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BENEFICIAL EFFECTS OF DIPHENHYDRAMINE IN DYSTONIA

NORA GRAÑANA*, MONICA FERREA*, MARIA CLARA SCORTICATI, SERGIO DIAZ, MARISA ARREBOLA, LUIS TORRES***, FEDERICO MICHELI***

Departmento de Neurología, Hospital de Clínicas José de San Martín, Facultad de Medicina, Universidad de Buenos Aires

Abstract The objective of this paper was to evaluate the efficacy of diphenhydramine hidrochloride (DPH) in dystonic patients. In 1995, Truong et al reported encouraging results in five patients with idiopathic torsion dystonia (ITD) treated with DPH, an H1 antagonist with sedative and anticholinergic properties. Five patients with generalized ITD, one with secondary generalized dystonia and one with idiopathic segmental dystonia were included in the prospective study. Initially the response to intravenous administration of DPH versus placebo in two sessions a week apart was evaluated. Two weeks later all patients started oral DPH in increasing doses (range 100-300 mg, mean 164 mg). The degree of dystonia was determined by a modified University of Columbia Scale evaluating the baseline score, after placebo and DPH I.V. administration then at one and six months after starting oral treatment. The results were analyzed by Friedman's test for repeated measurements. On comparing scores for baseline severity, I.V. placebo and I.V. DPH presented a highly significant correlation (12.09; $p = 0.00$) as well as comparing baseline score with oral DPH at one and 6 months, treatment (12.78; $p = 0.00$). Functional score results were 9.5 $p = 0.01$ and 8.4 $p = 0.02$ at one and 6 months respectively. The most common side effects were somnolence and dizziness. It can be concluded that DPH proved effective in our patients with mild to moderate adverse effects not requiring drug withdrawal in any case. However, I.V. challenge was unable to predict the long-term response to oral medication perhaps due to the limited number of cases.

Resumen: ***Efectos beneficiosos del clorhidrato de difenhidramina en pacientes con distonia.*** Se evaluó la eficacia del clorhidrato de difenhidramina (DFH) en pacientes con distonía. En 1995, Truong y col. reportaron resultados alentadores en 5 pacientes con distonía de torsión idiopática (DTI) tratados con clorhidrato de difenhidramina, antagonista H1 con propiedades sedantes y anticolinérgicas. Cinco pacientes con DTI generalizada, uno con distonía generalizada secundaria y uno con distonía segmentaria craneocervicobraquial participaron del estudio prospectivo. En primer término se evaluó la respuesta a la administración endovenosa (I.V.) de 100 mg de DFH y a placebo en dos sesiones separadas por 7 días. Dos semanas más tarde todos los pacientes iniciaron tratamiento con DFH vía oral (V.O.) en dosis crecientes (rango = 100-300 mg $\bar{X}$ = 164 mg). El grado de distonía fue determinado a través de la escala de distonías de la Universidad de Columbia modificada, evaluándose el score basal, luego de la administración endovenosa del placebo y de DFH, al mes y a los 6 meses de iniciado el tratamiento por vía oral. Los resultados fueron analizados mediante el test de Friedman para mediciones repetidas. Al comparar los scores de severidad del basal, el placebo (I.V.) y la DFH (I.V.) se halló una correlación altamente significativa (12.09; $p = 0.00$) y similares resultados fueron obtenidos al comparar el basal con la DFH (V.O.) al mes y 6 meses de tratamiento (12.78; $p = 0.00$). Los resultados del score de función fueron 9.5; $p = 0.01$ y 8.4; $p = 0.02$ al mes y 6 meses respectivamente. Los efectos colaterales más frecuentes fueron somnolencia y mareos. En conclusión, la DFH resultó efectiva en nuestros pacientes, los efectos adversos han sido leves o moderados no habiendo sido necesario suspender la droga en ningún caso. No hemos podido demostrar por ser pocos casos el valor predictivo de la administración I.V. en relación a la respuesta oral en el largo plazo.

