even when given in equipotent doses) may vary by clinically appreciable amounts. The results of this study support the hypothesis that nondepolarizing neuromuscular blocking agents of low potency may have a more rapid onset of action than that seen with agents of high potency. (Key words: Monitoring: electromyogram; neuromuscular blockade. Neuromuscular relaxants: dose-response relationship; d-tubocurarine; gallamine; onset time; pancuronium.)

IT HAS BEEN RECOGNIZED for many years that there is a need for a nondepolarizing neuromuscular blocking agent that can replace succinylcholine in the clinical practice of anesthesia.[1] Ideally, this drug should have an onset time to full paralysis of under 90 s, and a duration of action to 95% recovery of single twitch height of less than 15 min. Compared with such long-acting drugs as d-tubocurarine (dTc) and pancuronium, considerable progress has been made in the past decade in developing new shorter-acting agents. Mivacurium, for example, at 1.2 times its ED_{95} has a duration of action (to 95% return of single twitch) of only about 25 min.[2] However, the time to maximum effect following a dose of three times this drug's ED_{95} is greater than 2 min, and at less than fully paralyzing doses its time to maximum effect is still about 5½ min. These onset times are not greatly different from those achieved with other currently available nondepolarizing relaxants.

In the search for an ultrashort-acting nondepolarizing blocking agent, a question of more than academic interest is whether all nondepolarizing agents have similar onset times when given in equipotent doses. At present, there is little convincing clinical evidence that such differences actually exist. Blackburn and Morgan[3] did report that fazadinium has a faster onset time than either pancuronium or dTc, and Ramzan,[4] using Blackburn's data, suggested that there was a linear relationship between the time to depression of twitch height and the molecular weight of the cation of the relaxant molecule. Unfortunately, there are significant problems with Blackburn's and Morgan's report. First, they used a stimulation rate of 0.5 Hz, so it is difficult extrapolate what the onset time to 95% twitch depression would be under more standard experimental conditions. Second, it is unclear that equipotent doses of drug were actually employed. While the doses of dTc (0.50 mg/kg) and pancuronium (0.10 mg/kg) administered were roughly equivalent (1.15–1.4 times their respective ED_{95} values), the potency of fazadinium in humans has been incompletely studied. If Hull's estimate[5] of an ED_{95} for fazadinium of approximately 0.5 mg/kg is correct, then Blackburn's study is flawed, since they administered a dose of 1.0 mg/kg of the latter drug.

Donati[6] has postulated on theoretical grounds, all other factors being equal, that potent neuromuscular blocking agents should have a longer onset time than those that are less potent. He also suggests that, based on comparisons of pancuronium and dTc, these differences will probably be too small to be of practical importance. However, the potency ratio of these two drugs, which is only about 6.5:1, may not be large enough to demonstrate the validity of this principle.

Bowman *et al.*[7] have recently provided experimental evidence (in the cat) that speed of onset may indeed be inversely proportional to a drug's ED_{95}. During a study of various desacetoxy analogues of pancuronium and vecuronium, they found that this was indeed the case, and that the log of onset time bore a linear relationship with the log of a drug's ED_{95}. The most dramatic difference in speed of onset was between pancuronium and ORG 8764 where the potency ratio was 21:1.

Since the potency ratio of pancuronium to gallamine is on the order of approximately 30–35:1, if significant differences in onset time related to potency also exist in humans, they should be discernible when the effect of

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these two drugs are compared. We therefore studied the latency period, onset time, and time to maximum effect of both of these agents (as well as dTc) in an effort to document any such differences between these nondepolarizing blocking agents.

Methods

Fifty-five ASA 1–2, adult female patients (ages 18–65 yr) undergoing elective gynecological surgical procedures, for whom the administration of a muscle relaxant was indicated by the proposed surgery, were included in the study. All patients were free from neuromuscular disease and were within 15% of ideal body weight. The protocol was approved by our hospital's Human Subject Review Committee. The patients received diazepam 10 mg and glycopyrrolate 0.2 mg approximately 90 min prior to surgery. Anesthesia was induced with thiamylal sodium 4–5 mg/kg iv and maintained with inhalation of nitrous oxide and oxygen plus iv fentanyl. Tracheal intubation was not performed until after the study period (<15 min from time of induction). Controlled ventilation *via* mask was maintained during the test period.

Five consecutively selected groups were studied. In groups 1 and 2, the dose-response relationships of pancuronium and gallamine were determined so that equivalent doses of these two drugs could be selected. The ED_{95} of d-tubocurarine (dTc) was not examined, since it was previously found to be 0.44 mg/kg using identical methodology.[8] In groups 3, 4, and 5, the speed of onset of ED_{95} doses of pancuronium, gallamine, and dTc were measured.

