D-TUBOCURARINE DOSAGE BASED ON LEAN BODY MASS*

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THERE IS A GREAT VARIABILITY in the initial dosage of *D*-tubocurarine (DTC) recommended for relaxation during general anaesthesia. It varies from a low of .098 mg/Kg[49] to a high of 1 mg/Kg[41].

Foldes[29] and Kalow[37] recognized the fact that body build, amongst other factors, would influence the dosage requirement. Muscular patients would require more and fat patients less drug on a mg/Kg of total body weight basis. Long and Bachman[44] postulated that the lesser degree of paralysis and quicker recovery from D-tubocurarine in older children as compared to younger children, when given a dosage based on total body weight, probably was due to the difference in muscle mass. In infants muscle represents 20 per cent of body weight, whereas in older children it is 33 per cent.

Body build is reflected in the lean body mass (LBM) and percentage fat. In this paper the use of lean body mass instead of total body weight as a predictor of dose is explored.

METHOD

Thirty-seven adult patients with normal cardio-vascular, respiratory and hepatic systems, and free of known neuromuscular disorders were measured for height (inches), weight (Kg) and girth (inches) using the umbilical level at expiration. The percentage fat and lean body mass was calculated from Weisberg's formula:[60]

$$\text{Percent fat} = 90\text{–}2\,(\text{Height/ins.} - \text{Girth/ins.})$$
$$\text{LBM} = (100\text{–per cent fat})\% \times \text{WT(Kg)}.$$

Premedication consisted of atropine with pentobarbital or meperidine. Induction of anaesthesia was with thiopentone and anaesthesia maintained with nitrous oxide and one of three different anaesthetics, namely, halothane, methoxyflurane or meperidine. The ulnar nerve was supramaximally stimulated with a Block Aid Monitor (Burroughs Wellcome Co.), placing the subcutaneous needle electrodes near the wrist. Thumb movement was measured by a force displacement transducer (Grass FP 103) and recorded on a Grass Model 7 Polygraph. Endotracheal intubation was performed under relaxation with succinyldicholine which was given in doses of 1 mg/Kg LBM and the depression of twitch and tetanus were followed until full recovery.

Artificial ventilation was maintained with an Airshield's Ventilator at an average of 600 ml tidal volume at a rate of 16/min.

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After full recovery from the succinylcholine, which took an average of 9.6 minutes, D-tubocurarine was given at the rate of 3 mg every 2 minutes until complete neuromuscular block had been produced. The dose required to produce 90 per cent to 95 per cent depression of twitch height was recorded. Injections were made close to the vein into an intravenous infusion flowing at 100 drops/minute.

The time to 50 per cent recovery was also noted for ten patients in the methoxyflurane group.

Results

The various personal data of the patients studied and the amounts of D-tubocurarine required to produce 90 per cent to 95 per cent depression of twitch height is shown in Table I. These doses were better correlated to lean body mass than to body weight when administered with either halothane, meperidine or methoxyflurane (Table II).

If the one unusual case in the methoxyflurane series is excluded from the evaluation, an even better correlation of lean body mass to dose (0.54) than of body weight to dose (0.06) is found. This patient with lean body mass of 79 Kg required 15 mg D-tubocurarine and is the only one amongst 37 cases who does not fit the pattern of dosage and is unaccountable.

The mean doses related to lean body mass and body weight are shown in Table III. Much less relaxant is required when halothane is the anaesthetic used and more when it is methoxyflurane.

Increasing amounts of D-tubocurarine are needed with advancing age. Patients over 60 years of age require more mg/Kg of lean body mass than the 19 to 40 year group (Table IV). With all three tests the mean dosage in the older group was greater than the mean dosage in the younger group, although the difference between the means within each separate experimental grouping is not significant.

Males and females require approximately the same dosage mg/Kg lean body mass (Table IV).

Ectomorphs require less D-tubocurarine based on lean body mass than endomorphs when administration is associated with meperidine and methoxyflurane. The dose, however, is the same when D-tubocurarine is associated with halothane. Based on body weight, on the other hand the fat endomorph requires less of the relaxant than the thin ectomorph (Table III). Also fat people recover faster than thin people of almost equal weight (72.6 to 71.3 Kg) receiving almost equal doses (18.3 mg to 19 mg) (Table I).