Key words: diphenhydramine, dystonia

Over the last few years, a deeper insight has been gained into the pathogenesis and clinical spectrum of idiopathic dystonic disorders as well as their genetic background. Quite a number of distinct forms of dystonia have been discerned ranging from mild focal dystonia restricted to minor body segments causing at most cosmetic embarrassment to severe generalized dystonia leading to marked disablement or even lethal hazard[1]. Although dystonia is widely acknowledged as untreatable, a few well delineated forms including levodopa responsive dystonia, Wilson's disease, paroxysmal dystonia and acute neuroleptic-induced dystonia are amenable to drug therapy[2, 3].

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* Present address: Hospital de Pediatría Juan P. Garrahan. Buenos Aires
** Hospital Español, Buenos Aires.
*** Instituto de Ciencias Neurológicas Trelles Montes, Lima, Perú

Postal address: Dr. Federico Micheli, Olleros 2240, 1426 Buenos Aires, Argentina
Fax: 54-1-4811-3076; E-mail: fmicheli@sminter.com.ar

Recently, the advent of botulinum toxin has revolutionized the management of patients with focal or even segmental dystonia dramatically improving their quality of life. Regrettably, cases with the generalized form or even those with involvement of large body segments would require such high botulinum toxin doses as to rule out this treatment modality[4, 5]. So far, such patients may on occasion gain relief from several drugs. Although over half may respond to high doses of anticholinergic drugs or oral/intrathecal baclofen to a certain extent, the remaining cases must be treated with drugs chosen on a basis of trial and error, a time consuming and often unrewarding task. Combined therapy is thus frequently prescribed though with limited success. Quite recently, Truong et al[6] reported encourag-ing results in five patients with idiopathic dystonia following treatment with diphenhydramine. We here report our findings in 7 cases treated with IV and oral diphenhy-dramine formally assessed by means of a standardized evaluation scale.

Patients and Methods

Seven patients with dystonia were evaluated prospectively in a double blind placebo-controlled randomized study. Five patients were male and 2 female whose ages ranged from 12 to 74 years, mean age 25.6 years ($\bar{X}$= 25.6 + 21.824 years) (CI 95% = 5.39 - 45.75 years). Six patients presented generalized dystonia while the remainder had craniocervical segmental dystonia. Dystonia was secondary to perinatal hypoxia in one patient while it was idiopathic in the remaining 6. Mean disease duration was 12 years, ranging from 7 to 20 (Table 1). All patients initially received either placebo or 100 mg diphenhydramine hydrochloride (Benadryl-Parke Davis) in 10 mg/ml vials randomly instilled intravenously over a one-hour period in 2 separate sessions one week apart so that each patient was his or her own control and evaluated three hours after the infusion was completed. Prior antidystonic medication, if any, was not discontinued.

Two weeks later all patients started oral therapy with increasing dosis of diphenhydramine regardless of the response to the acute challenge.

Dystonic status was graded at baseline, after placebo or diphenhydramine instillation or viceversa and monthly while building up the oral dose by means of the University of Columbia Dystonia Scale[7] modified by García Alvarez with a maximum score of 65 points bearing in mind both anatomic distribution and functional involvement[8]. Side-effects and concomitant medication were carefully recorded.

Results were analyzed statistically by means of Friedman's test for repeated measures, data taking $\alpha = 0.05$ (Statistical Package Program: KWSTAT).

Patients features are summarized in Table 1 and index cases (2 and 7) are fully described.

Case reports

Case 2

This 74-year old woman had a personal history of lung tuberculosis at age 39, arterial hypertension and angina pectoris at age 52. At age 57 she was briefly treated with cinnarizine for dizziness. At age 63 she received cervical traction therapy for neck pain and 2 days later developed involuntary spasmodic backward neck movements consistent with retrocollis as well as right laterocollis two months later.

