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Pharmacology of Dihydroergotamine and Evidence for Efficacy and Safety in Migraine

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Dihydroergotamine mesylate (DHE), an ergot alkaloid, has been extensively utilized and studied in the treatment of episodic and chronic migraine. This article reviews the pharmacokinetics, pharmacodynamics, and clinical efficacy and safety of DHE, particularly in comparison to ergotamine tartrate (ET), a similar ergot alkaloid with a long history of use in the treatment of migraine. Structural differences between these 2 compounds account for clinically important distinctions in their pharmacokinetic, pharmacodynamic, and adverse event profiles. DHE is a significantly less potent arterioconstrictor than is ET, which makes it a potentially much safer drug. In addition, DHE is associated with a markedly lower incidence of medication-withdrawal headache, nausea, and vomiting than is ET. The safety and efficacy data presented here are derived from clinical trials and case series involving DHE administered by intravenous infusion, intramuscular or subcutaneous injection, or intranasal spray.

Key words: dihydroergotamine mesylate, ergotamine tartrate, migraine headache, efficacy, safety, tolerability, pharmacology

Abbreviations: DHE dihydroergotamine mesylate, ET ergotamine tartrate, AAN American Academy of Neurology

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Dihydroergotamine mesylate (DHE) is one of several interrelated chemical entities known as the ergot alkaloids. The basic chemical structure of all ergot alkaloids is the ergoline ring (Figure 1).[1,2] Ergotamine tartrate (ET) was the first pure ergot alkaloid, synthesized in 1918, although ergot extracts had been used for the treatment of certain types of headaches since the late 1800s.[3] The tartrate form of the molecule was first manufactured under the product name Gynergen® and was used in the early part of the 20th century for obstetric and gynecologic indications because of its uterotonic properties.

The first reported successful treatment of a case of severe and intractable migraine headache with subcutaneous ET was published in 1925.[3] After this, ET was actively marketed as a migraine therapy.[4] The results of controlled clinical trials of ET in the treatment of migraine were first published in 1934.[3] Research into the mechanisms by which the ergot alkaloids alleviated migraine conformed to the vascular theory of migraine prevailing at the time.[2,3] Evidence of ET's vasoconstrictive effect on extracranial blood vessels was cited as support for this theory as well as for the observed efficacy of the ergot alkaloids in the treatment of migraine.[5]

Ongoing research on the ergot alkaloids led to the synthesis in 1943 of DHE, differing from ET by the hydrogenation (reduction) of the double bond at the 9 to 10 positions of the ergoline ring (Figure 2).[1,2] This structural modification is believed to be responsible for the differences between the pharmacokinetic, pharmacodynamic, and adverse event profiles of DHE and ET.[2]

The earliest uses of DHE for the treatment of migraine were favorable. In an early report from Horton in 1945,[6] among 79 patients treated with intravenous DHE, 75% experienced marked to complete relief of

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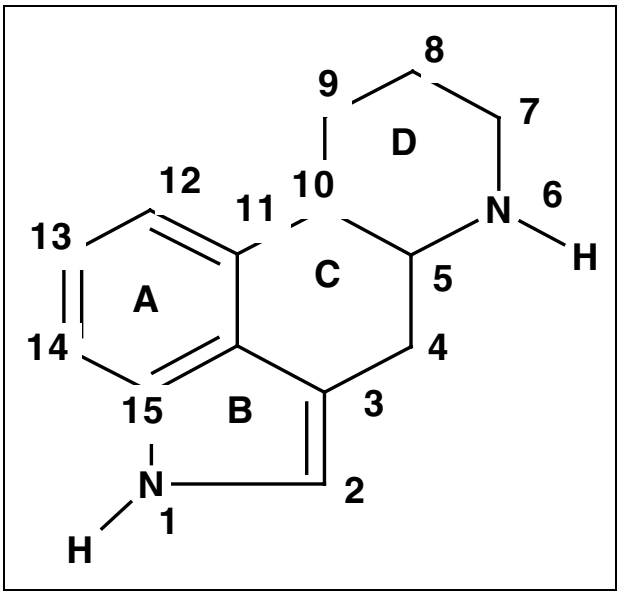

Fig 1.—Ergoline ring structure.

pain, and among 36 patients who received intramuscular DHE, 89% achieved excellent relief. Parenteral DHE thus appeared to be as effective as ET in relieving headache pain; moreover, it was associated with a lower occurrence of nausea.[6] Oral DHE, because of its extremely poor bioavailability, was never used in the treatment of acute migraine, though it was used for a number of years as a prophylactic agent.[7]

Interest in the use of parenteral DHE waned until 1986 when 2 articles were published describing its effectiveness in the treatment of intermittent migraine headaches and intractable migraine.[8,9] The remarkable efficacy and tolerability reported in these studies led to a sharp rise in the use of parenteral DHE among clinicians specializing in the treatment of headache. Thereafter, for the next 20 years and continuing today, parenterally administered DHE became an important therapeutic option in the treatment of treatment-resistant migraine attacks and persistent migraine. However, coincident with the emergence of an intranasal formulation of DHE, which might have led to its wider use on an ambulatory basis, the triptans were introduced and captured the attention of the field of pharmaceutical research.