Discussion

(i) The initial dosage of D-tubocurarine required for adequate skeletal muscle relaxation is commonly based on total body weight and suggested doses vary a great deal from author to author (see Table VI).

Also a marked variability in the degree of muscle paralysis was found to be produced by a dose of D-tubocurarine based on weight.[45,40,49,52] Bridenbaugh and Churchill-Davidson[6] could find no relationship between weight and dose in adults so that a given dose would produce a predictable response. Artusio *et al.*[2] could not

TABLE I

THE MEANS OF VARIOUS PARAMETERS OF PATIENTS GIVEN D-TUBOCURARINE WITH HALOTHANE, MEPERIDINE OR METHOXYFLURANE

Anaesthetic Agents	Somato-type	Age	Sex	HT	WT	GT	%F	LBM	Dose	n =	50% Recovery Time Mins
		YRS.		INS.	KG.	INS.		KG.	mg.		
Halothane	Ecto	24	2 m	69	56	25	8	51	12	2	
with	Meso	39	5F 1m	62.8	59.7	29.3	23.3	45.8	10.5	6	
DTC	Endo	72.5	2 m	65	66	36.5	33	43.5	10.5	2	
	Combined	42.7	F5, m5	64.5	60.2	29.9	22.2	46.4	10.8		
	means SD	20.0		4.2	8.0	4.2	8.8	6.3	2.5		
	n =	10		10	10	10	10	10	10		
	Range	19–75		60–75	51–73	24–37	4–34	37–57	6–15		
Meperidine	Ecto	30.5	2 m	68.5	57	26	6	54	18	2	
with	Meso	55.5	3m, 1F	66.5	71.8	33.5	24	54.5	17.25	4	
DTC	Endo	43.4	5F	61.4	62.5	33	33.2	41.4	15	5	
	Combined	45.5	6F, 5m	64.5	64.7	31.9	24.9	49.6	16.7		
	means SD	17		4.0	12.9	4.6	10.7	10.0	3.9		
	n =	11		11	11	11	11	11	11		
	Range	21–77		58–71	40–81	25–38	4–36	28–62	9–24		
Methoxy-	Ecto	39.7	3 m	69.3	71.3	30	11.3	63.6	19	3	55
flurane	Meso	33.4	2F, 3m	63.8	63.6	30.8	24	48.4	19.2	5	42
with	Endo	49.3	6F, 2m	62.1	72.6	39	42.8	39.7	18.3	8	27.5
DTC	Combined	42.5	m = 8	64	69.6	34.8	30.6	47.4	18.8		38.8
	means SD	17.9	F = 8	3.5	15.2	6.6	15.2	11.9	5.1		14.1
	n =	16		16	16	16	16	16	16		10
	Range	18–75		59–72	57–109	29–48	8–60	35–74	9–24		19–58

HT = height, WT = weight, GT = girth.
LBM = lean body mass, %F = % fat.

TABLE II

CORRELATION OF D-TUBOCURARINE DOSE FOR 90% TO 95% MUSCLE DEPRESSION WITH LEAN BODY MASS, WT, AND FAT %, WHEN ASSOCIATED WITH DIFFERENT ANAESTHETIC AGENTS

	Anaesthetic Agent		
	Halothane	Meperidine	Methoxyflurane
	r =	r =	r =
Dose / LBM	0.68	0.70	0.23
Dose / WT	0.52	0.57	0.002
Dose / % Fat	−0.23	−0.22	−0.24
n =	10	11	16

TABLE III

MEAN DOSES OF D-TUBOCURARINE FOR 90–95% MUSCLE DEPRESSION WHEN ASSOCIATED WITH DIFFERENT ANAESTHETIC AGENTS AND SOMATOTYPES

MG/KG LEAN BODY MASS

	Halothane	Meperidine	Methoxyflurane	Combined
Ectomorph	.24	.33	.30	.29
Mesomorph	.23	.32	.39	.31
Endomorph	.24	.36	.46	.35
3 Groups Combined	.24	.34	.38	.32

MG/KG WEIGHT

	Halothane	Meperidine	Methoxyflurane	Combined
Ectomorph	.21	.32	.27	.27
Mesomorph	.18	.24	.30	.24
Endomorph	.16	.24	.26	.22
3 Groups Combined	.18	.25	.27	.24

Ectomorph 4–18% fat; Mesomorph 20–28% fat; Endomorph 30% + fat.