Neurological examination was normal, except for retrocollis and right laterocollis with ipsilateral scapular elevation together with spasmodic contractions of the orbicularis oculi and facial grimacing consistent with Meige's syndrome.

The patient successively received trihexyphenydil for 3 months but as she developed confusion and memory failure, she was firstly switched to oral and later to pump-delivered subcutaneous lisuride reaching a final dose of 15 mg/hour with evident improvement lasting over a year.

Two years later she was successfully treated with botulinum toxin (Botox, Allergan) 175 IU in neck muscles and 25 IU in the orbicularis oculi and frontal muscles. Unfortunately after 6 sessions over two years she failed to improve in two successive trials presumably due to botulinum toxin antibody generation.

At age 67 a carpal tunnel syndrome was diagnosed and surgically treated, when a cervical spine MRI disclosed an acquired channel narrowing without clinical expression.

TABLE 1.– *Clinical features in 7 patients with dystonia*

Case	Sex/Age (years)	Age at onset (years)	Background	Dystonia	
				Type	Etiology
1	Fem. 16	6.5	All at 7 years	Generalized	Idiopathic
2	Fem. 74	63	Tuberculosis at 39 years AHT - Angina pectoris	Cervical + cranial Meige syndrome	Idiopathic
3	Male 25	5		Generalized	Idiopathic
4	Male 21	5		Generalized	Idiopathic
5	male 12	< 1	Spastic cerebral palsy: Double hemiparesis Mild mental retardation Generalized seizure	Generalized Jaundice	Perinatal hypoxia
6	Male 18	10	Brain trauma at 6 ears	Generalized	Idiopathic
7	Male 13	6		Generalized	Idiopathic

Case 7

This 13 year-old boy had no relevant personal or family history. At age 6 he developed dystonic posturing mostly in the limbs for which he received baclofen for a year with a current dose of 80 mg/day without benefit, since symptoms worsened to include loss of upper limb manual function with writing and speech disturbances.

Brain imaging studies including CT and MRI were normal as well as a thorough laboratory work-up including copper metabolism assessment ruling out Wilson's disease.

On examination severe generalized dystonia was evident but no cognitive, pyramidal or cerebellar disorders could be detected.

Results

Table 3 lists evaluation scores for baseline, intravenous placebo, intravenous DPH as well as oral DPH at one and six months.

Severity (S) and functional (F) components were analyzed separately by Frideman's chi square. Evaluations were carried out at baseline (S_B, F_B), after intravenous placebo (S_P, F_P), after intravenous DPH (S_{IV}, F_{IV}), after one month on oral DPH (S_{DPH}, F_{DPH}) and after six months on oral DPH (S_{DPH6}, F_{DPH6}).

On comparing baseline severity scores versus intravenous placebo and DPH a statistically significant difference found (S_B-S_p-S_{IV} = 12.09, $p < 0.001$, $\alpha = 0.05$). Similar results were obtained for oral DPH at 1 and 6 months follow-up (S_B-S_{DPH}-S_{DPH6} = 12.78, $p < 0.001$, $\alpha = 0.05$) (Fig. 1).

