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Supported by a United Parkinson Foundation fellowship (Dr. Kurlan), USPHS grant RR00044 (University of Rochester Clinical Research Center), and Eli Lilly Company.

Accepted for publication November 19, 1985.

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Repetitive intravenous dihydroergotamine as therapy for intractable migraine

Article abstract—For patients with chronic intractable headache, we compared a new treatment and a traditional one. Fifty-five patients (36 dependent on ergotamine, analgesics, diazepam, or corticosteroids) were given IV dihydroergotamine (DHE) and metoclopramide every 8 hours. Fifty-four age- and sex-matched patients (38 drug-dependent) were given diazepam intravenously every 8 hours. Forty-nine of the 55 DHE-treated patients became headache-free within 48 hours, and 39 of them sustained benefits in a mean follow-up of 16 months. In contrast, 7 diazepam-treated patients became free of headache within 3 to 6 days, and 31 had improved somewhat in 10 days. Repetitive IV DHE helps to terminate cycles of intractable migraine.

NEUROLOGY 1986;36:995-997

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That episodic migraine may become incessant and refractory to treatment is a phenomenon recognized first in 1982.[1] Treatment for continual headache is often difficult to evaluate because of drug dependence, which may even aggravate the underlying headache disorder because of "rebound" effects (severe headaches that result from falling drug levels). We have found that dihydroergotamine (DHE), a hydrogenated ergot alkaloid, used to terminate individual migraine attacks for 40 years,[2] can also be used to treat continuous migraine.

Patients and methods. *Patients.* We treated 109 patients, 55 with DHE and 54 with IV diazepam. All had continuous headache for at least 2 months and had met criteria for the diagnosis of common migraine[3] before headache became chronic and continuous. The severity and frequency of migrainous attacks at onset did not differ in the two groups. No efforts were made to match the two groups; they were enrolled into either treatment plan consecutively. Among the DHE-treated patients, there were 47 women and 8 men of mean age 42 years (range, 20 to 72 years). Thirty-five had had continuous headache for more than 2 years and 18 for more than 5 years. Thirty-six of them were judged to be drug-dependent, because a severe exacerbation of headache invariably ensued if a single dose of standard medication was delayed for even a few hours. Twenty-six were dependent upon analgesics (usually codeine, aspirin-caffeine-butalbital preparations, or oxycodone); 7 on ergotamine; 2 on diazepam; and 1 on prednisone. These patients all entered treatment between 1980 and 1983.

Among the diazepam-treated patients, there were 45 women and 9 men of mean age 39 years (range, 21 to 65). Thirty-eight had chronic headache for more than 2 years and 16 for more than 5 years. Thirty-eight were drug-dependent: 30 on analgesics; 7 on ergotamine; and 1 on diazepam. These patients entered treatment between 1975 and 1980. There was no overlap between the DHE- and diazepam-treated patients; ie, no diazepam-treated patient was also given DHE.

Administration of medications. A washout period for drug-dependent patients was not used. Both DHE and diazepam doses were given in 1 to 2 minutes through in-

Table 1. Results of treatment

	55 DHE-treated patients	54 diazepam-treated patients
Headache-free	49 within 48 hours	7 within 3-6 days
>50% improved	0	31 within 10 days
No substantial benefit	6	16

Table 2. Long-term results

	55 DHE-treated patients*	54 diazepam-treated patients
Headache-free	17	5
Occasional headaches (<monthly)	19	10
Headache 1-2 × monthly	9	10
Headache > weekly	4	15
Constant headache	6	14

* Kendall's tau = 0.35 ($p < 0.001$).

dwelling heparin-lock needles. Ten milligrams of diazepam was given every 8 hours. The subnauseating dose of DHE was determined as follows:

A test dose of 0.5 mg DHE was given with 10 mg metoclopramide. If nausea was reported or if head pain ceased within 1 hour, no additional DHE was given for 8 hours. Then, another 0.5 mg dose was administered and repeated every 8 hours thereafter for 2 days. If nausea was reported after the second dose, the dosage of DHE was reduced to 0.3 mg every 8 hours. If, after the first test dose, nausea was not reported and head pain had not abated after 1 hour, an additional 0.5 mg DHE was given, and 1.0 mg DHE with 10 mg metoclopramide was then continued every 8 hours for 2 days. ECG was recorded during the first two doses of DHE for patients older than age 60. Metoclopramide was stopped after 24 hours.

DHE rectal suppositories were prepared from 2 mg of the tartrate of DHE (obtained from Sigma Chemical Co.) made soluble in polyethylene 400 (60% by weight) and polyethylene 6000 (40% by weight). After the 2 days of IV treatment, 2-mg DHE suppositories were given every 12 hours; if this was ineffective, patients were taught to give themselves injections subcutaneously with 1 mg doses every 12 hours if headache persisted. Concomitant with the DHE, propranolol was given 60 mg twice daily. If, after 1 month, DHE was still necessary, propranolol was discontinued, and ergonovine was given 1.2 mg daily. DHE was stopped when headache occurred fewer than three times weekly and was of only mild intensity. Propranolol and ergonovine were also given after completion of diazepam treatment in hospital. The patients were discharged home on these programs; all analgesics and ergotamine were forbidden. All patients were seen personally for follow-up. The DHE patients were followed for 12 to 24 months, averaging 16 months; the diazepam-treated patients were seen for 3 to 5 years, averaging 4 years. There were no dropouts. DHE was used for 1 week to 4 months after the IV treatment (average, 3 weeks) with no untoward side effects reported. Propranolol and ergonovine, when successful, were continued for 1 year, at which time the drug was tapered to assess its continued need; if headache recurred, the drug was reinstituted for another year, when the process was repeated.