TABLE IV

MEAN DOSAGE OF D-TUBOCURARINE IN MG/KG OF LEAN BODY MASS BASED ON AGE, SEX, SOMATOTYPE WHEN ASSOCIATED WITH DIFFERENT ANAESTHETIC AGENTS

		Halothane	Meperidine	Methoxyflurane
AGE	19–29	.21	.34	.34
	30–39	.23	.30	.35
	40–49		.40	.47
	50–59		.27	.43
	60–69	.29	.33	.41
	70–79	.24	.43	.55
	19–40	.22 ± .04 (7)	.33 ± .03 (4)	.35 ± .10 (8)
	60 +	.26 ± .04 (3)	.38 ± .07 (2)	.51 ± .19 (8)
	P =	> .05 ns	> .05 ns	> .05 ns
SEX	Male	.25 ± .03 (5)	.33 ± .05 (5)	.42 ± .15 (8)
	Female	.21 ± .04 (5)	.35 ± .07 (6)	.41 ± .09 (8)
	P =	> .05 ns	> .05 ns	> .05 ns

ns = not significant.
In brackets, (n =).

TABLE V

CORRELATION OF 50% RECOVERY TIME FROM D-TUBOCURARINE WITH LBM, % FAT, WEIGHT AND DOSE WHEN ASSOCIATED WITH METHOXYFLURANE (n = 10)

(a)	Mean	Correlation of 50% recovery time with (a)
LBM	50.8 ± 12.8 Kg	0.501
% Fat	30.8 ± 18.2 %	−0.691
WT	75.7 ± 16.08 Kg	−0.342
Dose	18.9 ± 4.01 mg	−0.014

TABLE VI

INITIAL DOSAGE OF D-TUBOCURARINE RECOMMENDED IN MAN

.098–.12 mg/Kg	Pelikan et al[49]
0.16 mg/Kg	Baraka[4]
0.1 mg/Kg	Cohen, Paulson and Elert[13]
0.1–0.3 mg/Kg	Katz and Wolf[38]
.22 mg/Kg	Long and Bachman[44]
.35–.6 mg/Kg	Gerbershagen and Bergman[30]
.47 mg/Kg	Kovanev and Khmelevsky[42]
.5 mg.–1.0 mg/Kg	Katz, Norman, Seed and Conrad[41]
0.6 mg/Kg	Katz[40]
.64 mg/Kg	Baraka[4]
8–11.2 mg/m²	Walts and Dillon[59]
10–20 mg. initial dose	Gray and Halton[33]
10–20 mg. initial dose	Ryan[54]

show such a relation with regard to the respiratory response nor Pelikan, Tether and Unna[50] to grip strength or near point binocular conversion. However, Long and Bachman[44] did find some relation in children between compound muscle action potential and the dose of D-tubocurarine.

In the present study a better correlation was found of a dose producing a standard response with lean body mass than with body weight. This standard response was a 90–95 per cent depression of muscle twitch height (see Table II), which produced excellent abdominal muscle relaxation for operations. de Jong[17,18] also reported a similar experience. By using lean body mass as an index for dosage a better prediction of response can be obtained. This makes allowance for the short fat person and the tall thin person of equal weight who do not necessarily require equal doses. Foldes[29] and also Kalow[36] recognized the fact that body build would influence the dosage requirement suggesting that the muscular patient would require more, and the fat ones requiring less mg/Kg of body weight. Also, in this study fat people were found to require less than thin persons based on weight (Table III). However, based on lean body mass, fat people would require the same or sometimes even more than the very thin. A possible reason is that in these cases they have more muscle than expected relative to the lean body mass.

(ii) In adults age apparently made no difference, patients over 66 years requiring the same dose based on body weight[19] as did younger individuals. However, Gray[33] states that the aged need less and Durrans[20] that they need more. In this

study the aged needed more D-tubocurarine based on lean body mass (Table IV). Infants, however, were found to need less than older children.[44]

(iii) Sex did not influence the dosage of D-tubocurarine, males and females requiring similar amounts,[19] based on body weight. In the present study, females required a little less than males with halothane when based on lean body mass, but nearly similar doses when meperidine or methoxyflurane were used.

