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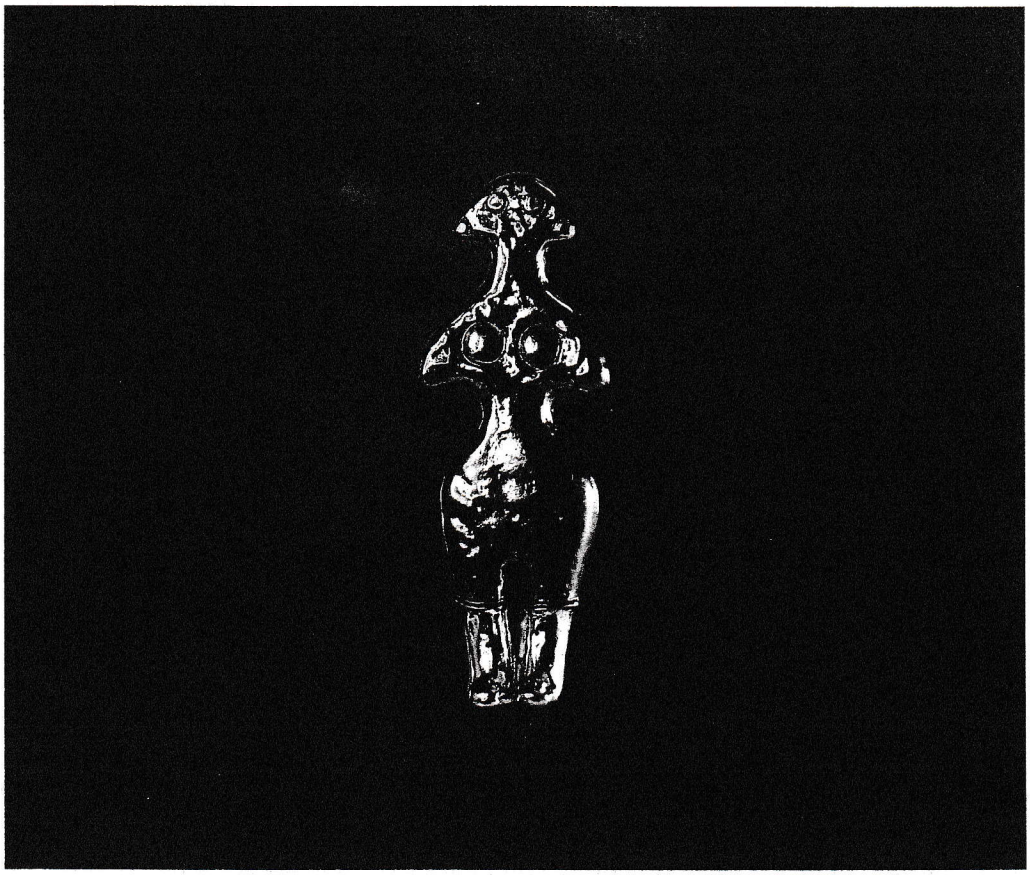

TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER
AT AMARILLO
School of Pharmacy

Pharmacotherapy

DHE: AN OLD DRUG MADE NEW

Randall L. Oliver, MD

Abstract. *Dihydroergotamine (DHE) has been available for over 50 years for the abortion of migraine, and prior to that, there was ergotamine tartrate, a similar medicine but one with more adverse effects. In recent years, additional methods of administration have made DHE more usable. Each form (intravenous, intramuscular, subcutaneous, and intranasal) has advantages and disadvantages. Intravenous administration is considered to be the best way to treat chronic daily headache and status migranosus, inpatient or outpatient. Intramuscular and subcutaneous administration of DHE are the best ways to get quick headache relief without requiring the patient to be hospitalized, in most cases. Intranasal is the most patient-friendly route of administration and is often as efficacious as the other forms of DHE, while still being as effective and safe for the abortion of migraine as new medications currently being marketed. Whatever the administration form, dihydroergotamine has proven to be an effective agent for the abortion of migraine.*

Descriptors. *DHE, dihydroergotamine, migraine*

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The purpose of this article is to provide a discussion of the use of dihydroergotamine (DHE) as an abortive agent for migraines. Not discussed in this article is the etiology of migraine or the use of new drugs such as sumatriptan, zolmitriptan, and rizatriptan except to compare them with DHE. DHE is an older drug than the triptans, yet it is effective in many patients.

