

Is using a patient's estimated lean body mass a suitable method of predicting their eventual therapeutic units of botulinum toxin for the treatment of cervical dystonia?

Abstract

Objective: To investigate whether there is a correlation between the eventual treatment dose of botulinum toxin administered and the estimated lean body mass of patients with cervical dystonia receiving a stable treatment regime

Setting: Adult dystonia outpatient clinics at the Royal Devon and Exeter (RD&E) Hospital

Design: Clinical Observational Study

Population/Participants: Patients attending adult dystonia outpatient clinics at the RD&E Hospital in the period 01/08/13 to 31/10/13 inclusive, receiving treatment for cervical dystonia with botulinum toxin type A (Dysport®). All participants were receiving a stable treatment regime.

Methods: Data was collected through anthropometric measurement of the patient's height and weight as well as the total dose of botulinum toxin received

Results: 119 patients on stable treatment regimes with botulinum toxin for cervical dystonia participated in the study: 36 men and 83 women. There was no correlation found between the estimated lean body mass and total units of botulinum toxin administered (correlation: 0.116), even when adjusted for gender (men correlation: 0.068; women correlation: -0.129) or when comparing total body mass to the units of botulinum toxin administered (men correlation 0.031; women correlation: -0.082).

Conclusions: The absence of correlation between the dose of botulinum toxin administered it remains the case that the safest way of treating patients with cervical dystonia is by titrating up the dose of botulinum toxin over a number of appointments and identifying the most appropriate muscles to inject through best clinical judgment.

Introduction

Botulinum toxin is one of the main treatment options for the focal control of abnormal posturing, pain and discomfort associated with dystonia. Botulinum toxin is injected into the affected muscles to target the neuromuscular-blocking action specifically to those muscles that are excessively contracting. Even with such focused therapy side-effects can occur; for the treatment of cervical dystonia this may be difficulty swallowing, dysarthria, dysphonia or difficulties breathing.

Currently, the treatment regime for cervical dystonia involves starting at a low dose of botulinum toxin and titrating to reach the optimal dose. The optimal dose is the minimum to achieve the desired outcome for both patient and clinician without there being adverse effects.[1] Dysport recommend a starting dose of 500 units divided between affected muscles for the treatment of cervical dystonia titrated in 250 unit steps at 12-week intervals.[2] It can require two or three re-injections of botulinum toxin to establish the eventual effective dose; it can therefore currently take a year to reach the optimal dose of botulinum toxin.

Recent evidence points towards lean body mass in preference to total body weight for the prediction of drug dosage.[3] Both these parameters will be assessed in this piece so as to determine whether either has a correlation with the total units of botulinum toxin administered.

Aims and Objectives

The main objective is to determine whether there is an association between a patient's estimated lean body mass and the eventual therapeutic dose of botulinum toxin in patients receiving a stable treatment regime. Ultimately this could lead the way to creating an algorithm for predicting the eventual dose of botulinum toxin based upon a patient's estimated lean body mass.

Methods

Participants were attendees at an adult dystonia clinic with a diagnosis of cervical dystonia at the Royal Devon and Exeter (RD&E) Hospital in the period 01/08/13 to 31/10/13. The study ran over a 3-month period in an attempt to include all patients receiving botulinum toxin treatment for cervical dystonia as in this study location treatment occurs at a maximum of every 12 weeks. Ethical approval was acquired from the Royal Devon and Exeter Research Review Service.

There were 119 participants (36 men and 83 women) recruited, with an average age of 63.7 (range 24.6 – 85.0). The participants were able to comprehend the study information and gave verbal consent to participate in the study. Only those on a stable treatment regime were recruited; this was defined as those patients that were receiving the same dose of botulinum toxin into each muscle as in the previous appointment with no additions, removals or substitutions to their regime. Only patients receiving botulinum toxin type A (Dysport®) were included in this study to allow for comparison of the administered dose.

