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Effect of Intravenous Injection of Biperiden and Clonazepam in Dystonia

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Summary: The acute effect of intravenous injections of biperiden and clonazepam was investigated in 14 patients with various forms of dystonia (segmental dystonia, 2; generalized dystonia, 6; and Meige's syndrome, 6). Eleven patients had primary dystonia, and 3 patients had a secondary form of dystonia. Doses of 5 mg of biperiden reduced dystonia when evaluated by total scores, global scores, and subjective scores. Two patients had marked side effects in the form of dizziness. Doses of 1 mg of clonazepam significantly reduced total scores and subjective scores, but the reduction in global score was insignificant. No patient had marked side effects following injection with clonazepam. These results correspond with earlier investigations of the long-term effects of anticholinergics and benzodiazepines. It is concluded that in some cases, intravenous injections can be used as a test for evaluating both effects and side effects of antidystonic medication prior to the institution of oral treatment. Long-term intravenous treatment might be considered in individual cases. **Key Words:** Dystonia—Biperiden—Clonazepam.

Dystonia is a syndrome characterized by involuntary, tonic, twisting movements (1). Although little is known about the etiology of primary dystonia, well-recognized pathological changes in the basal ganglia are often found in secondary, symptomatic dystonia (2,3). For this reason, it has been proposed that the idiopathic dystonias are a result of a disturbance in neurotransmitter function, rather than a structural change (4,5). Treatment with anticholinergics and levodopa ameliorates the symptoms in some idiopathic dystonia cases, but the effect is very unpredictable, and it has been difficult to find an effective treatment for many cases of primary dystonia. Therapy is symptomatic, and many drugs have been tried, e.g., anticholinergics, benzodiazepines, carbamazepine, dopamine antagonists, and levodopa (6,7). Treatment frequently results in embarrassing side effects in patients already seriously affected by their disease (6–8).

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In individual cases, it is impossible to predict if a drug will have any effect, and it would thus be valuable to be able to test the acute effect of a drug before instituting long-term treatment. The present trial investigated the acute effects of intravenous injection of biperiden or clonazepam on patients with dystonia.

MATERIALS AND METHODS

Fourteen patients (4 men and 10 women) with either segmental dystonia (2 patients), generalized dystonia (6 patients), or Meige's syndrome (6 patients) participated in the investigation (Table 1). Twelve were outpatients and 2 were inpatients; 11 had primary idiopathic dystonia and 3 had secondary symptomatic dystonia. The dystonia of patient no. 7 was secondary to birth injury and that of patient no. 8 resulted from cardiac arrest caused by an antidepressant used in a suicide attempt. Patient no. 12 was schizophrenic, and the dystonia was secondary to neuroleptic treatment. Mean patient age was 43.2 years (range 24–59 years), and mean duration of dystonia was 10.8 years (range 2–38 years).

TABLE 1. *Patient characteristics*

No.	Age (years)	Gender	Distribution of dystonia	Etiology	Duration (years)	Severity (global score)	Medical treatment at entry to the study
1	51	F	Segmental	Primary	6	4	Trihexyphenidyl, clonazepam, pimozide
2	56	F	Meige	Primary	11	5	Trihexyphenidyl, clonazepam
3	46	F	Meige	Primary	7	4	—
4	56	F	Meige	Primary	2	4	Clonazepam, clozapine
5	59	F	Segmental	Primary	15	3	Trihexyphenidyl, DOPA
6	46	F	Meige	Primary	3	3	—
7	32	F	Generalized	Secondary: birth injury	32	3	Trihexyphenidyl, clonazepam, DOPA
8	24	F	Generalized	Secondary: asystoly	4	5	Sulpiride, diazepam
9	43	F	Meige	Primary	5	3	Trihexyphenidyl, clonazepam
10	30	F	Generalized	Primary	15	5	Trihexyphenidyl, clonazepam
11	41	M	Generalized	Primary	4	4	Clonazepam
12	30	M	Generalized	Secondary: neuroleptics	5	4	Clonazepam, biperiden, carbamazepine
13	48	M	Generalized	Primary	38	3	—
14	43	M	Meige	Primary	4	2	Trihexyphenidyl, clonazepam

During the trial, the patients continued their original antidystonic treatment. Anticholinergic or benzodiazepine treatment was discontinued 3 days before testing. No deterioration was observed during this period.