Ergots have been used for treatment of migraines longer than any other migraine-specific drug (1). The first known use was in 1883 in Germany when Eulenberg used injections of ergot extract to treat headaches. Ergotamine was first derived in 1918 by Stoll in Switzerland. However, its first use was not for migraines but obstetrics and gynecology, hence the name *Gynergen*. In 1925, Rothlin initiated the use of subcutaneous injections of ergotamine tartrate (ET) for migraine abortion. An effective oral tablet form of ET was created in 1928 by Tzanck in France (2). A suppository for rectal administration of ET was developed. The suppository is preferred in some cases because of its more rapid absorption when compared to oral and sublingual tablets (1).

Unfortunately, ergotamine tartrate was found to have many adverse effects of which nausea is the most common. One study found that 42% of patients treated with an oral form of ET experienced nausea, compared with 17% of the placebo group (1). ET has also been linked to chronic problems such as peripheral ischemia due to vasoconstriction and emesis. There have also been reports of rebound headaches due to overuse (two to three times a week) and dependence when used over a long period of time (1).

The many side effects of ET encouraged researchers to find a safer form of ergot. In 1943, Stoll, the same man who originally isolated ergotamine, synthesized dihydro-

Randall L. Oliver, MD, Medical Director of the Oliver Headache & Pain Clinic, is board certified by the American Academy of Family Practice, and is a diplomate of the American Academy of Pain Management and the American Academy of Disability Analysts. Address reprint requests to: Dr. Randall L. Oliver, 2828 Mt. Vernon Avenue, Evansville, IN 47712.

ergotamine (DHE) in cooperation with Hoffman. DHE was first tested in 1945 in the United States by Horton, Peters, and Blumenthal. From its beginnings, it was found to be much safer than ET for the abortion of migraine headaches (2). DHE is effective for virtually all forms of migraine headache including migraine with or without aura, status migrainosus, chronic daily headaches, and cluster migraines (3). The forms of DHE administration, however, differ from those of ET because of its larger molecular structure. Any oral DHE tablet would undergo hepatic metabolism and not be properly absorbed from the gastrointestinal tract (4). One study has cited poor results from an oral form of DHE in 12 children. Migraine was terminated in 5, but headache recurred in 2 of the 5 (5).

DHE has a high affinity for 5HT-1A, 5HT-1D, alpha-1 adrenergic, and alpha-2 adrenergic receptors, as well as other serotonergic, adrenergic, and dopaminergic receptors (4). The preferred forms for DHE are intravenous (IV), intramuscular (IM), subcutaneous (SC), and intranasal (IN). All are used in practice today, and each has its advantages and drawbacks.

Intravenous DHE has been used for the abortion of migraines since the mid-1940s. However, the treatment lost favor with patients presenting with mild migraines because of the cost and time needed for a hospital stay. In 1986, Raskin introduced repetitive IV DHE dosing in combination with metoclopramide to lessen the nausea associated with IV DHE (6). This treatment is most effective in breaking a constant migraine cycle. Raskin's test group consisted of individuals with status migrainosus due to analgesic rebound or chronic daily headache. These were evenly divided into an IV DHE group and a diazepam group for treatment. In the IV DHE group, 89% of patients were headache-free within 2 days, while only 13% of the diazepam group were headache-free after 3-6 days (6).

In 1990, another study was published in which IV DHE aborted headaches in 92% of chronic daily headaches with analgesic rebound, 85.7% of chronic daily headaches without analgesic rebound, 88.9% of short duration, and 100% of cluster headaches. In this study, patients received 10 mg of metoclopramide over 30 minutes followed by 0.5 mg IV DHE over 1 minute. Repetitive doses were given at 8 hours for improving headaches and 1.0 mg at 8 hours for more persistent headaches. In minor complications, severe nausea was treated with increased metoclopramined (20 mg), restlessness was treated with diphenhydramine, and diarrhea was managed with a diphenoxylate-atropine combination. Only 2 of 298 patients were dropped from the study due to complications (6).

