

Dantrolene Sodium Suspension in Treatment of Spastic Cerebral Palsy

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Introduction

Spasticity is a significant problem in many patients with cerebral palsy and if it is interfering with function, attempts to reduce its severity are desirable. Methods commonly employed include physical therapy, surgery, bracing, nerve-blocking techniques, electrical stimulation and drugs. Since dantrolene sodium became available, reports have appeared indicating that it has some efficacy in the treatment of spasticity in cerebral palsy (Chyatte and Basmajian 1973, Haslam *et al.* 1974, Denhoff *et al.* 1975, Ford *et al.* 1976).

Although dantrolene sodium has been shown to be physiologically active in reducing the force of muscle response to peripheral nerve stimulation and in decreasing clonus (Basmajian and Super 1973, Chipman *et al.* 1974, Monster 1974, Sheplan and Ishmael 1975, Joynt 1976), reports of its effect in improving functional ability have varied (Joynt 1976; Gelenberg and Poskanzer 1973; Jonsson *et al.* 1975*a,b*). Since the ability to improve function would be more significant than the physiological effect, the present study was designed specifically to evaluate functional improvement in children with spastic cerebral palsy.

We used a new formulation of the drug, dantrolene sodium suspension, developed for use in children. The drug was also evaluated for physiological activity, safety and side-effects.

Method

Cerebral-palsied children were selected from a pediatric rehabilitation clinic on the basis of their ability to participate in the study, and because spasticity was interfering with function. The 21 children appeared to be neurologically and psychologically stable at the time they entered the study. They were randomly assigned to drug-treatment and placebo groups. Age, weight, diagnosis, blood pressure, pulse rate and drug dosage were recorded at each of four visits. Hand preference was noted. Laboratory evaluations included full blood count, with smear and differential, platelet count, reticulocyte count, and urinalysis with microscopic evaluation. Blood chemistry investigations included BUN, creatinine, glucose, uric acid, cholesterol, bilirubin, serum protein with A:G ratio, lactic dehydrogenase, alkaline phosphatase, serum glutamic oxalacetic transaminase, calcium, phosphorus, sodium, potassium, chloride and creatine phosphokinase.

At the initial visit, a complete history and physical examination were performed by the physician. On the three subsequent visits the patient and family were questioned specifically about muscle spasms and range of motion that the family observed when dealing with the child, possible drug side-effects, activities of daily living, their general impression of the child's daily performance, and whether or not they thought the drug was helpful. These factors were rated by values from 1 to 9, with 5 being the pre-treatment baseline score, higher numbers indicating improvement (mild, moderate, marked) and lower numbers indicating deterioration.

Each of the four extremities was examined, and the following factors were given a numerical rating based on the following scoring system: tone (rated 0 to 6; 3=normal), clonus (0 to 6; 0=normal), strength (0 to 5; 5=normal), reflexes (0 to 6; 3=normal), spasms (0 to 3; 0=normal). Spasms were rated by the severity of muscle contractions that were produced in other areas during the range-of-motion examination of a joint of one of the extremities. Mild spasms (rated 1) would include motion at another joint, such as knee flexion or extension occurring while the ankle was being examined. Severe spasms (rated 3) were, for example, a mass flexion pattern of the trunk and arms occurring while a leg was being examined. The scores for a given result from each extremity were totalled to produce the final score assigned to that particular examination.

Physiological measurements of the force of plantar flexion produced by a tap on the tendo calcaneus, supramaximal tibial nerve stimulation, and voluntary plantar flexion were made in a slightly modified form of those described previously by Sheplan and Ishmael (1975) and Joynt (1976). These tests were performed

with the patient lying prone, and the foot held in a shoe strapped to a plate with the ankle at 90°. The center of rotation of the foot-plate assembly was aligned with the patient's anatomical ankle-joint, and the number of foot-pounds of torque generated by plantar flexion against the foot-plate was measured by a strain gauge. The tendo calcaneus was tapped by a standard reflex hammer held by the examiner. Tibial nerve stimulation was performed by a bipolar surface stimulator placed over the mid-popliteal fossa and adjusted gradually to a supramaximal current.