Group 1 (Pancuronium Dose-response, n = 10). The indirectly evoked integrated compound action potential of the adductor pollicis muscle to supramaximal stimulation of the ulnar nerve was measured and recorded using a Datex™ 221 NMT monitor. Supramaximal nerve stimulation was achieved using the nerve stimulator incorporated into the Datex™ unit (pulse width 100 μs, constant current, 0–70 ma range). The test hand was immobilized, and approximately 200–300 grams of resting tension was applied to the thumb. Stimulating and recording electrodes were 3M infant Red Dot™ electrodes. After anesthesia was induced and before any muscle relaxants were administered, control twitch height and train-of-four (T4/T1) fade ratio were established. Train-of-four stimulation was given every 20 s during the period of observation, and single twitch depression (height of first twitch in a train/control twitch) (T1/Tc) and train-of-four fade were continuously recorded.

A cumulative dose-response curve was determined by incremental administration of pancuronium until twitch tension was depressed by at least 90%. The first dose administered was 0.036 mg/kg; incremental boluses ranging from 0.01 to 0.015 mg/kg were given when the evoked T1/Tc ratio was stable (±1%) for three consecutive trains. The size of each incremental dose was individualized so that the second or third dose would not result in total twitch suppression. At least three doses were administered to each patient.

At the end of surgery, residual paralysis was reversed with neostigmine to a T4/T1 ratio of at least 0.70. Only individuals in whom the T1/Tc ratio returned to 1.0 ± 0.15 were included in the study.

Group 2 (Gallamine Dose-response, n = 15). The protocol used in this group was identical to that in group 1, except that the test drug was gallamine. The initial dose was 1.0 mg/kg, and incremental boluses ranged from 0.5 to 1.0 mg/kg.

The ED_{50} and ED_{95} for pancuronium and gallamine were calculated by averaging the values for these parameters as determined by log-probit regression analysis of each individual patient.

Groups 3, 4, and 5 (Pancuronium 0.07 mg/kg, n = 10; Gallamine 2.4 mg/kg, n = 10; or dTc 0.45 mg/kg, n = 10). The experimental method in this group was identical to that employed in group 1 except that a single ED_{95} bolus of either pancuronium, gallamine, or d-tubocurarine was administered. T1/Tc and T4/T1 were recorded every 20 s thereafter until these values were stable for at least 2 min. Time intervals were measured from the beginning of the bolus injection. Individuals in whom complete twitch suppression occurred were excluded from the study.

Mean T1/Tc ratios, at 20-s intervals after drug administration, as well as the peak twitch depression produced were calculated for groups 3, 4, and 5. These mean values were then compared using one-way analysis of variance, and Fisher's Protected Least Significant Difference (PLSD) test for multiple comparisons. Observed differences were considered significant when $P = <0.05$. The estimated onset times to 5, 20, 50, and 80% twitch depression in all groups were obtained by Stineman interpolation of these data points.[9]

Results

Groups 1 and 2 (Pancuronium and Gallamine Dose-response Relationships). On a mg/kg basis, pancuronium bromide appears to be about 34 times more potent a neuromuscular blocker than gallamine triethiodide (table 1). Since the molecular weights of the cations of these two compounds are 573 and 510, respectively, their calculated ED_{95} values of 0.069 and 2.38 mg/kg reflect a molar potency ratio of approximately 39:1.

Groups 3, 4, and 5 (Pancuronium, Gallamine, and d-Tubocurarine Onset Times). When administered as a single bolus, pancuronium 0.07 mg/kg, gallamine 2.4 mg/kg, and dTc 0.45 mg/kg all produced comparable degrees of neuromuscular blockade (fig. 1; table 2). Their re-

TABLE 1. Log-probit Analysis of Dose-Response Relationships for Pancuronium and Gallamine

	Pancuronium	Gallamine
(n) patients	10	15
(n) observations	30	45
Mean values of individual patients (± SE)		
ED_{50} (mg/kg)	0.036 ± .002	1.14 ± 0.10
ED_{95} (mg/kg)	0.069 ± .003	2.38 ± 0.14

spective peak effects of 92.7, 93.3, and 93.7% twitch depression were not significantly different from each other.

However, the rates of onset of action of these drugs when given in equipotent dosage were measurably different (tables 2, 3; fig. 1). The T1/Tc ratios measured from 40 s to 200 s were least in the group receiving gallamine and highest with pancuronium. For example, the time to 50% twitch depression in the gallamine group was 66 ± 5 (SEM) s compared to 99 ± 11 s for dTc and 141 ± 8 s for pancuronium. These differences were all statistically significant (see *P* values in tables 2 and 3). Expressed somewhat differently, the time from drug administration to 90% of maximum effect was about 160 s for gallamine, 200 s for dTc, and slightly over 4 min for pancuronium.