Subjects were tested single-blind on two different occasions with an interval of at least 1 week. On the first test day, an intravenous saline injection was given followed by 2 injections of 2.5 mg biperiden. The interval between the injections was 35 min. The same procedure was used for the next test, but this time, 2 injections of 0.5 mg clonazepam were used.

Dystonic movements were registered at 30 min after each injection, for a total of three scorings for each patient with biperiden and clonazepam, respectively. Registration consisted of standardized video recordings, evaluated blindly in randomized order by two trained neurologists using a dystonia scale (Table 2). By means of this scale, a graduation from 0 to 6 was made for each of six body regions; speech and swallowing also were scored. Together, a total score was estimated (maximum 48 points). Furthermore, an overall impression of the clinical state resulted in a global score (maximum 6 points) (Fig. 1). At the time of the video recordings, the patients made a subjective evaluation of effect (subjective score) using a 4-point scale (0, no effect; +, mild; + +, moderate; + + +, marked effect). Side effects also were recorded using a 4-point scale (0, no effect; +, mild, + +, moderate; + + +, severe side effects).

The effect of the oral treatment after the trial was not evaluated, but most patients continued the pretrial treatment (one preferred to continue with intravenous treatment).

A paired *t* test was used for analysis of the effect of the test drugs. Correlations were evaluated by the Spearman rank-correlation test.

RESULTS

Effect of Biperiden

By comparing the total scores 30 min after the second injection of biperiden with those 30 min after placebo injection, a score reduction was found for 7 patients of 14, 21, 30, 50, 50, 60, and 100%, respectively, whereas no reduction was found in the other 7 patients (Table 3). By analysis of the difference in scoring values as a whole, a significant reduction in both the total score ($p < 0.05$, paired *t* test) and the global score ($p < 0.05$) was found. A

TABLE 2. *Dystonia scale*

Eyes	0–6
Mouth	0–6
Speech	0–6
Swallowing	0–6
Neck	0–6
Trunk	0–6
Arms	0–6
Legs	0–6
Total	0–48
Global	0–6

Scoring code: 0 = no dystonia; 1 = slight dystonia, clinically insignificant; 2 = mild, obvious dystonia; 3 = moderate, perhaps intermittently dystonia; 4 = moderate, permanent dystonia with impaired function; 5 = severe dystonia with some function; 6 = severe dystonia with abolished function.

TABLE 3. *Effect of antidystonic treatment*

No.	Improvement: percent reduction in total score[a]		Subjective evaluation of improvement[b]	
	Biperiden	Clonazepam	Biperiden	Clonazepam
1	50	100	+ + +	+ + +
2	0	0	0	0
3	0	27	+ +	+ +
4	50	9	+ + +	+ + +
5	0	20	0	0
6	14	0	+	+
7	30	18	+	+ +
8	0	0	0	0
9	60	75	+ + +	+ + +
10	0	0	+ +	+
11	21	11	+	0
12	0	0	+	0
13	0	0	0	+
14	100	43	+ +	+

[a] Percent reduction in total score 30 min following the second injection with test dose in relation to total score 30 min following injection with placebo.
[b] 0, no effect; +, slight; + +, moderate; + + +, marked improvement.

similar trend with reduction in both total score and global score was found 30 min after the first injection of biperiden, but the reduction was not significant.

Subjective evaluation of biperiden was 3+ in 3 patients, 2+ in 3, 1+ in 4, and the remaining 4 patients observed no effect. By comparing the subjective scores with the placebo results, a significant effect of biperiden ($p < 0.001$) was also obtained.

Analysis of correlation revealed a significant correlation between the subjective scores and both the total scores ($R = 0.644$, $p < 0.05$) and the global-scores ($R = 0.732$, $p < 0.01$).

The evaluation of the duration of the effect of injections was over a relatively short period, but generally, the effect lasted for several hours. In patient no. 1, the effect of injections of both biperiden and clonazepam lasted for nearly a week. Although this patient had been severely disabled and using crutches, she now receives weekly intravenous injections of biperiden and has remained almost free of dystonic symptoms.

Effect of Clonazepam

Thirty minutes following the second injection of clonazepam, there was a reduction in total scores in 8 patients of 9, 11, 18, 20, 27, 43, 75, and 100%, respectively, related to values obtained 30 min after placebo injection. In 6 patients, there was no reduction; none deteriorated (Table 3). Analysis of the difference in scoring values revealed a significant reduction in total score ($p < 0.05$), whereas the reduction in global score was insignificant ($p > 0.10$). A slight reduction in both total score and global score was found 30 min after the first injection of clonazepam, but the reduction was not significant.