Functional tests were applied to evaluate general activities of daily living. Tests for the arms and hands included unscrewing two halves of barrels of three sizes, buttoning and unbuttoning buttons of three sizes, following a pattern with a pencil on paper, and using each hand separately to pick up and place a cylinder and to eat a marshmallow with a teaspoon. Tests of mobility were performed as they were applicable to a given individual, and included rolling, crawling, standing, walking (with aids if needed), wheelchair

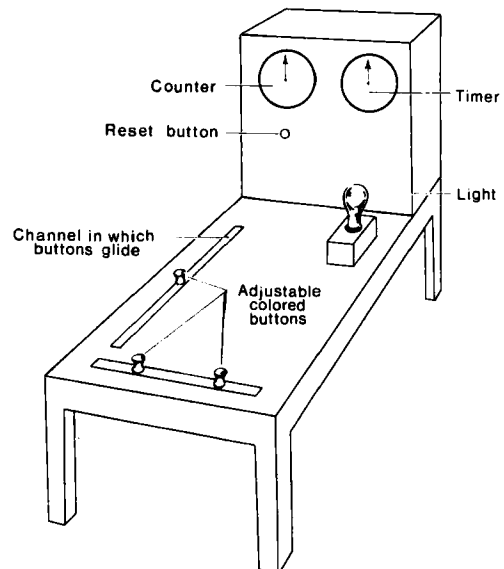


Fig. 1. Device for testing mobility in extremities.

use, and climbing stairs. Only the appropriate tests of mobility were given: for example, wheelchair mobility was not tested in patients who did not use a wheelchair, nor was climbing stairs tested in a child who could not do so. A total of 24 functional tests were performed.

Mobility tests for individual extremities were designed to measure motion in specific patterns. A board similar to that used by Stern *et al.* (1969) was designed, with adjustable colored buttons (Fig. 1). For testing the arms, the board was placed in front of the patient with the two closest buttons in the coronal plane, separated by a distance equal to the patient's shoulder width. The third button was located in a sagittal plane opposite the arm being tested, a shoulder's width in front of the patient. The child touched the buttons

in a horizontal plane, then in a vertical plane and then in a triangular pattern, so that shoulder adduction and abduction; shoulder and elbow flexion and extension; and a combination of these motions could be evaluated. For testing the legs, buttons were similarly placed to require adduction and abduction of the hip, and flexion and extension of the knee. A single button was used to test ankle plantar flexion and

TABLE I
Diagnoses of patients in study

Diagnosis	No.
Spastic diplegia	7
Spastic quadriplegia	7
Spastic hemiplegia	5
Spastic paraplegia	1
Total	20

TABLE II
Strength of voluntary plantar flexion (ft/lb ankle torque)*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1		Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1
2	—				1	0.05	0.05	—	2.2
3	1.2	1.9	2.0	—	6	5.6	0.4	-3.0	2.4
4	0.8	-0.1	-0.3	—	7	—			
5	—				8	6.0	-2.0	-3.6	-1.0
11	2.0	0.6	0.8	0.5	9	3.5	-3.0	-2.0	-3.2
12	3.4	-1.4	-0.2	-1.1	10	4.0	-3.3	-0.5	-2.8
14	5.0	1.0	1.0	1.0	13	17.5	-5.0	-0.5	-2.5
17	2.2	-0.5	-0.1	-0.6	15	12.0	-5.5	-4.0	-7.0
20	3.0	1.6	2.2	0.5	16	30.0	0	0	0
Mean		0.443	0.771	0.06	19	30.0	-15.0	0	-12.0
SD		1.18	1.04	0.87	21	—			

STATISTICAL ANALYSIS

	Visit 1					Visit 2/visit 1			
	<3.75	Median 3.75	>3.75	Total		<-0.3	Median -0.3	>-0.3	Total
Placebo	6	0	1	7	Placebo	2	0	5	7
Drug	2	0	7	9	Drug	6	0	3	9
Total	8	0	8	16	Total	8	0	8	16
p = 0.0203					(N.S.)				
	Visit 3/visit 1					Visit 4/visit 1			
	<-0.2	Median -0.2	>-0.2	Total		<-0.8	Median -0.8	>-0.8	Total
Placebo	1	1	5	7	Placebo	1	0	4	5
Drug	8	0	0	8	Drug	6	0	3	9
Total	9	1	5	15	Total	7	0	7	14
p = 0.003					(N.S.)				