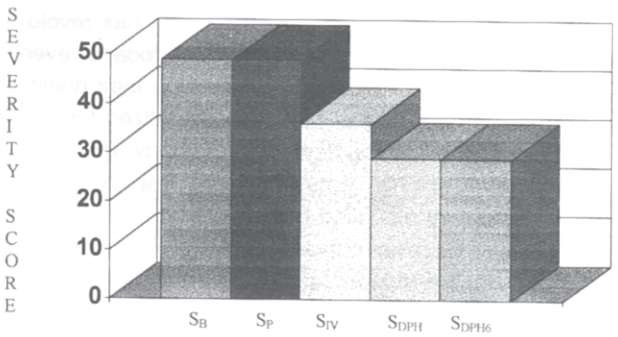

Fig. 1

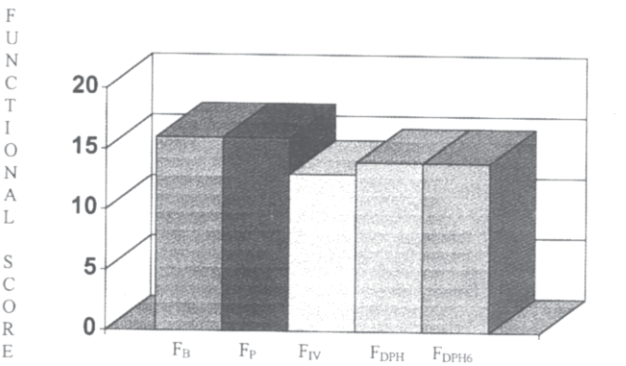

FIG. 2 – Functional scores at baseline (F_B), placebo (F_P), intravenous DPH (F_{IV}), oral DPH at one month (F_{DPH}) and oral DPH at six months (F_{DPH6})

Fig. 2

TABLE 2.– *Description of treatments received and presence of side effects*

Case	Therapy		Current	Side effects	
	Benefit (transient)	No benefit	therapy	Placebo	DPH
1	Trihexyphenydil Diazepam	-	L-dopa 600 mg/d + benserazide 150 mg/d	-	-
2	Lisuride Botulinum toxin	Trihexyphenydil	-	Skin rash Somnolence Dizziness	Somnolence Dizzines
3	Trihexyphenydil	Baclofen	Baclofen 40 mg/d	Sweating Pallor	Dizziness Drowsiness
4	Trihexyphenydil Baclofen	Diazepam	Baclofen 70 mg/d PO Diazepam 40 mg/d	Skin rash Pallor Seating	Dizziness Drowsiness Nausea Dry mouth
5	-	L-dopa Trihexyphenydil	-	-	-
6	Trihexyphenydil Diazepam	Nifedipine	Diazepam 30 mg/d	Left foot pain	Drowsiness Dry mouth Irritability
7	-	-	Baclofen 80 mg/d	Drowsiness	Drowsiness

TABLE 3.– *Severity and functional dystonia scores. (Columbia Dystonia Scale modified by García Alvarez, 1994)*

Case	Baseline		Placebo		DPH I.V.		DPH Oral (1mo)		DPH Oral (6mo)	
	S_B	F_B	S_P	F_P	S_{IV}	F_{IV}	S_{DPH}	F_{DPH}	S_{DPH6}	F_{DPH6}
1	79	13	79	13	65	12	51	12	51	12
2	14	0	13	0	1	0	1	0	1	0
3	56	19	56	18	45	13	34	13	34	13
4	42	20	41	20	41	19	37	19	37	19
5	57	25	57	25	34	25	29	23	32	25
6	55	18	55	18	43	13	40	12	40	12
7	41	16	41	16	21	11	9	16	8	16
Mean (st.d)	49 (20)	15.8 (7.9)	49 (20)	15.7 (7.8)	35 (20)	13 (7.6)	28.7 (17.7)	13.5 (7.2)	29 (17.9)	13.8 (7.7)

Significant although lower differences were disclosed for functional scores: correlations for baseline versus intravenous placebo and DPH (F_B - F_P-F_{IV} = 9.50, p = 0.01, α = 0.05) and for oral DPH at one and 6 months (F_B-F_{DPH}-F_{DPH6} = 8.40, p = 0.02, α = 0.05) (Fig. 2). Mean total daily oral DPH dose was 164 mg/d, ranging from 100 to 300 mg/d.

Side effects listed in Table 2 following intravenous acute challenge and oral administration were mild to moderate so that drug discontinuance was not required in any case.