In a retrospective study of 54 cluster headache patients, 100% had complete relief of their headaches, with 82.8% reporting no side effects. At the 3-month follow-up, 92.9% of the episodic cluster patients were headache-free, while at 6 months all were headache-free. Also at the 3-month interval, 44.4% of the chronic cluster patients were headache-free and 75% at 6 months (7). In an outpatient study of repetitive IV DHE administration at home, 69% of patients with chronic daily muscle contraction-type headache and severe migraine were headache-free after 2 days. Effectiveness decreased to 65% in 3 weeks, 24% in 6 weeks, and 30% in 10 weeks. In patients exhibiting refractory daily headaches or frequent severe migraine, 80% showed an excellent response at 2 days, decreasing to 66% at 6 weeks. Total at-home response was 73% at 2 days and 43% at 6 weeks (8).

Another study published in the *American Journal of Pain Management* detailed a review of 50 outpatient treatments with intravenous DHE and found a 91.3% reduction in pain severity with relatively few side-effects (9). We have had these same responses with both inpatient and outpatient administration of IV DHE. For our patients, we followed Raskin's protocol. Outpatients are given a heparin lock containing metoclopramide and IV DHE. After instruction, nearly all were able to self-administer the drug intravenously at home without complications. We have observed the intravenous DHE to be an effective agent against vascular headache while having no effect on muscle tension headache. The response is usually quite dramatic with an obvious improvement in the headache or no response at all.

Another common administration form of DHE is the intramuscular route. The IM form is more feasible for patients without a hospital stay, and is preferred over the IV method. The IM form most often used is 1 mg dihydroergotamine mesylate (DHE 45). The maximum dose is 3 mg a day or 8 mg in 3 days to break the migraine cycle. In a study by Winner *et al.* of 311 patients experiencing migraine with or without aura who were administered IM DHE, 46% had only mild or no head pain after 30 minutes and 72% after 60 minutes. At 24 hours, 77% of patients were relieved. IM DHE also improved functional ability in 75% of patients by 60 minutes. Nausea was decreased from 62% before administration to 30% by 60 minutes (10). In another retrospective study, 71% of patients administered DHE mesylate were headache-free between 30 minutes and 4 hours following injection. Side effects were common but not serious, with 25% reporting sedation, 24% nausea, 15% worsening headache, 11% body aches, 5% diarrhea, and 13% relapse of headache within 24 hours (11). A study of 29 at-home

users of IM DHE in Oklahoma showed that this therapy can be effective even out of the office. The patients were taught to self-administer 0.5 mg DHE and 100 mg trimethobenzamide and to reinject another 0.5 mg DHE if necessary to abort headache. Forty-five percent reported at least 50% relief of headaches, and 82% of these continued to use the IM DHE. The study also underlined the importance of a good initial response for the patient to continue treatment (12). At our office, we have found that prescribing of IM DHE is safer than IV DHE and with fewer side effects, especially nausea. For patients who do not fear needles, IM DHE is a very good alternative to the IV form.

The other injectable route of DHE administration that has been studied is subcutaneous (SC). While our office has no experience with this method of administration, other researchers have reported favorable results. In a study comparing the efficacy and tolerability of SC DHE and SC sumatriptan succinate in 295 individuals, 73.1% of patients treated with 1 mg SC DHE were headache-free at 2 hours, while 85.3% of those treated with 6 mg sumatriptan were headache-free in the same interval. However, by 4 hours post-injection, 85.5% of those treated with SC DHE had relief, and 83.3% maintained relief with sumatriptan. Within 24 hours, headache recurrence was only 17.7% in the patients treated with SC DHE and 45% in the patients treated with sumatriptan (13). Another study of home subcutaneous administration of DHE in 51 patients in Canada was less favorable – only 53% reporting excellent or good relief and a full 35% discontinuing use due to side effects including nausea and vomiting, limb pain, chest and throat tightness, and soreness at the injection site (14).