*Positive numbers = increase; negative numbers = decrease.

dorsiflexion by a tapping motion on the button. Whenever a button was contacted with sufficient force, a click would be heard and a light would flash, indicating that a score had registered. The child was asked to touch the buttons in the prescribed pattern as quickly as possible, and the time taken to accomplish 10 button-contacts was recorded automatically by a timer. A total of 12 mobility tests of the extremities was performed.

The functional and extremity mobility tests were quantified by the time (seconds) needed to perform the standard tasks. The maximum time allowed to complete a task was 60 seconds, so a score of 60 indicated either that the task actually took 60 seconds or that it could not be performed at all. Duplicate evaluations were performed for each task and the

scores were averaged. Maximum cooperation was strongly encouraged by the examiners but was difficult to achieve at times, so there was considerable inter-test variability for the same individual at different visits (see data tables).

Sixty-one variables were studied, including the 36 timed variables for testing function and mobility of extremities.

A double-blind procedure was used, with random assignment of patients to the two groups. The medication and placebo were pre-packaged in identical form and containers, and were identifiable by patient number only. A cross-over technique to compare drug and placebo in the same patient was not used because previous studies indicated that the presence of side-effects from dantrolene

TABLE III
Weight change (lbs)*

Patient no.	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1	Patient no.	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1
2	53	1.7	—	—	1	45	—	—	2.0
3	85	—	—	—	6	62.3	3.7	—	2.2
4	64	—	—	2.0	7	41	—	-5.0	7.0
5	38	1.0	—	0.3	8	46	-2.0	-4.0	-6.0
11	30	0.3	0.5	1.5	9	33	-1.2	-2.0	-0.5
12	35.5	6.5	6.5	6.5	10	34.5	-0.5	—	0.5
14	78.5	2.5	5.0	0.5	13	66	2.3	0	2.5
17	33	6.5	6.0	7.8	15	69	-6.2	-1.0	-1.5
20	34	2.5	3.0	2.3	16	99	3.0	3.5	5.8
					19	95	0	-0.5	—
					21	35	0.5	0.5	1.0

STATISTICAL ANALYSIS

	Visit 2/visit 1 Median			Total		Visit 3/visit 1 Median			Total
	<1.1	1.1	>1.1			<0.5	0.5	>0.5	
Placebo	2	0	5	7	Placebo	0	1	4	5
Drug	6	0	3	9	Drug	6	1	1	8
Total (N.S.)	8	0	8	16	Total	6	2	5	13

p=0.032

	Visit 4/visit 1 Median			Total
	<2.0	2.0	>2.0	
Placebo	3	1	3	7
Drug	5	1	4	10
Total (N.S.)	8	2	7	17

*Positive numbers = gain; negative numbers = loss.

TABLE IV
Side-effects*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1		Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1
2	5	1	1	0	1	5	2	—	0
3	5	0	0	0	6	5	2	0	0
4	5	1	0	0	7	5	1	1	0
5	5	0	0	0	8	5	2	2	0
11	5	0	0	0	9	5	0	0	0
12	5	0	0	0	10	5	1	0	0
14	5	0	0	0	13	5	1	0	0
17	5	1	0	0	15	5	1	1	0
20	5	0	0	0	16	5	1	0	0
					19	5	1	0	0
					21	5	1	0	0

STATISTICAL ANALYSIS

Visit 2/visit 1				Visit 3/visit 1			
	No change (0)	Side-effects (>0)	Total		No change (0)	Side-effects (>0)	Total
Placebo	6	3	9	Placebo	8	1	9
Drug	1	10	11	Drug	7	3	10
Total	7	13	20	Total	15	4	19

p=0.0072 (N.S.)