The participants first received their botulinum toxin treatment. Following this the patients had their height recorded in centimetres to 1 decimal place and their weight recorded in kilograms to the nearest 0.05kg. These anthropometric measures were then input into a formula according to the patient's gender (Appendix A) to give an estimated lean body mass given to the closest 0.01 [4]

Statistical analysis was performed using Microsoft Excel 2011 for Mac Version 14.3.8. The results were recorded in a number of tables. The participants were first analysed by anthropological measurements according to gender to calculate their estimated lean body mass (Appendix B). Their estimated lean body mass was then compared to the units of botulinum toxin injected into the specific muscles and their total units of botulinum toxin injected (Appendix C). From this the correlation between estimated lean body mass and total units of botulinum toxin injected was calculated, as was the correlation between body weight and total units of botulinum toxin injected. The correlation was calculated with all participants (i.e., men and women combined) before the correlation was calculated for men and for women separately (Appendix D).

Results

A total of 119 participants contributed to the study. Ages of participants ranged from 24.6 to 85.0 (mean \pm standard deviation: 63.7 ± 12.4 years). There were 36 men and 83 women.

Figure 1: demographics of the study population

	Male	Female
Average height (cm)	175.6 (\pm 6.6)	162.5 (\pm 5.7)
Average weight (kg)	80.59 (\pm 15.37)	68.93 (\pm 12.09)
Average estimated lean body mass	56.47 (\pm 6.50)	45.05 (\pm 4.92)

	Average dose per muscle (units)	Range (units)
Left splenius	257	75 - 500
Right splenius	260	75 - 500
Left sternocleidomastoid	88	50 - 150
Right sternocleidomastoid	102	50 - 150
Left trapezius	233	75 - 750
Right trapezius	211	100 - 400
Left levator scapulae	225	200 - 250
Right levator scapulae	156	100 - 200
Left semispinalis	250	250 - 250
Left extensors	152	50 - 400
Right extensors	160	50 - 400

When analysed as a total patient population (both men and women included), a patient's estimated lean body mass does not correlate with their total units of botulinum toxin (0.116) (Appendix D).

When analysed according to gender, a man's estimated lean body mass does not correlate with their total units of botulinum toxin (0.068), nor does their total body weight correlate with their total units of botulinum toxin (0.031) (Appendix E).

A woman's estimated lean body mass does not correlate with their total units of botulinum toxin (-0.129), nor does their total body weight correlate with their total units of botulinum toxin (-0.082) (Appendix F).

Discussion

The results from this study show that there is not a correlation between a person's eventual total units of botulinum toxin and their lean body mass, nor their total body mass. The lean body mass and total body mass were both compared to the units of

botulinum toxin delivered so as to determine whether either these measures had any bearing on the correlation.

The purpose of this study was to determine whether there was the potential for the creation of an algorithm to calculate a person's units of botulinum toxin when on a stable regime so as to manage the symptoms of cervical dystonia as rapidly and as safely as possible. As there is not a correlation between lean body mass and units of botulinum toxin from this study it is not possible to consider this at the current time.

The issues that would be encountered should a patient's weight or estimated lean body mass be used to predict a patient's initial dose would be that there is a limit on the amount of botulinum toxin that can be injected as patients need to build up tolerance. Additionally there is a possibility that rapid progression to therapeutic dose could reduce tolerance. Another problem is that the muscles requiring treatment may not be initially known and so the location of injection may need to be trialed to see the effect before adjusting the dose and injection location to optimise treatment.

As there is not a correlation between the total units injected and a patient's lean body mass or total body mass, a potential area of study may be comparing a patient's lean body mass to the units of botulinum toxin injected into each individual muscle.

Conclusions

There was not found to be a correlation between the units of botulinum toxin administered to a patient with cervical dystonia on a stable treatment regime and their lean body mass, or total body mass. At this time there is no scope for the creation of an algorithm. From the findings of this study it still remains that the safest way of treating patients with cervical dystonia is by titrating up the dose of botulinum toxin over a number of appointments and identifying the most appropriate muscles to inject through best clinical judgment.