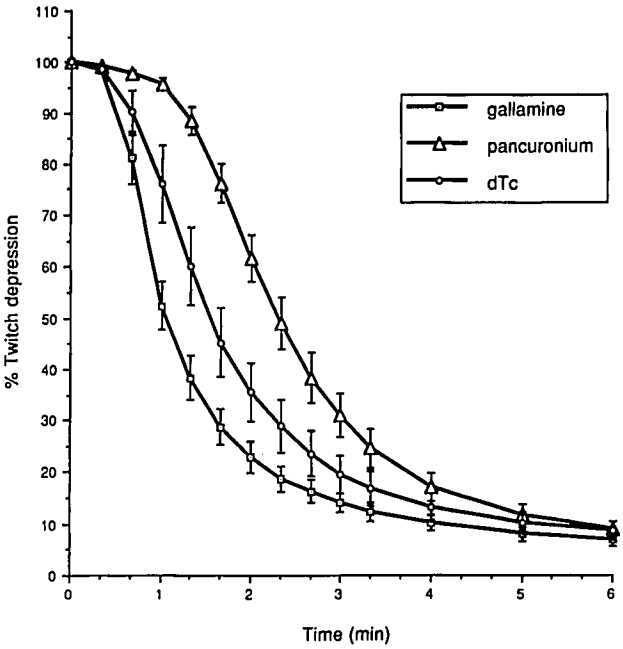

FIG. 1. Onset times of single twitch depression compared to control of pancuronium 0.07 mg/kg, d-tubocurarine 0.45 mg/kg, and gallamine 2.4 mg/kg. Although the maximum effect in all three groups was identical (92.7%, *vs.* 93.7% *vs.* 93.3% twitch supression) the onset of blockade was fastest in the gallamine group. For example, time to 50% twitch depression was 141 ± 8 s for pancuronium and only 66 ± 5 s for gallamine. d-Tubocurarine was intermediate with an onset time of 99 ± 11 s. Error bars represent standard errors of the mean.

Discussion

The ED_{50} determined in this study for pancuronium of 0.036 mg/kg is identical to the value previously reported by Gramstad *et al.*[10] and Savarese *et al.*,[11] and the ED_{95} of 0.069 mg/kg is also very similar to values of 0.064 and 0.070 mg/kg found by these authors. There have, however, been very few well conducted investigations of the potency of gallamine. Donlon *et al.*[12,13] reported an ED_{95} for this drug of between 1.78 and 1.91 mg/kg. Unfortunately, he used a rate of nerve stimulation (0.25 Hz) now recognized to overestimate drug potency.[14] Shanks *et al.*[15] found the ED_{95} of gallamine to be 2.8 mg/kg; however, his methodology (using a constant-rate infusion) is unique to the author and is therefore somewhat difficult to evaluate. He did, however, find a potency ratio of pancuronium to gallamine of 35:1, similar to the figure of 34:1 found in this study.

There are multiple factors that may influence the onset of neuromuscular blockade. In his excellent review, Donati[6] suggests that onset of action depends largely on patient characteristics, such as cardiac output, circulation time, and muscle blood flow. The properties of the re-

TABLE 2. Mean T1/Tc Ratios (as %) at Various Times after Drug Administration

	20 s	40 s	60 s	80 s	100 s	2 Min	3 Min	4 Min	5 Min	Max Effect %
Gallamine ± SEM	98.3	80.9	52.4	38.2	28.6	22.8	14.1	10.3	8.0	93.3
	0.3	5.2	4.8	4.4	3.5	2.9	1.9	1.4	1.3	1.1
d-Tubocurarine (dTc) ± SEM	98.6	90.1	76.1	60.1	45.2	35.5	19.5	13.2	10.2	93.7
	0.4	4.4	7.6	7.5	6.7	5.6	3.7	2.7	2.1	1.8
Pancuronium (pan-c) ± SEM	99.3	98.2	95.6	88.4	76.1	61.6	30.9	17.1	11.8	92.7
	0.3	1.0	1.3	2.7	3.8	4.5	4.2	2.7	2.0	1.4
P Values										
Gallamine *vs.* pan-c	NS	<0.050	<0.001	<0.001	<0.001	<0.001	<0.005	NS	NS	NS
Gallamine *vs.* dTc	NS	NS	<0.010	<0.025	<0.050	NS	NS	NS	NS	NS
dTc *vs.* pan-c	NS	NS	<0.050	<0.005	<0.001	<0.001	<0.050	NS	NS	NS