*1 = mild; 2 = moderate.

TABLE V
Spasms (subjective)*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1		Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1
2	5	0	0	0	1	5	2	—	0
3	5	0	0	0	6	5	0	0	0
4	5	0	0	0	7	5	1	—	0
5	5	0	0	0	8	5	0	0	0
11	5	0	0	0	9	5	0	0	0
12	5	0	0	0	10	5	0	0	0
14	5	0	0	0	13	5	0	0	0
17	5	0	0	0	15	5	0	0	0
20	5	0	0	0	16	5	1	0	0
					19	5	0	0	0
					21	5	0	0	0

STATISTICAL ANALYSIS

Visit 2/visit 1			
	No change (0)	Improved (>0)	Total
Placebo	9	0	9
Drug	8	3	11
Total	17	3	20

p=0.089

*0 = improved; 1 = mild; 2 = moderate.

destroyed the blinding at the time of cross-over (Joynt 1976, Gelenberg and Poskanzer 1973). The drug was provided in a 5mg/cc suspension and was administered by a calibrated dropper or measuring cup, as appropriate. Following the initial evaluation (visit 1), treatment was begun with a drug dosage of 4mg/kg/day and was increased gradually during the next three weeks to an optimum level, 12mg/kg/day being the approximate maximum. The children were re-evaluated after three weeks (visit 2) and six weeks (visit 3). The drug was then discontinued and the children were tested again three weeks later (visit 4). At visit 2, dosage was adjusted to an optimum level depending on the results of the history and physical examination at that time, and was then maintained at this level until visit 3.

Other medications were not altered during the treatment period. Concomitant medications included mephobarbital, phenobarbital, phenytoin, antibiotics,

decongestants, vitamins, imipramine and (in one patient) diazepam.

Data analysis

All data were converted to integers and placed in a computer for statistical analysis. For each variable, the change that occurred in each patient from visit 1 to each of the subsequent visits was determined, and drug-treated and placebo groups were compared. Thus the patient served as his own control, and only the differences from the initial testing values were analysed. The data tables show the initial (visit 1) test values, and subsequent columns indicate these differences.

As mentioned earlier, during the timed testing procedures a maximum of 60 seconds was allowed to perform a given test. Because the data were open-ended at the upper end, they would not follow a normal random distribution, so a non-parametric statistical procedure—the median test—was used to analyse the

TABLE VI
Range of motion (subjective reports)*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1		Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1
2	5	1	1	0	1	5	2	—	0
3	5	0	1	0	6	5	1	0	0
4	5	0	0	0	7	5	1	-1	0
5	5	0	0	0	8	5	1	1	0
11	5	0	0	0	9	5	0	0	0
12	5	0	0	0	10	5	1	1	0
14	5	0	0	0	13	5	0	0	0
17	5	0	0	0	15	5	0	0	0
20	5	1	0	1	16	5	1	0	0
					19	5	1	1	0
					21	5	0	0	0

STATISTICAL ANALYSIS

	Visit 2/visit 1				Visit 3/visit 1		
	No change (0)	Improved (>0)	Total		No change (0)	Improved (>0)	Total
Placebo	7	2	9	Placebo	7	2	9
Drug	4	7	11	Drug	7	3	10
Total	11	9	20	Total	14	5	19
p=0.064				(N.S.)			

*>0 = improvement.

variables, including those in the non-timed testing areas, which could be expected to follow a normal distribution. This analysis involves finding the median value of a test for all the children (drug and placebo), and counting the values above and below the median in each group. A chi-square test of the resulting table is then performed to compare the placebo group with the drug group. The statistical analysis is shown in each data table for each of the variables that showed statistical significance, and the tables also indicate the mean values and standard deviations in the placebo patients. These figures provide a rough guide as to test reproducibility from week to week in a non-treated patient group, if it is assumed that there is minimal learning in the three-week interval between

tests. (Ideally, in the placebo patients the inter-test difference would be zero.)

