A COMPARISON OF DANTROLENE SODIUM AND DIAZEPAM IN THE TREATMENT OF SPASTICITY

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INTRODUCTION

THE pharmacologic management of spasticity since the introduction of muscle relaxants has for the most part continued to be disappointing. As a result, clinicians have had to resort to various non-pharmacologic measures such as chemical nerve and motor point blocks (alcohol and phenol) and/or surgical procedures (tendon lengthenings and releases, and rhizotomies) in an effort to modify or abolish spasticity. In the United States today, the pharmacologic agent most widely used in the therapy of spasticity is diazepam.¹ In our experience, this drug does not effectively modify or abolish severe spasticity, whether due to spinal cord or to cerebral dysfunction, without usually inducing profound sedation. In the study reported here, the effects of diazepam were compared with those of the relatively new peripherally acting muscle relaxant, dantrolene sodium,² on the basis of certain clinical and electrophysiological parameters.

TABLE I—Diagnoses of 62 patients treated with dantrolene sodium

	Patients	
	Bo.	%
Cerebral vascular accident	24	38·7
Spinal cord injury or disease	18	29·0
Multiple sclerosis	12	19·5
Cerebral palsy	4	6·4
Miscellaneous	4	6·4

SUBJECTS AND METHODS

Sixty-two patients, 41 men and 21 women aged 16-72 years (mean age 46·2 years), with spasticity of various causes (see Table I), were treated with dantrolene sodium. Of this total, 16 participated in an eight-week double-blind crossover study divided into four two-week treatment periods, in each of which fixed doses of dantrolene sodium (100 mg. q.i.d.), diazepam (5 mg. q.i.d.), or a placebo were administered separately or concomitantly. Of the 16 patients, five were unable to complete the study because of intolerance to the drugs in the fixed dose regimen used (three to diazepam, one to dantrolene sodium, and one to the combination of these two). Eleven patients completed the study.

¹ Diazepam (Valium; Roche Laboratories, Nutley, New Jersey): 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

² Dantrolene sodium (Dantrium; Eaton Laboratories, Norwich, New York): 1-([5-(p-nitrophenyl) furfurylidene] amino) hydantoin sodium hydrate.

FIG. 1

Mean values obtained by electrophysiologic studies: mechanical tendon tap and electrical twitch tension (tibial nerve), during four types of treatment, each given over a two-week period.

FIG. 2

Mean values obtained by clinical studies: resistance to passive stretch, tendon jerk, ankle clonus, and general muscle strength, during four types of treatment, each given over a two-week period.

Electrophysiologic and clinical evaluations were repeated weekly on each patient throughout the study. *Electrophysiologic measurements:* calf muscle tensions in response to mechanical achilles tendon tap and electrical stimulation of the tibial nerve were determined with the rotational joint apparatus by the technique of Herman *et al.* (1972), and recorded in foot/pounds. *Clinical evaluations:* resistance to passive stretch was graded along a scale of 1 to 6 as follows: 1, flaccid; 2, decreased tone; 3, normal tone; 4, mild resistance; 5, moderate resistance; 6, marked resistance. Tendon jerk was graded according to the following scale: 1, absent; 2, hypoactive; 3, normal; 4, mildly hyperactive; 5, moderately hyperactive; 6, markedly hyperactive. Ankle clonus was graded 1, absent; 2, mild,

TABLE II—Means and standard errors (S.E.) of electrophysiologic and clinical findings in 11 patients

	Dantrolene sodium	Diazepam	Dantrolene and diazepam	Placebo
<i>Electrophysiologic findings</i>				
Tendon tap tension (foot/pounds)	1.85 ± 0.42	2.75 ± 0.74	2.37 ± 0.61	2.93 ± 0.70
Twitch tension (foot/pounds)	2.07 ± 0.50	3.01 ± 0.78	2.21 ± 0.48	2.91 ± 0.61
<i>Clinical findings</i> ¹				
Resistance to passive stretch	4.36 ± 0.35	4.14 ± 0.40	3.44 ± 0.37	4.91 ± 0.31
Tendon jerk	3.70 ± 0.50	3.00 ± 0.50	2.70 ± 0.58	5.45 ± 0.21
Ankle clonus	2.91 ± 0.49	3.64 ± 0.45	1.95 ± 0.36	3.64 ± 0.43
General muscle strength	3.73 ± 0.27	3.68 ± 0.23	3.77 ± 0.30	3.59 ± 0.31

¹ See text for explanation of grading.

unsustained; 3, marked, unsustained; 4, mild, sustained; 5, moderate, sustained; 6, marked, sustained. General muscle strength (by manual muscle testing) was graded 1, normal; 2, good; 3, fair; 4, poor; 5, trace; 6, paralysed.

RESULTS

The electrophysiologic and clinical findings in the 11 patients that completed the study are summarised in Figures 1 and 2; the means and standard errors for each of the treatment periods are listed in Table II.

Electrophysiologic Findings. Tension reduction was greatest with dantrolene sodium, next with the combination of dantrolene sodium and diazepam, and least with diazepam alone.