(iv) The dosage of D-tubocurarine required is influenced by the anaesthetic drug administered with the muscle relaxant. With halothane the dosage required to produce 90–95 per cent muscle depression was 0.24 mg/Kg LBM; with meperidine 0.34 mg/Kg LBM; and with methoxyflurane 0.38/Kg LBM (Table III). Similarly, the average doses used were 10.8 mg ± 2.5, 16.7 mg ± 3.9 and 18.8 mg ± 5.1 respectively. These values fall into the range of the 10–20 mg initial doses used by Gray and Halton[52] and by Ryan.[54]

Halothane and methoxyflurane do not affect nerve conduction[57] but do have a direct effect on the neuromuscular junction increasing its refractory period.[23] Although halothane decreases muscle tone, it does not per se decrease muscle twitch height.[39] But, like diethyl ether,[28] it magnifies the action of D-tubocurarine,[5] increasing both the depression of muscle twitch and its duration of action, probably by its effect on the post-junctional membrane, decreasing its miniature end-plate potentials.[39]

Methoxyflurane produces some degree of muscle relaxation.[56,34] It decreases muscle tone in low concentrations by abolishing the spinal reflex, but it has no significant effect on muscle twitch height.[47] Artusio, *et al.*[13] and Campbell, *et al.*[8] found the dose response relationship of D-tubocurarine with methoxyflurane to be similar to that with diethyl ether or other anaesthetics. In the present study this was not found to be so and a larger dose of D-tubocurarine was required with methoxyflurane than with halothane.

Thiopentone intensifies the action of D-tubocurarine, nitrous oxide has no effect on D-tubocurarine action, but meperidine may potentiate it.[29] A diversity of other factors also operate upon the intensity of response to D-tubocurarine.

Suxamethonium given prior to D-tubocurarine increases the duration and intensity of its action even though there had been first a 100 per cent return to muscular power from suxamethonium.[41] In the present study all patients received suxamethonium initially for endotracheal intubation before D-tubocurarine was administered.

(v) Acidosis raises the plasma concentration of D-tubocurarine,[4,58] binds more of it to the plasma proteins,[31,4] and increases its neuromuscular blocking action.[4,29,38,48,42,25] Alkalosis produces the opposite effects.

(vi) An increased sensitivity to D-tubocurarine[29] occurs in states where the extracellular potassium falls,[25] in dehydration, in muscle diseases,[61] with temperature reduction and with certain drugs, as for instance chlorpromazine.[22]

(vii) The intensity and duration of response of the patient to D-tubocurarine is also dependent on its redistribution from the plasma into the body tissues. Kalow[36] described three overlapping phases to account for the redistribution and Fleischli and Cohen[26] used a simulated analog computer to calculate these changes.

Phase 1

Following the intravenous injection of D-tubocurarine the plasma concentration is high after 1–2 minutes.[37] Some is bound to plasma proteins, more of it to globulin than to albumin.[1]

The plasma level then falls rapidly over the next 10 minutes and after 15–20 minutes a new steady rate of decline is achieved which is fairly constant for the next 2 hours. At 5 or 6 minutes the level has fallen to half its original level,[26,37,61] and it is during this time that the D-tubocurarine reaches the muscle end-plates and causes skeletal muscular paralysis, as is evidenced by the fact that it begins to act within 2 minutes.[40] However, in the present study where the drug was given slowly instead of in a single injection its peak of action of 90–95 per cent muscle paralysis was reached only in 10 minutes, although the onset of action began within 3 minutes.

At 10 minutes following a single injection the plasma concentration is 60 per cent of the initial concentration. In 20 minutes it is 40 per cent and at 60 minutes 25 per cent.[12] Ryan[54] and Pittinger *et al.*[51] report smaller percentages, namely 18–20 per cent at 20 minutes and 9.5–9.6 per cent at 60 minutes. Fleischli and Cohen[26] and Dal Santo[16] estimate that 80–90 per cent of the drug has disappeared from the plasma by 30 minutes.