Results

Twenty-one patients with cerebral palsy and spasticity were originally examined. One patient on placebo discontinued treatment early because of lack of improvement, and would not return for further evaluation. One patient in the treated group (patient 1) discontinued the medicine after three weeks because of side-effects, but did return for a subsequent re-evaluation. This patient was therefore included in the analysis, although there were no visit 3 details. Thus 20 patients were included in the analysis, 11 of whom received the drug and nine the placebo.

TABLE VII
Tibial nerve stimulation (ft/lb torque at ankle)*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1		Visit 1	Visit 2/ visit 1	Visit 3/ visit 1	Visit 4/ visit 1
2	—				1	0.01	0.03	—	1.24
3	4.0	1.5	1.5	0.25	6	6.0	-2.3	-5.4	0
4	4.8	0.7	-0.4	-3.3	7	2.0	-0.3	-1.4	2.0
5	—				8	3.4	-1.9	-1.8	-0.3
11	2.0	-0.2	-0.5	-0.8	9	2.5	-2.4	-1.5	-0.8
12	4.1	-1.35	-1.1	-1.9	10	3.0	-2.35	-1.2	-1.5
14	3.0	0.8	2.0	0.8	13	6.0	-1.0	0.5	0
17	2.8	-1.1	0.1	-0.4	15	5.5	-3.3	-2.2	-0.2
20	0.7	0.5	1.9	0.4	16	10.0	-2.0	-4.0	-2.0
Mean		0.121	0.5	-0.71	19	19.5	-8.0	-12.0	-7.0
SD		1.05	1.27	1.45	21	2.3	-1.5	-0.6	0.2

STATISTICAL ANALYSIS

	Visit 2/visit 1					Visit 3/visit 1			
	Median			Total		Median			Total
	<-1.225	-1.225	>-1.225			<-1.1	-1.1	>-1.1	
Placebo	1	0	6	7	Placebo	0	1	6	7
Drug	8	0	3	11	Drug	8	0	2	10
Total	9	0	9	18	Total	8	1	8	17
p=0.025					p=0.013				
	Visit 4/visit 1								
	Median			Total					
	<-0.25	-0.25	>-0.25						
	Placebo	4	0	3	7				
Drug	5	0	6	11					
Total	9	0	9	18					
(N.S.)									

*Positive numbers = increased torque; negative numbers = decreased torque.

At the beginning of the study the placebo and drug-treated groups were statistically similar, except that those in the drug-treated group were somewhat stronger (Table II). (With the number of variables that were studied, it is to be expected that at least one might show a statistical difference at the 0.02 level.)

There were 12 male and eight female children in the study. Ages ranged from four to 15 years. Diagnostic categories are shown in Table I. Etiology in the patient with paraparesis was undetermined: this child presented at nine years with progressive spastic paraparesis, not strictly cerebral palsy in the usual sense.

For the drug-treated patients, the average dantrolene dose was 7.8mg/kg/

day (range 0.75 to 14.78mg) at visit 3, when theoretically the optimum dosage had been established. If the patient who discontinued the medicine because of early side-effects is excluded, the average dose was 8.35mg/kg/day (range 4.17 to 14.78mg).

Weight change at visit 3 was significant ($p < 0.04$), but not at visits 2 or 4 (Table III). The treated patients tended to lose weight slightly and the placebo patients to gain weight.

Several patients complained of side-effects. There was a significant difference in the treated group at visit 2 ($p < 0.008$), but not at visits 3 or 4 (Table IV). This suggests that side-effects tend to become less troublesome or to disappear with time. The reported side-effects included fatigue

TABLE VIII
Unscrewing medium-sized barrels (time in seconds)*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4		Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4
2	60	0	0	0	1	12	5.95	—	7.5
3	60	0	0	0	6	6.25	1.45	-0.15	-2.5
4	5.4	-0.8	1.35	-2.55	7	5.2	-5.8	-7.7	-5.85
5	3.35	-0.9	-0.75	0.2	8	1.3	0	-0.95	-0.55
11	1.4	-0.2	-0.35	-0.05	9	8.05	3.7	3.9	4.45
12	2.1	0.05	-2.0	-0.9	10	39.1	-12.25	-20.9	-20.9
14	1.3	0.4	0.2	-0.2	13	2.55	0.65	-0.05	-0.1
17	2.8	-3.1	-2.45	-2.9	15	31.55	25.5	21.55	-4.45
20	4.05	-3.45	-3.7	-12.1	16	0.5	0.1	-0.3	-0.1
Mean		-0.89	-0.86	-2.06	19	3.45	2.0	-0.65	1.85
SD		1.42	1.57	3.94	21	2.0	0.5	1.2	0.8