Discussion

Although not mentioned in recent reviews as a therapeutic option for dystonia, DPH has been widely employed in neuroleptic[3, 9] as well as in diazepam-induced acute dystonic reactions[10] and despite the fact that antihistamine drugs are not currently recognized as a valid alternative in the treatment of movement disorders, they were one of the first agents used to relieve parkinsonian symptoms[11]. Quite recently Truong et al[6] reported DPH usefulness in 5 patients with idiopathic dystonia receiving an acute I.V. challenge of 50 mg followed by up to 500 mg/day orally, three of whom with jerky clonic dystonia, markedly benefited from treatment, while the remaining two featuring tonic dystonia had less obvious relief. The authors concluded that acute IV challenge is a valuable predictor of oral response, concluding that DPH should be considered a useful therapeutic tool in patients with idiopathic dystonia particularly those presenting lightning jerks.

We have repeated the approach described ty Truong et al[6] in 7 patients with dystonia treated both with intravenous and oral DPH and assessed by a formal evaluation. A double blind IV challenge with 100 mg of DPH elicited a positive though variable response in both arms of the severity and functional scale. Side effects were common, particularly somnolence which was well tolerated without drug discontinuance[12]. Effects were assessed up to 3 hours after the infusion was completed, patients reporting benefits up to 24-48 hours, a period widely outlasting sedation, which usually abated within a few hours[13, 14].

In the case of oral administration, side effects were markedly milder and mainly restricted to slight somnolence especially evident whenever the dose was raised, developing tolerance thereafter. In no case did the dose require to be lowered.

All seven cases benefited from DPH and elected to continue treatment after completing the protocol. DPH intravenous acute administration was not a good predictor of oral treatment outcome. Improvement in severity scores exceeded those recorded for functional benefit but even so failed to reflect the findings at clinical assessment, which proved still more satisfactory. In interpreting the results it should be recalled that our cases were selected from poor responders to routine treatment.

DPH is an ethanolamine derivative with antihistaminic, anticholinergic, sedative and local anesthetic properties, besides interacting with opioides, but its global effect in dystonia seems to exceed the joint action of such features[15]. In support DPH has been claimed to be effec-tive in cases refractory to combined treatment with these agents[16].

The mechanism of action by which DPH exerts its beneficial effects in dystonia remains unknown and only speculations can be made. While the pharmacological basis of idiopathic dystonia seems to involve alterations in dopaminergic striatal pathways regulated in turn by cholinergic and GABAergic mechanisms[10], other neurotransmitters including opioides have been implicated[15]. Recently, Van't Groenewout et al[16] have shown that acute dystonic reactions induced by unilateral micro injections of haloperidol into the rat red nucleus are attenuated by DPH. Likewise administered, histamine induces torticollis in a dose dependent manner, which is

antagonized by histamine H1 and H2 antagonists[16], demonstrating that histamine dysfunction may play a role in the pathophysiology of dystonia. In addition DPH is a potent inhibitor of dopamine uptake into striatal synaptosomes as well as benzotropine, trihexyphenidyl and orphenadrine, all three drugs exerting antidystonic activity.

Antihistamine drugs are common over the counter medications seldom leading to serious side effects even when high doses are required. Toxicity is dominated by anticholinergic signs including autonomic and central nervous system side effects and cardiac toxicity[13].

A single case of rhabdomyolysis complicating antihistamine overdose has been reported; however the communication of a patient with rhabdomyolysis due to hereditary torsion dystonia is likewise exceptional[14].

It should be born in mind that as tetrabenazine, benzodiazepines and neuroleptics used in the treatment of dystonia, DPH is also liable to induce acute dystonic reactions[17, 19]. In addition Joseph and King[20] recently reported the case of a previously healthy 3-year-old boy who presented an acute dystonic reaction induced by therapeutic doses of an histaminic cold preparation, who was successfully treated with benzotropine.

To conclude, our results suggest that DPH is a useful drug in the management of generalized and segmental dystonia in which botulinum toxin is not a possible alternative. Larger studies are needed to validate our results and to compare the efficacy of DPH with that of anticholinergics and baclofen.

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