Subjective scoring of clonazepam was 3+ in 3 patients, 2+ in 2, and 1+ in 4, whereas the remaining 5 patients observed no effect. By comparing subjective scores with placebo values, there was a significant effect of clonazepam ($p < 0.01$).

Analysis of correlation revealed a significant correlation between subjective scores and total scores ($R = 0.640$, $p < 0.05$), but no correlation with global scores ($R = 0.517$, $0.10 > p > 0.05$).

Side Effects

Following intravenous injections of biperiden, 2 patients had severe side effects, 7 had moderate, 2 slight, and 3 patients had none. Two patients experienced severe dizziness, whereas 6 had it in a slight to moderate degree. A slight to moderate sedative effect was observed in 4 patients, dryness of mouth in 9, blurred vision in 6, and 4 patients had disturbances of concentration. Euphoria was experienced by 1 patient (2+), and 1 suffered from nausea (2+).

Following intravenous injections of clonazepam, 1 patient had moderate side effects, 5 patients slight side effects, and 8 patients had none. No patient had severe side effects during clonazepam treatment. Moderate and slight dizziness were each experienced by one patient. A slight degree of seda-

tion was observed in 3 patients, dryness of mouth in two, and blurred vision in 1 patient.

DISCUSSION

The present tests revealed a significant antidystonic effect for biperiden, whereas the global score effect of clonazepam was insignificant. The assumption that the effect of clonazepam is at least partly achieved by a nonspecific sedation is supported by the lack of correlation between the subjective and global scores. This also is in accord with the findings that benzodiazepines are often of supplementary value in anticholinergic treatment of dystonia (8). Occasionally, a convincing effect of clonazepam on blepharospasms has been found (9,10). However, although Jankovic and Ford (11), in a prospective evaluation of Meige's syndrome, found an effect of clonazepam in 31 of 46 patients, it was marked and lasting in only 5. In a retrospective study of 115 patients with torsion dystonia treated with clonazepam, the response was variable, with the generalized dystonias responding poorly and the focal oromandibular dystonias somewhat better (12).

The beneficial effect of intravenous biperiden injection is in agreement with earlier, similar investigations of the effect of anticholinergics. Tanner et al. (13) found an improvement in all 6 patients with Meige's disease after scopolamine injection. Lang et al. (3) reported that injections of benztropine had some effect on 4 of 6 patients with cranial dystonia, but at the expense of sedation. Conversely, no effect of benztropine was obtained in 9 patients with spasmodic torticollis and 5 with writer's cramp, and it was concluded that cholinergic mechanisms are not of general or primary importance in the pathogenesis of adult-onset focal dystonias. High-dosage chronic anticholinergic oral therapy has yielded good results. Using a daily dose of 20 mg trihexyphenidyl, Fahn found a sustained moderate to marked improvement in 20 of 52 dystonic patients (38%), wheres 50% had no response or were taken off medication because of intolerable adverse effects (14). In a corresponding investigation, Burke et al. (15), using 30 mg trihexyphenidyl daily, found that 22 of 31 patients with torsion dystonia (71%) showed a clinically significant response.

The results of the present investigation are thus in accord with the cited long-term investigations of oral anticholinergic and benzodiazepine treatments. The present study made no comparison between these drugs in this test and their efficacy in oral long-term treatment, but the results indicate that intravenous injection in some cases can be used as a test for the evaluation of the effects and side effects of antidystonic drugs prior to oral antidystonic treatment. This assumption is in agreement with an investigation by Tanner et al. (16) of 10 patients with adult-onset focal or segmental dystonia. It was observed that acute parenteral scopolamine was predictive of the response of peak chronic trihexyphenidyl dose in 80% of the patients. Hipola et al. (17) also found that intravenous administration of clonazepam predicted the response of prolonged oral medication in 3 of 4 cases. Giménez-Roldán (18), in a later study by the same Spanish group, states that of 13 patients with cranial dystonia on whom both trihexyphenidyl and clonazepam had satisfactory effect by acute pharmacological test, 7 also experienced satisfactory effects on long-term oral trihexyphenidyl; only 2 patients experienced a corresponding effect on long-term oral clonazepam. It was concluded that clonazepam was less effective as a predictor than the anticholinergics. Thus, these results would indicate that clonazepam only has a prolonged effect on a few dystonic patients and is primarily a valuable supplement to other antidystonic treatment. It may be concluded that intravenous injections of antidystonics in some cases can be used as a screening test prior to long-term antidystonic treatment, but that the test would appear to be most reliable for anticholinergics. Further investigations on the issue would be desirable, using a prospective design with acute tests in untreated dystonic patients before institution of long-term treatment with the same drugs.