STATISTICAL ANALYSIS

	Visit 1/visit 2				Visit 1/visit 3			
	Median			Total	Median			Total
	<0.025	0.025	>0.025		<-0.3	-0.3	>-0.3	
Placebo	7	0	2	9	5	0	4	9
Drug	3	0	8	11	4	1	5	10
Total	10	0	10	20	9	1	9	19
p=0.035								
	Visit 1/visit 4							
	Median			Total				
	<-0.15	-0.15	>0.15					
Placebo	5	0	4	9				
Drug	5	0	6	11				
Total	10	0	10	20				
(N.S.)								

*Positive numbers = improved; negative numbers = worsened.

(five patients), drowsiness (three), anorexia (two), diarrhea (one) and vomiting (one).

Analysis of historical reports from the patient and family indicated that spasms were reduced in the treated patients at visit 2 ($p < 0.09$), but not subsequently (Table V). Subjectively, reported improvement in range of motion was also better in the treated patients at visit 2 ($p < 0.07$) (Table VI). There was no statistical difference between the two groups in subjective reports from the patient or families regarding changes in activities of daily living, general daily performance, or whether or not the treatment appeared to be helpful.

The results of the physical examination

(tone, clonus, strength, reflexes, spasms, blood pressure and pulse) showed no significant differences between the placebo and drug-treated groups, nor were changes in laboratory values significantly different.

Of the physiological tests performed, the response to tibial nerve stimulation showed a significant difference between the two groups. In the treated group a reduced response was seen at visit 2 ($p < 0.03$) and at visit 3 ($p < 0.02$), but not at visit 4 after the drug had been discontinued (Table VII). The voluntary strength of plantar flexion was also reduced from placebo values at visit 3, but not at visit 2 (Table II).

The timed functional tests and extremity

TABLE IX
Left arm—vertical alignment of buttons (elbow flexion-extension)*
(time in seconds)

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4		Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4
2	60.00	0	0	0	1	15.80	-16.41	—	-6.49
3	56.22	22.49	39.53	37.99	6	21.03	5.33	-27.12	-21.79
4	6.78	0.26	0.05	-1.99	7	53.79	-5.17	-6.21	-6.21
5	5.31	-2.57	-5.79	-7.3	8	12.18	-4.78	-5.53	-4.55
11	13.88	2.05	4.29	5.61	9	31.46	-15.32	-9.11	-12.37
12	12.67	1.36	1.06	-0.19	10	58.39	-1.61	-1.61	-1.61
14	11.50	6.4	5.86	6.7	13	6.84	0.32	1.66	1.71
17	12.67	-4.56	-2.23	-1.38	15	26.66	7.13	1.14	1.08
20	31.72	7.86	11.01	16.4	16	2.09	0.05	-0.10	0.02
Mean		3.70	5.98	6.20	19	3.77	0.98	1.16	0.6
SD		8.05	13.49	13.70	21	6.50	0.26	-0.71	0.22

STATISTICAL ANALYSIS

	Visit 1/visit 2					Visit 1/visit 3			
	<0.26	0.26	>0.26	Total		<0	0	>0	Total
Placebo	3	1	5	9	Placebo	2	1	6	9
Drug	6	1	4	11	Drug	7	0	3	10
Total	9	2	9	20	Total	9	1	9	19
(N.S.)					p=0.051				

	Visit 1/visit 4			
	<-0.095	-0.095	>0.095	Total
Placebo	4	0	5	9
Drug	6	0	5	11
Total	10	0	10	20
(N.S.)				