References

1. Francisco GE. Botulinum toxin: dosing and dilution. American Journal of Physical Medicine and Rehabilitation. 2004;83(Supplement 10):S30-7
2. Ipsen Biopharmaceuticals, Inc. Dysport Prescribing Information. 2012
3. Morgan DJ, Bray KM. Lean Body Mass as a predictor of Drug Dosage. Clinical Pharmacokinetics. 1994;26(4):292-307
4. Hume R. Prediction of lean body mass from height and weight. Journal of Clinical Pathology. 1966;19:389-91

Appendix A: calculation of estimated lean body mass[3]

Weight (W) in kilograms; height (H) in centimetres

Men: $(0.218 \times W) + (0.33929 \times H) - 29.5336$

Women: $(0.29569 \times W) + (0.41813 \times H) - 43.2933$

Appendix B: anthropometric values and calculated estimated lean body mass

Males		
Height (cm)	Weight (kg)	eLBM
190.0	101.60	68.266460
173.0	67.05	51.162675
173.0	87.30	57.806700
170.0	67.40	50.259640
177.0	75.35	55.243065
188.0	93.50	64.930270
167.0	77.60	52.588390
170.0	80.25	54.475725
178.0	89.40	60.192160
165.0	74.55	50.909105
173.0	53.75	46.798945
180.0	99.90	64.315790
178.0	80.40	57.239260
178.0	76.40	55.926860
178.0	102.00	64.326220
174.5	83.60	57.101665
177.0	77.20	55.850050
173.0	74.00	53.442970
188.0	122.90	74.576410
180.0	80.70	58.016270
184.0	60.00	52.581760
172.0	102.70	62.520150
181.5	103.60	66.038695
173.0	72.50	52.950820
168.0	71.00	50.762220
172.0	70.90	52.086570
160.5	76.30	49.956475
175.0	68.80	52.415430
167.0	57.80	46.092010
182.0	91.20	62.139900
171.5	79.20	54.640155
178.0	93.30	61.471750
182.0	87.00	60.761880
176.0	51.00	46.914540
181.0	77.40	57.272830
169.0	70.20	50.839030

Females		
Height (cm)	Weight (kg)	eLBM
162.0	61.60	42.658264
158.0	63.70	41.606693
163.0	52.10	40.267339
163.0	71.85	46.107217
162.0	62.80	43.013092
165.5	65.90	45.393186
163.0	80.85	48.768427
168.0	71.10	47.976099
161.0	70.20	44.783068
174.0	80.50	53.264365
161.0	77.45	46.926821
151.0	72.70	41.340993
167.0	75.40	48.829436
164.0	72.70	46.776683
163.0	80.55	48.679720
160.0	68.80	43.950972
160.0	75.55	45.946880
153.0	54.60	36.825264
171.0	65.60	47.604194
165.0	83.60	50.417834
162.0	52.50	39.967485
156.0	61.25	40.045993
154.0	64.45	40.155941
165.5	61.65	44.136504
164.5	79.40	48.966871
161.0	63.55	42.816730
175.0	73.15	51.509174
156.0	58.70	39.291983
170.0	61.75	46.047658
165.0	93.40	53.315596
170.0	86.90	53.484261
164.0	104.90	56.297901
161.5	73.45	45.953126
156.0	69.75	42.559358
173.0	67.80	49.090972
157.5	58.60	39.889609
168.0	53.55	42.786740

Average height	Average weight	Average eLBM
175.6	80.49	56.468690

163.5	52.35	40.550327
153.0	62.50	39.161215
163.5	62.20	43.462873
160.0	69.20	44.069248
166.0	75.20	48.352168
158.0	74.40	44.770576
153.0	55.60	37.120954
157.0	59.30	39.887527
167.0	68.00	46.641330
156.0	66.60	41.627934
167.5	63.00	45.371945
155.0	53.60	37.365834
152.0	49.60	34.928684
165.0	58.70	43.055153
164.0	98.50	54.405485
151.0	47.30	33.830467
153.0	80.50	44.483635
161.0	52.80	39.638062
167.5	88.00	52.764195
171.5	84.00	53.253955
164.5	59.00	42.934795
162.0	54.00	40.41102
160.0	93.00	51.10667
170.0	75.70	50.172533
160.0	69.70	44.217093
155.0	50.00	36.30135
170.0	77.60	50.734344
165.5	89.90	52.489746
167.0	65.20	45.813398
158.0	60.20	40.571778
164.0	78.60	48.521254
159.0	72.30	44.567757
158.5	51.10	38.090064
161.5	65.30	43.543252
171.0	61.60	46.421434
173.0	83.00	53.585460
168.0	59.80	44.634802
163.0	83.00	49.404160
163.0	73.00	46.447260
157.5	55.00	38.825125
162.0	86.00	49.873100
169.0	68.00	47.477590
171.0	59.70	45.859623
161.0	62.90	42.624531
166.0	72.80	47.642512
158.0	77.10	45.568939
157.0	72.80	43.879342