Equilibrium between plasma and interstitial fluid concentration is established in 10–20 minutes[12] or 13.2 minutes.[54] The half life of D-tubocurarine in plasma is 42 minutes[54] or 45.6 minutes in extracellular fluid.[35]

Phase 2

The plasma concentration falls rapidly because of redistribution of the D-tubocurarine into the tissues. These could conceivably be subdivided into 3 major groups based on the time-sequence of blood-flow. These groups have already been used to advantage in explaining the uptake of thiopentone[53] and halothane.[21] These 3 subgroups can be conveniently considered as follows:

(*a*) the vessel-rich group, notably the kidneys and liver which can be named the "excretory site".

(*b*) the muscle group, which is the "active site" of Wylie and Churchill-Davidson.[62]

(*c*) the vessel-poor group (bones, cartilage) and fat group which can be named the "inactive site".

(a) Vessel-rich group

The bulk of the drug enters the vessel-rich group (VRG) of tissues first, as they receive 70–75 per cent of the cardiac output.[21,53] The vessel-rich group comprises 9 per cent of the body weight, yet the liver receives 28 per cent of the cardiac output, the kidneys 23 per cent, the brain 14 per cent and the heart 5 per cent.

Although the liver and kidneys receive the largest share of the drug initially because of their disproportionately large blood-flow it takes some while for bile excretion and urine excretion of D-tubocurarine to occur. Peak concentration occurs in the liver within 5 minutes, and in the kidney in 90 minutes.[18]

At 10 minutes 8 per cent of the drug given is found in the urine, at 30 minutes only 15 per cent but by 24 hours 60–70 per cent.[26] According to others 85 per cent is excreted in 7 hours[16] or 75 per cent in 24 hours. Up to 30 minutes, the distribution of D-tubocurarine is not influenced by renal factors.[14]

This disparity in time would account for the interval needed for sufficient drug to reach the muscle end-plates and to produce its paralysis before being excreted. With its return from muscle and from the inactive sites back into the plasma more enters the kidneys for excretion, thus probably producing the slow rise in the urine concentration. Even with bilateral nephrectomy[24,45] there is no prolonged paralysis from D-tubocurarine, and this probably is due to its distribution into other tissues.[15]

At one time it was held that one third of D-tubocurarine was metabolized in the liver but Stead and Andrews [55] have shown that the liver played no part in this. Small amounts accumulate in the liver and finally about 2 per cent of the injected drug[26] or 11.3 per cent passes unchanged into the bile.

(b) Muscle Group

Muscle is the "active site". Muscle constitute 50 per cent of the body weight[21] and because of the good blood-supply (16–18 per cent of the cardiac output)[21,53] a big share of the injected drug will enter this large tissue mass early.[26] This is noted clinically by the onset of muscle paralysis within 2–3 minutes from a single dose.

At 5 minutes following injection 50 per cent of the dose is in the muscle, at 10 minutes only 35 per cent and by 15 minutes it had decreased to 28 per cent.

(c) "Inactive sites"

Besides muscle the drug enters other tissues, the "inactive sites", where no pharmacological action takes place. These sites represent the "inactive tissue depots" described by Marsh,[46] Kalow[35] and Foldes,[27] the "acceptor tissue depot" described by Cavalitto,[9] Fleischli and Cohen,[26] and the "non-active site of loss" described by Chagas.[10]

The most likely possibility is that these inactive sites are the vessel-poor group (VPG) and fat group (FG) described by Price.[53] The vessel-poor group made up of bone, cartilage and ligaments constitutes 22 per cent of body weight, and the fat group made up of adipose tissue constitutes 19 per cent of body weight. Because of their blood-supply the drug enters these tissue groups much more slowly than the muscle group, yet the vessel-poor group represents nearly 41 per cent of body weight while receiving only 6.9 per cent of cardiac output, as against 50 per cent of body weight and 18 per cent of cardiac output for the muscle group. However, Fleischli and Cohen[26] have calculated the theoretical volume of the "acceptor tissue depot" volume as being 21.2 per cent, a slightly lower figure than the 21 L volume of the vessel-poor and fat groups given by Price.[53] However, Cohen *et al.*[13] could not find any D-tubocurarine in the fat tissues.