*Positive numbers = improved; negative numbers = worsened.

mobility tests showed minimal changes, of doubtful significance. Statistically the treated patients performed better at visit 2 on unscrewing medium-sized barrels ($p < 0.04$) (Table VIII). The drug-treated patients were slightly worse than the placebo patients at visit 3 in left-arm mobility in a vertical direction ($p < 0.06$) (Table IX), in unbuttoning a medium-sized button ($p < 0.03$) (Table X), and in buttoning a small button ($p < 0.06$) (Table XI).

Discussion

Dantrolene sodium has been widely promoted as an effective drug for the treatment of spasticity in various upper motor-neuron diseases. Reports have indicated that it has some use in adults with spinal-cord injury, hemiplegia, multiple

sclerosis and other disorders (Chyatte and Basmajian 1973; Gelenberg and Poskanzer 1873; Chipman *et al.* 1974; Glass and Hannah 1974; Jonsson *et al.* 1975a,b; Sheplan and Ishmael 1975; Steinberg and Ferguson 1975; Joynt 1976; Schmidt *et al.* 1976).

Reports of its use in children with spastic cerebral palsy are also available. Haslam *et al.* (1974) studied 23 children in a double-blind cross-over study comparing dantrolene sodium suspension and placebo. The 15-day treatment periods were separated by a 10-day 'washout' period. Neurological function, nursing care, physical therapy and occupational therapy variables were studied. Improvement was observed in reflexes, scissoring tendency and self-help skills. Denhoff *et al.* (1975) compared dantrolene sus-

TABLE X
Unbuttoning medium-sized buttons (time in seconds)*

Patient no.	Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4	Patient no.	Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4
2	17.8	14.05	12.25	5.65	1	12.5	-5.0	—	2.85
3	60	0	0	0	6	2.25	0.95	-0.9	0.25
4	3.6	-0.4	0.35	0.15	7	60	44.95	0	27.2
5	60	21.75	23.6	0	8	5.8	-11.9	3.05	2.4
11	32.25	21.45	27.0	14.85	9	60	0	0	0
12	8.85	5.8	4.3	0.35	10	60	0	0	0
14	6.4	2.25	2.2	3.5	13	2.25	-0.75	-1.2	-1.9
17	6.6	2.05	4.4	-8.2	15	16.75	2.65	-15.45	6.2
20	60	0	0	0	16	0.4	-0.1	—	-0.1
Mean		7.44	8.23	1.81	19	1.7	-0.25	0.25	-1.05
SD		9.19	10.42	6.15	21	11.5	9.3	2.1	3.35

STATISTICAL ANALYSIS

Visit 1/visit 2				Visit 1/visit 3				
Median				Median				
<0.475	0.475	>0.475	Total	<0.3	0.3	>0.3	Total	
Placebo	6	0	3	9	2	0	7	9
Drug	7	0	4	11	7	0	2	9
Total	13	0	7	20	9	0	9	18

(N.S.) p=0.028

Visit 1/visit 4				
Median				
<0.2	0.2	>0.2	Total	
Placebo	3	0	6	9
Drug	5	0	6	11
Total	8	0	12	20

(N.S.)

*Positive numbers = improved; negative numbers = worsened.

pension and placebo in 28 children, with a cross-over technique using two six-week treatment sessions separated by a two-week 'washout' period. He concluded that more children improved neurologically while on dantrolene than on placebo. Ford *et al.* (1976) studied 15 children on dantrolene for eight weeks, and made detailed objective measurements of gait and balance, and of fine motor functions of the hands. Improvement was generally insufficient to warrant continuation of the drug.

The present study also attempted to document changes in functional variables. A testing procedure based on the time taken to perform a standard task seemed to be the most objective way to measure functional performance. This method is

also simple to apply and does not require further analysis of the performance. Others have also reached this conclusion (Stern *et al.* 1969; Jebson *et al.* 1969, 1970; Potvin *et al.* 1972; Taylor *et al.* 1973).

Improvement and deterioration were seen in a rather scattered and unrelated manner, and thus did not indicate conclusively that dantrolene produces significant functional improvement or decrement.