Average height	Average weight	Average eLBM
162.5	68.93	45.046583

Appendix C: dose of botulinum toxin and location administered

eLBM	Dose botulinum toxin injected into muscle										Total botulinum toxin dose administered
	L splenius	R splenius	L SCM	L trapezius	R trapezius	L levator scapulae	L semispinalis	R semispinalis	L extensors	R extensors	
68.266460	225			200					300	300	1025
51.162675	400				300						850
42.658264		175	100		125						400
41.606693	500	500									1000
40.267339									250	250	500
46.107217	250	250									500
43.013092	375			375	100						850
45.393186	100	100									200
48.768427	250									100	450
47.976099	250	250									500
44.783068	200	200									400
53.264365	100	75		100							275
46.9268	300	250									550

21											
41.3409 93	325				250						725
48.8294 36	250	250									500
57.8067 00	250	500	75								825
50.2596 40	100								150	150	400
46.7766 83				250			250				500
48.6797 20	250		125	750	250	2					1625
43.9509 72	175	225			200						600
45.9468 80	250		50								375
55.2430 65	250	100		200							625
64.9302 70		375	100		400						875
36.8252 64	275	325									600
47.6041 94	200	200	50	200					150		800
50.4178 34	225	250			125						600
39.9674 85				200	200						400
52.5883 90	500	500									1000
40.0459 93	175	250	100	200							725
40.1559 41		350			350	100					950
44.1365 04	250	250		200	200						900
54.4757 25	150	225									375

48.9668 71	175	175								50	50	450
42.8167 30	100	100										200
51.5091 74	150	200	75							50	50	525
39.2919 83	275			200								625
46.0476 58	250	275										525
53.3155 96	275	275										550
60.1921 60	400											475
53.4842 61	250	250			150							750
50.9091 05	125			300								550
56.2979 01		200	75									275
45.9531 26	250	250										500
42.5593 58	350	350										700
49.0909 72	200	300	75									575
46.7989 45	200			225	175							675
39.8896 09	225	300										525
42.7867 40	250	250										500
40.5503 27	150	275			250							675
39.1612 15	250	250										500
43.4628 73	350											500
44.0692		275	75	150								500

48											
64.3157 90	500	500									1000
48.3521 68	250	250							50	50	600
44.7705 76	300	300									600
57.2392 60	150	150	150	100	100						800
55.9268 60		250	100		200	200					750
64.3262 20	400										500
57.1016 65	250	200							400	400	1250
55.8500 50		300	75		300						675
53.4429 70	250		125								375
74.5764 10					200						200
58.0162 70	275	275									550
52.5817 60	500			500		2					1200
62.5201 50		250	100		200					150	700
66.0386 95	300	200									500
52.9508 20		250	100		250						600
50.7622 20	325	275									600
52.0865 70	250	250		100							600
49.9564 75	125	125		250	125						725
52.4154 30		200	50	250	250						750

46.0920 10	200	400	125	200	250						1175
62.1399 00		700			700						1400
54.6401 55	500	500									1000
37.1209 54	275	300									575
39.8875 27	150	150									300
46.6413 30	225	225									450
41.6279 34	300	300									600
45.3719 45		300	100	150							550
37.3658 34	250	250									500
34.9286 84	275	250	50	150							725
43.0551 53	400	250		250							1000
54.4054 85	275										375
33.8304 67		250		100	100			200	200		950
44.4836 35	250	400		150	150			200	400		1550
39.6380 62	175	250	75								500
52.7641 95	250					125					475
53.2539 55	225	200									425
42.9347 95	275	275									625
40.4110 20	275	275						125	125		800
51.1066	275	150		275							800