Intranasal (IN) administration of DHE has very recently been introduced onto the market, yet it was formulated by pharmacists years earlier. The relative bioavailability of IN DHE versus IM DHE is 38.4%, with peak plasma levels achieved at 0.9 hour. Intraindividual variations of bioavailability were 29% in IN DHE versus 20% for IM DHE. Therefore, absorption of the 4-mg IN DHE is roughly equal to that of 1-mg IM DHE (15). One pharmacist-formulated IN DHE form from a local pharmacy — the formulation used in our office — consisted of 4 mg DHE, sterile water with preservative, 180-proof alcohol, and a minute amount of HCl to balance the pH of the solution (16). Before 1996, the IN form varied from place-to-place, but nearly all worked well, provided the pharmacist did not precipitate the DHE. The intranasal form of DHE has been marketed as Migranal® which contains 4 mg DHE mesylate, caffeine, dextrose, carbon dioxide, and water to 1 ml (17).

The market form of IN DHE has been the subject of many studies in recent years. In the definitive article by the Dihydroergotamine Nasal Spray Multicenter Investigators, 206 patients were enrolled, with 102 treated with IN DHE and 104 with placebo. There were two study groups, with one group reporting 71% IN DHE responders and the other 59% responders in 4 hours. Nausea was lessened in 70% of one group compared to 37% in the placebo group. There was no significant difference in vomiting between IN DHE and placebo (18,19).

In a related study, headache relief was 70% and recurrence was only 14% after 24 hours in those whose headaches were relieved. No serious side effects were reported; the only minor side effects were nasopharyngeal due to the nasal route of administration. In the study, the 2-mg DHE mesylate provided superior efficacy when compared with the 3-mg DHE, and, of course, it provoked fewer side effects (20).

In a study comparing the efficacy of SC sumatriptan and IN DHE, 317 patients received random treatment. One hundred forty-five were treated with sumatriptan, and 144 were treated with IN DHE, yielding 63% relief with sumatriptan and 22% with DHE, both in one hour. Relief was achieved and maintained for 24 hours in 54% of sumatriptan-treated patients and 39% of IN DHE patients. However, adverse effects were reported in 43% of sumatriptan-treated patients and only 22% of IN DHE-treated patients (21). It is important to realize that this may not be a viable comparison of these medicines because of the different administration methods.

In our practice, we use the local pharmacy-compounded DHE more often than the Migranal®. While the compounded product may have a shorter half-life than Migranal® which is preserved in an ampule, the Migranal® system can be somewhat cumbersome to use and may provoke patient complaints. In addition, the local pharmacy-compounded DHE is more cost-effective than Migranal®, even with its shorter shelf-life. Our local pharmacy can provide DHE nasal spray at approximately $40.00 per unit containing up to 20 doses. The Migranal® is a single-dose unit at approximately $17.00 per dose in our community. It would seem prudent to use Migranal® if a patient has irregular migraines and needs a product with a long shelf-life. Conversely, one can use the pharmacy-compounded DHE if cost is a concern, or if the patient is using the DHE more often, or if shelf-life is not a concern.

Our results with the commercial intranasal Migranal® and the local pharmacy-formulated DHE have been comparable. In addition, we have found that the intranasal form of DHE often works as well as either the intravenous (IV) or IM DHE. While many patients find the intranasal DHE preferable to either an IV or IM form,

occasional patient preferences may still lean towards the IM form due to the patient's desire not to administer a drug nasally or to avoid the burning sensation that may accompany the intranasal form.

Since 1883, dihydroergotamine has been used in many forms with a high success rate in the treatment of migraine. Its many dosage forms and routes of administration make it patient and physician-friendly. Even though it is one of the oldest migraine medications, it still remains an effective and relatively safe agent for the abortion of migraines and the treatment of migraine, when used according to the established guidelines.

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