However, our studies did show that dantrolene was physiologically active in children, as it is in adults. The response to tibial nerve stimulation showed that the force of the muscle response was reduced significantly compared with placebo, and also that voluntary muscle strength was decreased, as occurs in adults (Joynt 1976).

TABLE XI
Buttoning small-sized buttons (time in seconds)*

Patient no.	Placebo				Patient no.	Drug			
	Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4		Visit 1	Visit 1/ visit 2	Visit 1/ visit 3	Visit 1/ visit 4
2	60	0	10.55	0	1	60	0	—	0
3	60	0	0	0	6	3.6	0	-2.4	-2.1
4	15.1	10.0	10.1	10.1	7	60	7.85	26.2	0
5	60	26.0	0	0	8	60	22.45	48.2	23.75
11	20.4	-13.35	9.65	-13.4	9	60	0	0	0
12	60	0	47.6	0	10	60	0	0	0
14	9.9	-10.8	3.05	2.9	13	9.95	0.75	-0.7	4.65
17	60	0	0	47.15	15	60	0	26.65	17.0
20	60	0	0	0	16	2.55	0.65	-0.35	-0.05
Mean		1.32	8.99	5.19	19	3.85	-7.4	-0.6	0.65
SD		11.5	15.2	16.8	21	5.5	52.6	38.4	5.12

STATISTICAL ANALYSIS

	Visit 1/visit 2					Visit 1/visit 3			
	<0	Median	>0	Total		<0	Median	>0	Total
Placebo	2	0	5	9	Placebo	0	4	5	9
Drug	1	5	5	11	Drug	4	2	4	10
Total	3	10	7	20	Total	4	6	9	19
(N.S.)					p = 0.054				
	Visit 1/visit 4								
	<0	Median	>0	Total					
Placebo	1	0	5	9					
Drug	2	4	5	11					
Total	3	9	8	20					
(N.S.)									

*Positive numbers = improved; negative numbers = worsened.

In addition, no significant toxicity was found on clinical examination or by laboratory testing. When the drug was continued, side-effects were no greater after six weeks than with placebo.

It would seem, therefore, that although dantrolene sodium is physiologically active, its usefulness in improving function in patients with spastic cerebral palsy is uncertain. It is possible that there may be some functional benefit in individual cases.

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SUMMARY

A double-blind study was carried out on 20 children with spasticity secondary to cerebral palsy, in order to compare the effects of dantrolene sodium suspension and a placebo. The drug was found to be physiologically active in reducing the force of muscle contraction, but objective functional improvement, as measured by multiple performance tests, was irregular and probably not significant.

RÉSUMÉ

Suspension de dantrolène sodium dans le traitement de l'infirmité motrice cérébrale

Une étude en double aveugle a été entreprise chez 20 enfants IMC spastiques, pour comparer une suspension de dantrolène et un placebo. Le médicament s'est révélé physiologiquement actif en réduisant la force de la contraction musculaire, mais l'amélioration fonctionnelle objective, mesurée par de multiples épreuves de performance, a été irrégulière et probablement non significative.

ZUSAMMENFASSUNG

Dantrolen Sodium Suspension zur Behandlung der spastischen Cerebralparese

Bei 20 Kindern mit einer Spastik aufgrund einer Cerebralparese wurde eine Doppelblindstudie durchgeführt, um die Wirkung von Dantrolen Suspension mit der eines Placebo zu vergleichen. Es stellte sich heraus, daß das Medikament physiologisch wirksam war, indem es die Muskelverspannung reduzierte, eine objektive funktionelle Besserung dagegen war irregulär und wahrscheinlich nicht signifikant, was anhand von verschiedenen Tests festgestellt wurde.

RESUMEN

Suspensión de dantrolene sódico en el tratamiento de la parálisis espástica cerebral

Se realizó un estudio doble-ciego en 20 niños con espasticidad secundaria a parálisis cerebral, con el objeto de comparar los efectos de una suspensión de dantrolene y un placebo. Se halló que el fármaco era fisiológicamente activo para reducir la fuerza de la contracción muscular, pero la mejoría funcional objetiva medida por medio de diversos tests, de realización, era irregular y probablemente no significativa.

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