70											
50.1725 33	200	300	100		100	100					800
44.2170 93	100	100	75						125	125	600
36.3013 50		175									175
50.7343 44	200										300
52.4897 46	350				300						650
45.8133 98	300	300									600
40.5717 78	200	200			100						600
48.5212 54	250	125	50								425
44.5677 57	150	150									300
38.0900 64		250	50		150						450
43.5432 52	250	300							75	75	700
46.4214 34	250	250			100				75	75	800
53.5854 60	75	75									150
44.6348 02	250										350
49.4041 60	125	125									250
46.4472 60	250	250			150						650
38.8251 25		150	75		100						325
49.8731 00		275	150	200							625
61.4717 50	500	500									1000

60.7618 80	250	250									500
46.9145 40		100	75	75					75	75	400
57.2728 30	500		100	400							1100
50.8390 30	325	275									600
47.4775 90	250			200		200					725
45.8596 23	150	250									450
42.6245 31		175	100	125							400
47.6425 12	300			500							900
45.5689 39		300	100	250		300		200			1150
43.8793 42	225			150							375

Appendix D: ranking for calculation of correlation between estimated lean body mass and dose

Total botulinum toxin dose administered (units)	RANK eLBM	RANK total dose	Correlation
			0.115814299
1025	2	9	
850	38	21	
400	95	97	
1000	99	10	
500	104	73	
500	68	73	
850	91	21	
200	76	116	
450	53	90	
500	57	73	
400	78	97	
275	28	113	
550	61	65	
725	100	33	
500	52	73	
825	13	23	
400	45	97	
500	64	73	
1625	54	1	
600	86	50	
375	72	103	
625	20	46	
875	4	20	
600	117	50	
800	59	24	
600	44	50	
400	107	97	
1000	32	10	
725	106	33	
950	105	16	
900	84	18	
375	22	103	
450	51	90	
200	93	116	
525	37	70	
625	111	46	
525	70	70	
550	27	65	
475	11	88	
750	25	30	
550	40	65	
275	17	113	
500	71	73	
700	97	38	
575	50	63	
675	63	41	

525
500
675
500
500
500
1000
600
600
800
750
500
1250
675
375
200
550
1200
700
500
600
600
600
725
750
1175
1400
1000
575
300
450
600
550
500
725
1000
375
950
1550
500
475
425
625
800
800
800
600
175
300
650
600
600
425
300
450
700
800

108	70
94	73
102	41
112	73
89	73
85	73
6	10
56	50
79	50
15	24
18	30
5	73
16	4
19	41
26	103
1	116
12	65
33	5
7	38
3	73
30	50
42	50
36	50
47	33
35	30
69	6
8	3
21	10
116	63
109	110
65	90
98	50
77	65
115	73
119	33
90	10
23	103
120	16
82	2
110	73
31	88
29	95
92	46
103	24
39	24
46	24
83	50
118	119
43	110
34	44
74	50
101	50
55	95
81	110
114	90
88	38
67	24

150
350
250
650
325
625
1000
500
400
1100
600
725
450
400
900
1150
375

24	120
80	108
49	115
66	44
113	109
48	46
9	10
10	73
62	97
14	8
41	50
60	33
73	90
96	97
58	18
75	7
87	103

Appendix E: Calculation of the correlation between botulinum toxin dose and weight and estimated lean body mass for men

Men weight (kg)	Men eLBM	Men total units	RANK men weight	Rank eLBM	RANK total	
						Correlation weight
101.60	68.266	1025	5	2	6	0.030679
67.05	51.162	850	32	28	12	223
87.30	57.807	825	11	13	13	Correlation eLBM
67.40	50.26	400	31	32	32	0.068378
75.35	55.243	625	23	19	21	269
93.50	64.93	875	7	4	11	
77.60	52.588	1000	18	24	7	
80.25	54.476	375	16	21	34	
89.40	60.192	475	10	11	31	
74.55	50.909	550	24	29	26	
53.75	46.799	675	35	35	19	
99.90	64.316	1000	6	6	7	
80.40	57.239	800	15	15	14	
76.40	55.927	750	21	17	15	
102.00	64.326	500	4	5	28	
83.60	57.102	1250	13	16	2	
77.20	55.85	675	20	18	19	
74.00	53.443	375	25	22	34	
122.90	74.576	200	1	1	36	
80.70	58.016	550	14	12	26	
60.00	52.582	1200	33	25	3	
102.70	62.52	700	3	7	18	
103.60	66.039	500	2	3	28	