Phase 3

This prolonged phase covering many hours is involved in the destruction or transformation of the drug.[15] Cohen, Brewer and Smith[34] could only find 1 per cent of the injected D-tubocurarine converted to non-curare forms.

Recovery Time

In this study the average time to 50 per cent recovery of muscle power was 38.8 minutes when given with methoxyflurane at a dose of 0.38 mg/Kg LBM or 0.27 mg/Kg WT. Fat people of almost equal weight as thin ones (72.6 and 71.3 Kg) recovered twice as fast as the thin people, the times being 27.5 minutes compared to 55 minutes. Recovery rate was best related to fat per cent (Table I and V).

Walts and Dillon[59] found recovery time to 50 per cent muscle power took 39 minutes following 8 mg/m^2. Recovery time to 90 per cent of initial height following 0.1 mg/Kg weight was 29.0, 31.0, and 26.6 minutes in 3 different cities.[41]

Levy[43] showed the decline of activity of D-tubocurarine to be linear with time. The duration of action is also controlled by dose and blood pH, acidosis producing a longer action,[7,42] and by dilution and redistribution to inactive receptors rather than by urinary excretion.[62]

The half-life of D-tubocurarine in plasma is 42.5 minutes and in extracellular fluid it is 45.6 minutes.[35,36] About 18 per cent of the dose injected is still in the muscle and about 12 per cent in the plasma at this time of 45 minutes.[26] This helps to account for the fact that a second injection of one half the initial dose given at 45 minutes will have the same effect as the full initial dose.[39,49]

Lean Body Mass

Lean body mass consists of the vessel-rich, muscle and vessel-poor groups excluding the fat group.

At its peak of action, at about 10 minutes following injection of D-tubocurarine, the major part (85 per cent) of the drug has entered the lean body mass. Fifty per cent is in the vessel-rich group (30 per cent in plasma, 10 per cent in liver, 4 per cent in kidney, 5 per cent in urine and 1 per cent in bile) and 35 per cent is in the muscle.[26] Of the remaining 15 per cent a small amount is in the vessel-poor group and the rest is in the fat group. Since fat has 3¼ times the blood flow of the vessel-poor group but their weights of 19 and 22 Kg respectively are quite close, fat accumulates more drug than the vessel-poor group. However, both accumulate D-tubocurarine much more slowly than the other tissues because of their poor blood-supply.

By excluding fat from weight and thereby using the lean body mass instead of body weight, a closer correlation with dose is obtained and the response is more predictable. Theoretically, if one could exclude the weight of the vessel-poor group and just use the vessel-rich and muscle groups for correlation with dose, an even better correlation might be obtained. But no simple method has yet been devised clinically to estimate the skeletal bone mass of a particular patient. However, lean body mass can be measured in a clinical setting with ease and thus it is a practical method for predicting dose.

Others have described the metabolism of D-tubocurarine in terms of the total body water (TBW), which is a measure of the lean body mass. The total body water consistently represents 72 per cent of the lean body mass from infancy

through adult life.[11] Kalow[38] described D-tubocurarine as leaving the plasma to enter the total body water and dal Santo[36] as entering the extra-vascular compartment (interstitial and intracellular).

Summary

The dosage of D-tubocurarine recommended varies greatly with different authors. The body build, reflected in the lean body mass (LBM), influences the dose. The dose which produces a 90–95 per cent depression of neuromuscular blockade is better correlated to the lean body mass than the body weight.

Age and body somatotype influence this dosage.

Less D-tubocurarine is required when halothane is the anaesthetic, than when methoxyflurane or meperidine are used.

The average recovery time to 50 per cent muscle power when 0.38 mg/Kg LBM is given with methoxyflurane is 38.8 minutes and this was best related to percentage fat.

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Résumé

La dose de d-Tubocurarine nécessaire pour produire une dépression de 90–95 pour cent du blocage neuromusculaire se calcule mieux d'après la masse maigre du corps que d'après le poids corporel. Cette dose peut varier selon l'agent anesthésique employé concomittamment; avec l'halothane, la dose est 0.24 mg/kg de masse maigre; avec le meperidine, 0.34 mg/kg de masse maigre et, avec le méthoxyflurane, 0.38 mg/kg. Le retour de 50 pour cent de la force musculaire est deux fois plus rapide chez le sujet gras que chez le sujet maigre.

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