Results. The average dose of DHE was 0.7 mg (range, 0.3 to 1.0 mg). Forty-nine DHE-treated patients were headache-free within 48 hours (table 1), and only 7 diazepam-treated patients were rendered headache-free in 3 to 6 days. In 37 DHE patients, headache improved gradually; the others noted dramatic improvement after the first injection. Ten percent of the DHE-treated patients and 30% of the diazepam-treated patients did not benefit. Side reactions of DHE were few: 15 had diarrhea, invariably controlled with diphenoxylate; 3 reported leg muscle pains; and 2 had abdominal discomfort. Reduction of dosage always lessened these symptoms sufficiently to continue therapy. There was no claudication pain or angina pectoris. The average length of the hospital admission for the DHE-treated patients was 3.8 ± 0.5 (SE) days (range, 2.5 to 6) compared with 8.4 ± 2.2 (SE) days (range, 5 to 13) for the diazepam-treated patients ($p < 0.01$, Student's t test).

At follow-up, 36 DHE-treated patients reported good to excellent results compared with 15 of the diazepam-treated group (table 2). As a whole, the DHE-treated patients fared significantly better than the diazepam-treated group (tau = 0.35; $p < 0.001$), in large part because DHE, not analgesics, was used for any continuing headaches, and recurrence of drug dependence was negligible. This was not possible for the diazepam-treated group, and 16 of them were again drug-dependent at follow-up.

Discussion. This was a nonblinded, nonrandomized study of two treatments for intractable migraine given in different years. The study was therefore suboptimal in design. However, intractable migraine has historically been a therapeutically resistant problem with only rare placebo responses observed (Raskin, unpublished observations); dihydroergotamine was therefore impressively effective. It was tolerated better than IV ergotamine, despite similarities of chemical structure. Furthermore, ergotamine dependence was treated easily by substituting DHE, without a rebound effect when the DHE was discontinued.

The vascular effects of DHE are largely venous[4]; the pharmacologic activity and long duration of action are explained best by considering the biologic behavior of the major metabolite, 8-hydroxydihydroergotamine.[5,6] Both DHE and the metabolite are bound selectively to brain monoaminergic receptor sites.[7,8] DHE may also stimulate central 5-hydroxytryptamine receptors[9] in a pattern similar to that of other drugs that are effective in migraine.[10]

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Accepted for publication November 6, 1985.

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From benign fasciculations and cramps to motor neuron disease

Article abstract—Fasciculations and cramps may occur in motor neuron disease or as part of a more benign syndrome. A man with apparently benign fasciculations and cramps for 4 years developed progressive muscle weakness and wasting. Such a previously undocumented evolution of benign fasciculations and cramps to motor neuron disease may further implicate anterior horn cell dysfunction in the pathogenesis of muscle fasciculation-cramp syndromes.

NEUROLOGY 1986;36:997-998

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Muscular fasciculations often imply the diagnosis of motor neuron disease. The self-reported incidence of benign fasciculations is, however, quite high among medical personnel.[1] Attempts have been made to distinguish "benign" from "malignant" fasciculations by rate of discharge[2] and shape of potentials[2] or degree of self-awareness by the patient.[3] None of these methods is reliable, however. Weakness and wasting are needed to evoke a diagnosis of motor neuron disease. If these features are absent and cramps are also noted, the syndrome is assumed to be benign fasciculations and cramps as described by Denny-Brown and Foley.[4] This benign syndrome has never been documented to evolve into motor neuron disease,[5] but we have seen such a case.

A 61-year-old man was admitted to a hospital in September 1980 for what proved to be nonspecific low back pain. A physician noted that "all his muscles twitch." Cramps and twitches had begun in his legs and had since spread to involve his entire trunk and arms. By 1983, the cramps were precipitated by minimal exertion and relieved by rest, massage, or stretching. The cramps also occurred in sleep, however, and often awakened him. He had anywhere from a dozen to over 100 cramping episodes per day. Each episode lasted less than 30 seconds. Separate trials of diazepam and methocarbamol had in the past failed to relieve his back pain, cramps, and twitchings. He had never had poliomyelitis nor any other type of myelitis. He had generalized muscle fatigability, but denied any specific weakness.

He was 5'8" tall, and when seen in August 1983 he weighed 200 pounds. Fasciculations were seen in all limbs and on the trunk. They were visible to examiners only occasionally, despite his constant subjective appreciation of them. No muscle weakness or atrophy was seen by several examiners, including two neurologists. There was no muscle hypertrophy, tenderness, or rigidity. Myotonia was not elicited by exertion or percussion. Cranial nerve, sensory, and cerebellar function were normal. Reflexes were normal with plantar flexor responses. Normal laboratory studies included ESR, CBC, electrolytes, blood chemistries, CK, Mg, lead levels, ANA, thyroid studies, FTA-ABS, CXR, ECG, and EEG. Motor and sensory nerve conduction studies were normal. EMG revealed increased insertional activity with fibrillations, positive sharp waves, diminished interference pattern, and fasciculations in several arm and leg muscles. Left deltoid muscle biopsy revealed denervation atrophy. Hematoxylin and eosin staining disclosed several groups of 8 to 10 angular atrophic fibers. Some fibers were noted to contain central targets, but no inflammation, muscle degeneration, or regeneration was found.

On visits in October 1983, and in January and March 1984, he reported cramps despite therapeutic trials of clonazepam, baclofen, phenytoin, and quinine. No weakness or atrophy was seen on these visits. He began to feel weak in the early summer of 1984, and by September there was weakness and atrophy of both shoulder girdles and proximal arms against resistance. There

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Neurology 1986;36;995
DOI 10.1212/WNL.36.7.995