TABLE 3. Onset Times (Seconds ± SEM) of Pancuronium [Pan-c] 0.07 mg/kg, Gallamine 2.4 mg/kg, or d-Tubocurarine [dTc] 0.45 mg/kg

				P Values		
	Gallamine	dTc	Pancuronium	Pan-c *Versus* Gallamine	Pan-c *Versus* dTc	Gallamine *Versus* dTc
Time to T1/Tc = 0.95	29 ± 2.2	40 ± 4.1	68 ± 5.2	<0.001	<0.001	NS
Time to T1/Tc = 0.80	42 ± 2.7	63 ± 6.0	97 ± 5.7	<0.001	<0.001	<0.025
Time to T1/Tc = 0.50	66 ± 5.2	99 ± 10.7	141 ± 8.4	<0.001	<0.005	<0.025
Time to T1/Tc = 0.20	136 ± 14.3	178 ± 24.6	222 ± 18.4	<0.010	NS	NS

laxant, such as potency, affinity for muscle, and diffusion characteristics, are less important. All other factors being equal, however, he proposes that potent neuromuscular blocking agents should have longer onset times. Regardless of the potency of the relaxant, a large proportion of receptors must be occupied before blockade is complete. A critical number of molecules must reach the synaptic cleft before a neuromuscular block ensues. Donati argues that, if equipotent doses of relaxant are given, this critical number will be carried in a larger volume of blood if the drug is potent. Since this larger volume of blood will take more time to reach the neuromuscular junction, potent drugs should have a slower onset. Bowman[7] has a simpler explanation. Since a larger number of molecules are administered when drug potency is low, according to the laws of mass action, a higher concentration of molecules might be expected to be necessary to achieve rapid receptor block and, therefore, rapid paralysis.

Prior to this investigation, there have not been any studies comparing the speed of onset of pancuronium and gallamine. There is, however, a strong suggestion that dTc has a shorter latency period than pancuronium, despite the fact that its time to maximum effect is, if anything, longer than that seen with the latter drug. Cashman *et al.*[16] found a latency of onset time (injection to 5% twitch depression) of 41 s for dTc compared to 56 s for pancuronium. The latency period they report for pancuronium is similar to the value of 60–65 s found in this investigation. The slightly shorter latency values reported by Cashman are not unexpected. His dose of pancuronium was 40% greater than that employed in this study, and he administered train-of-four (TOF) stimulation at 10-s intervals rather than every 20 s. It is well established that the rate of neuromuscular blockade is effected by the pattern of nerve stimulation. Curran *et al.*[17] recently demonstrated that the apparent initial onset time was more rapid when nerve stimulation was applied more frequently. Following 0.4 mg/kg of atracurium, the mean time to 90% blockade was 3.4 min with single twitch (0.08 Hz) stimulation, compared with only 2.0 min when trains-of-four were applied at the same interval.

When comparing pancuronium (0.07 mg/kg) to dTc (0.40 mg/kg), Donati *et al.*[18] also found that dTc had a shorter initial onset time, despite the fact that the maximum peak effects observed were greater with pancuronium. The times to 50% single twitch depression in their study were approximately 60 and 90 s for dTc and pancuronium, respectively. In an earlier communication from the same department, Doherty[19] reported the onset time to 50% block with pancuronium to be 114 s. In the present study, using the same dose of pancuronium, we found the time to 50% twitch suppression to be approximately 140 s. However, since the studies of Donati[16] and Doherty[18] were conducted in patients anesthetized with nitrous oxide–halothane and with trains-of-four administered at 12-s intervals, the longer onset times that we encountered are, perhaps, not unexpected. Blackburn[3] also found the time to 50% twitch depression to be shorter by about 15 s with dTc when it was compared with that following pancuronium. The data from the present study is in general agreement with the above information. As noted in table 3, the time to 50% twitch depression was about 40 s longer in the pancuronium group than in those individuals receiving dTc.

While these data suggest that high potency may be associated with a longer latent onset time, the differences observed (15–40 s) between pancuronium and dTc are probably too small to be of clinical importance. In a previous study from this department,[8] we found the ED_{95} of dTc to be 0.44 mg/kg. Therefore, the molar potency ratio of pancuronium to dTc is 6:1. Since the molar potency ratio (cation) of pancuronium to gallamine is almost 39:1, if low potency confers rapid onset, gallamine should exhibit an even greater reduction in latency than dTc when compared with that following pancuronium. This is, indeed, the case. When administered in doses equivalent to 1× the ED_{95}, gallamine has an onset time that is not only statistically shorter than pancuronium, but also acts noticeably faster clinically. Not only is the time to 80% twitch depression almost 90 s faster with gallamine, but the initial onset of action is discernible less than 1 min after drug administration.