The present study found that individual patients experienced a sustained effect from biperiden and clonazepam injections. Repeated biperiden injections produced a much better effect in patient no. 1 than the earlier combination of oral clonazepam, trihexyphenidyl, and pimozide. Thus, the administration of such intravenous biperiden doses might be worthy of consideration as a treatment strategy in cases resistant to traditional antidystonic treatment.

REFERENCES

1. Marsden CD. Dystonia—the spectrum of the disease. In: Yahr MD, ed. *The basal ganglia*. New York: Raven Press, 1976:331–367.
2. Lang AE. Dopamine agonists in the treatment of dystonia. *Clin Neuropharmacol* 1985;8:38–57.
3. Lang AE, Sheehy MP, Marsden CD. Anticholinergics in adult-onset focal dystonia. *Can J Neurol Sci* 1982;9:313–9.

4. Stahl SM, Berger PA. Bromocriptine, physostigmine and neurotransmitter mechanisms in the dystonias. *Neurology* 1982;32:889–92.
5. Hornykiewicz O, Kish SJ, Becker LE, Farley I, Shannak K. Brain neurotransmitters in dystonia musculorum deformans. *N Engl J Med* 1986;315:347–53.
6. Marsden CD. Treatment of torsion dystonia. In: Barbeau A, ed. *Disorders of movement*. Lancaster: MTP Press, 1981: 81–104.
7. Fahn S, Marsden CD. The treatment of dystonia. In: Marsden CD, Fahn S, eds. *Movement disorders 2*. London: Butterworth, 1987:359–82.
8. Pakkenberg H, Pedersen B. Medical treatment of dystonia. In: Casey DE, Chase TN, Christensen AV, Gerlach J, eds. *Dyskinesia—research and treatment (Psychopharmacology suppl. 2)*. 1985:111–7.
9. Merikangas JR, Reynolds CF. Blepharospasm—successful treatment with clonazepam. *Ann Neurol* 1979;5:401–2.
10. Ziegler DK. Prolonged relief of dystonic movements with diazepam. *Neurology* 1981;31:1457–8.
11. Jankovic J, Ford J. Blepharospasm and orofacial-cervical dystonia—clinical and pharmacological findings in 100 patients. *Ann Neurol* 1983;13:402–11.
12. Greene P, Shale H, Fahn S. Experience with high dosages of anticholinergic and other drugs in the treatment of torsion dystonia. In: Fahn S, et al, eds. *Advances in neurology, vol. 50: dystonia 2*. New York: Raven Press, 1988:547–56.
13. Tanner CM, Glantz RH, Klawans HL. Meige disease—acute and chronic cholinergic effects. *Neurology* 1982;32:783–5.
14. Fahn S. High dosage anticholinergic therapy in dystonia. *Neurology* 1983;33:1255–61.
15. Burke RE, Fahn S, Marsden CD. Torsion dystonia—a double-blind, prospective trial of high-dosage trihexyphenidyl. *Neurology* 1986;36:160–4.
16. Tanner CM, Wilson RS, Goetz CG, Shannon KM. The predictive value of acute antimuscarinic drugs for the chronic efficacy of antimuscarinic drugs in adults with focal dystonia. In: Fahn S, et al, eds. *Advances in Neurology, vol. 50: dystonia 2*. New York: Raven Press, 1988:557–60.
17. Hipola D, Mateo D, Giménez-Roldán S. Meige's syndrome—acute and chronic responses to clonazepm and anticholinergics. *Eur Neurol* 1984;23:474–8.
18. Giménez-Roldán S, Mateo D, Orbe M, Muñoz-Blanco JL, Hipola D. Acute pharmacologic tests in cranial dystonia. In: Jankovic J, Tolosa E, eds. *Advances in neurology, vol. 49: facial dyskinesias*. New York: Raven Press, 1988:451–66.