72.50	52.951	600	26	23	22
71.00	50.762	600	27	31	22
70.90	52.087	600	28	27	22
76.30	49.956	725	22	33	17
68.80	52.415	750	30	26	15
57.80	46.092	1175	34	36	4
91.20	62.14	1400	9	8	1
79.20	54.64	1000	17	20	7
93.30	61.472	1000	8	9	7
87.00	60.762	500	12	10	28
51.00	46.915	400	36	34	32
77.40	57.273	1100	19	14	5
70.20	50.839	600	29	30	22

Appendix F: Calculation of the correlation between botulinum toxin dose and weight and estimated lean body mass for women

Women weight (kg)	Women eLBM	Women total units	RANK women weight	RANK eLBM	RANK total	
						Correlation weight
						-
61.60	42.658	400	60	59	66	0.081649135
63.70	41.607	1000	51	63	4	
						Correlation eLBM
52.10	40.267	500	80	68	46	-
						0.129283676
71.85	46.107	500	35	33	46	
62.80	43.013	850	55	55	10	
65.90	45.393	200	46	40	81	
80.85	48.768	450	13	20	59	
71.10	47.976	500	36	24	46	
70.20	44.783	400	37	42	66	
80.50	53.264	275	15	6	78	
77.45	46.927	550	20	28	40	
72.70	41.341	725	32	64	17	
75.40	48.829	500	24	19	46	
72.70	46.777	500	32	29	46	
80.55	48.68	1625	14	21	1	
68.80	43.951	600	41	50	29	
75.55	45.947	375	23	36	70	
54.60	36.825	600	73	81	29	
65.60	47.604	800	47	26	11	
83.60	50.418	600	10	13	29	
52.50	39.967	400	78	71	66	
61.25	40.046	725	62	70	17	
64.45	40.156	950	50	69	6	

61.65	44.137	900	59	48	8
79.40	48.967	450	17	18	59
63.55	42.817	200	52	57	81
73.15	51.509	525	28	10	43
58.70	39.292	625	68	75	26
61.75	46.048	525	58	34	43
93.40	53.316	550	3	5	40
86.90	53.484	750	7	4	16
104.90	56.298	275	1	1	78
73.45	45.953	500	27	35	46
69.75	42.559	700	38	61	21
67.80	49.091	575	44	17	38
58.60	39.89	525	70	72	43
53.55	42.787	500	76	58	46
52.35	40.55	675	79	66	23
62.50	39.161	500	56	76	46
62.20	43.463	500	57	53	46
69.20	44.069	500	40	49	46
75.20	48.352	600	25	23	29
74.40	44.771	600	26	43	29
55.60	37.121	575	71	80	38
59.30	39.888	300	66	73	75
68.00	46.641	450	42	30	59
66.60	41.628	600	45	62	29
63.00	45.372	550	53	41	40
53.60	37.366	500	75	79	46
49.60	34.929	725	83	83	17
58.70	43.055	1000	68	54	4
98.50	54.405	375	2	2	70
47.30	33.83	950	84	84	6
80.50	44.484	1550	15	46	2
52.80	39.638	500	77	74	46
88.00	52.764	475	6	8	58
84.00	53.254	425	9	7	64
59.00	42.935	625	67	56	26
54.00	40.411	800	74	67	11
93.00	51.107	800	4	11	11
75.70	50.173	800	22	14	11
69.70	44.217	600	39	47	29
50.00	36.301	175	82	82	83
77.60	50.734	300	19	12	75
89.90	52.49	650	5	9	24
65.20	45.813	600	49	38	29
60.20	40.572	600	63	65	29
78.60	48.521	425	18	22	64
72.30	44.568	300	34	45	75
51.10	38.09	450	81	78	59
65.30	43.543	700	48	52	21
61.60	46.421	800	60	32	11

83.00	53.585	150	11	3	84
59.80	44.635	350	64	44	73
83.00	49.404	250	11	16	80
73.00	46.447	650	29	31	24
55.00	38.825	325	72	77	74
86.00	49.873	625	8	15	26
68.00	47.478	725	42	27	17
59.70	45.86	450	65	37	59
62.90	42.624	400	54	60	66
72.80	47.643	900	30	25	8
77.10	45.569	1150	21	39	3
72.80	43.879	375	30	51	70