There is probably an even greater difference in neuromuscular function at 60 and 80 s than the data in tables 2 and 3 indicate. In the patients receiving pancuronium, the average TOF fade ratio at these times were 1.02 and 0.95, respectively. The comparable figures from those receiving gallamine were 0.41 and 0.28 (table 4). This

means that, at 80 s after drug administration, the T4/Tc ratio (fourth twitch in a train-of-four divided by the control single twitch) was still 0.73 following pancuronium, but only 0.11 after gallamine. Pearce *et al.*[20] have suggested that it is really the absolute height (force of contraction) of the fourth and subsequent twitch responses that is important in determining sustained muscle power. If this is so, then the measured differences in the onset of these two neuromuscular blockers becomes even more meaningful.

Although it would have been of interest to administer larger multiples of the ED_{95} of gallamine in an effort to try to duplicate the onset time of succinylcholine, in view of the drug's long elimination half-life[21] and the limited duration of the surgical procedures in our study groups, we did not feel that this would be a prudent or ethical course of action.

Pancuronium is approximately six times as potent as dTc, and dTc has 6.5 times the potency of gallamine; hence, the results of this study lend support to the hypothesis that nondepolarizing neuromuscular blocking agents of limited potency have the potential for a more rapid onset of action than that seen with agents of high potency. As expected (if this theory is correct), both dTc and gallamine have onset times that are significantly shorter than that produced by pancuronium. Gallamine (as predicted) also appears to have a faster onset of action than dTc. Although this difference was only statistically significant at 60, 80, and 100 s, the smaller difference in onset time between dTc and gallamine *versus* dTc and pancuronium is consistent with Bowman's hypothesis. If, for example, the log of the ED_{95} dose (in μmol/kg of the respective cations) is plotted against the log of onset time (to a T1/Tc ratio of 0.50), the coefficient of correlation of the resulting best fit line has a value of 0.999 (fig. 2).

Additional evidence that increasing efficacy is associated with slow onset may be found in recent work[22,23] on the long-acting blocker doxacurium. This very potent new drug (ED_{95} of 0.024 mg/kg or 100× the potency of gallamine [200× on a molar basis]) has a time to maximum effect of 10–13 min. The effect of drug potency on the speed of onset of action of neuromuscular blockers may, therefore, be of more than theoretical interest, and may have implications regarding the clinical utility of these agents. As Bowman[7] has suggested, it appears that, when the nondepolarizing equivalent of succinylcholine is discovered, it is likely to be a neuromuscular blocking drug of low potency.

TABLE 4. Mean Train-of-four Ratios at Various Times after Drug Administration

	60 s	80 s	120 s
Gallamine ± SEM	0.41 0.03	0.28 0.02	0.15 0.03
d-Tubocurarine (dTc) ± SEM	0.80 0.05	0.59 0.08	0.29 0.04
Pancuronium (pan-c) ± SEM	1.02 0.01	0.95 0.02	0.74 0.04
P Values			
Gallamine *vs.* pan-c	<0.001	<0.001	<0.001
Gallamine *vs.* dTc	<0.001	<0.001	<0.025
dTc *vs.* pan-c	<0.005	<0.001	<0.001

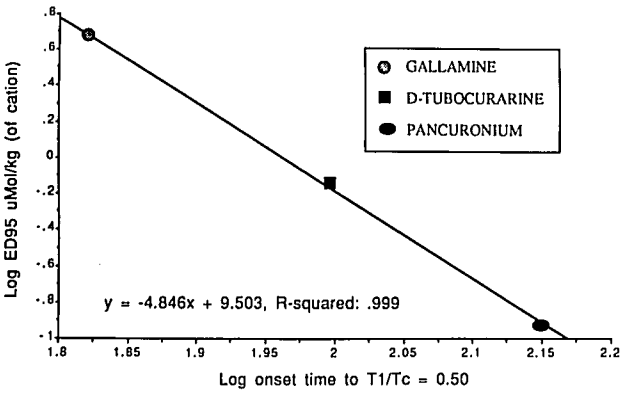

FIG. 2. The relationship between the onset time (seconds) to 50% single twitch depression and the ED_{95} (expressed as micro-moles/kg) of the cation of gallamine, d-tubocurarine, and pancuronium. When the log of the ED_{95} is plotted against the log of onset time, the relationship is linear with a coefficient of correlation of 0.999.

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