Clinical Findings. Resistance to passive stretch, tendon jerk and ankle clonus were reduced more with the combination of dantrolene sodium and diazepam than with either alone, and least with placebo alone (see Table II and fig. 2). Muscle strength (by manual muscle testing) did not appear to be significantly altered during any of the treatment periods (see Table II and fig. 2), although a subjective report of loss of muscle strength was the most common side effect encountered.

DISCUSSION

The apparently peripheral action of dantrolene sodium on muscle makes it unique among skeletal-muscle relaxants (Clinical Investigators Manual, 1970). Ellis and Carpenter (1972) showed in rat diaphragm and phrenic nerve preparations that dantrolene sodium had no effect on neuromuscular transmission, while it increased the threshold concentration of caffeine for contracture in the frog rectus and sartorius muscles. They offered the hypothesis that dantrolene sodium's peripheral action results from antagonism of calcium release within muscle. More recently, Putney and Bianchi (1973) demonstrated experimentally that dantrolene sodium did not significantly affect the resting influx of calcium, but did significantly decrease the calcium influx in response to electrical stimulation or to potassium depolarisation. They concluded that the uncoupling action of dantrolene sodium may be due in part to inhibition of the trigger calcium influx associated with membrane depolarisation.

Herman *et al.* (1972) compared dantrolene sodium and diazepam with respect to their effects on torque and electromyographic (EMG) responses to stretch of ankle-extensor muscles in a paraplegic patient. Their observations with respect to torque were in accord with ours: reduction in torque was greater with dantrolene sodium, and Herman *et al.* found that this was associated with little change in integrated EMG activity. The torque reduction seen with diazepam was attributed to the marked reduction in EMG activity in both agonist and antagonist muscles. They observed a general reduction in EMG activity with diazepam, which they ascribed to the suppression of polysynaptic pathways in spinal cord segments that might be expected of such a centrally-acting muscle relaxant. It therefore seems plausible that a portion of the tension reduction that is achieved with dantrolene sodium alone might well be cancelled out by the addition of diazepam. This may explain in part the nine instances in our study in which the reduction achieved with the combination of the two drugs was less than that obtained with dantrolene sodium alone.

The fixed-dose charter of the drug regimen may have been responsible for the fact that about one-third of the original 16 patients were prevented by drug-intolerance reactions from completing the study. Dantrolene sodium was responsible for such reactions in one or possibly two of the five instances. Recent investigations have shown that tolerance and acceptance of this drug are improved by starting with smaller doses than those we used, and increasing by 25-mg. increments. Figure 3 shows tension reduction in a patient so managed, who displayed no intolerance reaction. No untoward effect of either drug was evident in complete blood count, platelet count, SMA-12 battery, or urinalysis from any patient in the comparison study.

Although standard statistical comparison of the results of treatments in this comparative study did not yield significance at the generally acceptable probability levels of 0.05 or 0.01, trends, particularly with reference to the electrophysiologic data, were observable in the relatively small sample, suggesting a difference in effectiveness between dantrolene and diazepam. These trends, together with our clinical experience with the two drugs used, indicate to us that dantrolene sodium is more efficacious than diazepam in the pharmacologic management of a substantial number of patients with spasticity, while in others a combination of the two appears to be more effective than either drug alone. We plan to continue our clinical study

by nonparametric comparison, carrying out a 2×2 factorial design analysis of the findings in additional patients.

FIG. 3

Mechanical tendon tap and electrical twitch tension responses to dantrolene sodium starting at 25 mg. and increased in 25-mg. increments, then temporarily discontinued after reaching the 175-mg. dose level: all doses q.i.d., to totals shown.

SUMMARY

This is a report on the effect of Dantrolene Sodium which the authors have examined on 62 patients in comparison with Diazepam. They found that Dantrolene Sodium is more efficient than Diazepam in the treatment of patients with spasticity. In some cases the combination of the two drugs was found to be more effective than either drug alone. However, in 16 patients the study could not be completed because of drug-intolerance reactions.

RÉSUMÉ

Rapport sur l'effet du Dantrolene Sodium que les auteurs ont examiné sur 62 malades en le comparant au Diazepam. Ils ont trouvé que le Dantrolene Sodium est plus efficace que le Diazepam pour le traitement de malades souffrant de spasticité. Dans certains cas, la combinaison des deux médicaments s'est avérée plus efficace que l'un des médicaments utilisé seul. Cependant, chez 16 malades, l'étude n'a pu être terminée à cause de réactions d'intolérance au médicament.

ZUSAMMENFASSUNG

Die Wirkung von Dantrolene verglichen mit Diazepam wurde bei 62 Patienten untersucht. Die Autoren fanden Dantrolene mehr effektiv als Diazepam in der Behandlung von Spastizität. In einigen Fällen wurde die Kombination beider Drogen als wirksamer gefunden. Aber in 16 Patienten konnte die Behandlung wegen Intoleranzreaktionen nicht beendet werden.

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