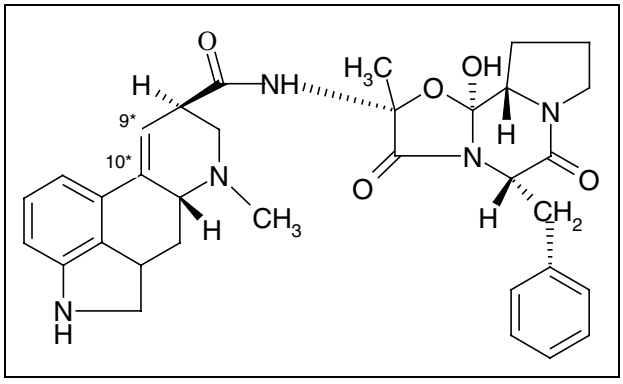

Fig 2.—Chemical structure of dihydroergotamine. (*DHE has hydrogen atoms at positions 9 and 10, hence its name.)

The purpose of this article is to review the features of this important medication, which differs considerably from ET. The pharmacologic properties of DHE confer a robust efficacy profile, as well as safety and tolerability characteristics[2] that are superior to that of ET and equivalent to that of the triptans. Following an overview of the pharmacology of DHE, this article presents a comprehensive summary of the clinical trial data establishing the safety and efficacy of DHE in the treatment of episodic and chronic migraine headache.

PHARMACOKINETIC PROFILE OF DHE

Absorption.—The absolute bioavailability of DHE administered by the intramuscular or intravenous route is 100% (Sandoz Pharmaceuticals, data on file), and that of intranasally administered DHE is approximately 40% (Table 1) (Sandoz Pharmaceuticals, data on file).[10-14] The time to peak plasma level (C_{max}) of DHE varies considerably, according to the route of administration, ranging from 1 to 2 minutes for intravenous and 24 minutes for intramuscular, to 30 to 60 minutes for intranasal administration. Unfortunately, the oral bioavailability of the parent compound is less than 1%, as a consequence of poor gastrointestinal

Table 1.—Bioavailability of DHE Based Upon Route of Administration

Route	Bioavailability (%)
Intravenous	100
Intramuscular	100
Intranasal	40
Oral (tablets)	<1

Table 2.—Pharmacokinetic Parameters of DHE and ET in Normal Volunteers

Parameter	DHE			ET*	
	Intramuscular[†,‡]	Intravenous[†,§]	Intranasal[¶]	Oral	Rectal
Dose (mg)	1	1	1[‖]	2	2
C_{max} (ng/mL)	2.9	<10	1.0	<0.1	0.5
T_{max} (minutes)	24	1-2	54	69	50
$T_{1/2}$					
Phase 1 (minutes)	59	—	60		10.5
Phase 2 (hours)	10–13	10–13	8	—	3.4

Since these data are derived from different studies, they may not be directly comparable. Adapted with permission from Silberstein.[10]
[‖]The recommended clinical dose of intranasal DHE is 2 mg, whereas it is 1 mg for IV and IM.
*Sanders et al.[13]
[‡]Schran et al.[12]
[§]Tfelt-Hansen and Lipton.[14]
[†]Sandoz Pharmaceuticals Corporation, data on file.
[¶]Humbert et al.[11]

absorption and substantial (>90%) first-pass metabolism of what little drug is absorbed.[15-17]

Elimination.—DHE undergoes a biphasic pattern of elimination. DHE is primarily metabolized by hepatic degradation, with metabolites predominantly excreted in the feces via biliary excretion. This process is responsible for the first phase of DHE elimination (half-life, 0.7 to 1 hours).[12] The second phase of elimination (half-life, 10 to 13 hours) (Sandoz Pharmaceuticals, data on file) is determined by the very slow dissociation of DHE and its metabolites from their target receptors.[14]

Comparison With ET.—Although the actual molecular difference between ET and DHE is minimal, the pharmacokinetic and pharmacodynamic differences between these 2 closely related compounds are of major clinical importance. Table 2 compares the pharmacokinetic parameters of DHE and ET. These differences may partially explain why headache recurrence and medication overuse headache are common with ET but rare with DHE. Peak plasma levels of ET occur at approximately 60 minutes following oral or rectal administration.[12-14] However, plasma levels of ET reached following rectal administration are significantly higher (>10×) than those reached following oral dosing.[13] In contrast to DHE, parenteral formulations of ET were poorly tolerated and are no longer available.[10] The metabolism and elimination of ET is similar to that of DHE. ET also undergoes biphasic elimination—first phase half-life, ~10 minutes, and second phase half-life, 3.4 hours—although the half-life of the second phase is shorter.[13] Thus, differences in route of administration, elimination half-life, and/or peak serum concentration may contribute to important clinical distinctions between DHE and ET.

PHARMACODYNAMIC PROFILE OF DHE

Antimigraine Activity.—The biologic activity of DHE and of all the ergot alkaloids correlates poorly with their plasma concentration. That is, despite remarkably low concentrations, in the picogram range, their biologic activity may persist for days.[17,18] Tight tissue binding is one possible explanation for the persistence of drug effect, as evidenced by the long second phase of elimination, representing DHE's slow dissociation from the receptor sites where it is pharmacologically active. It is also possible that DHE binds nonspecifically to other receptor sites, which subsequently release it slowly back into the circulation, making it available to bind secondarily to active sites.[10] The presence of high concentrations of active metabolites is likely another factor contributing to the prolonged biologic effect of DHE. Biologic activity is retained only by those metabolites that possess the characteristic ergoline ring and peptide-chain structure of the ergot alkaloids.[10,19] One major active metabolite of

Table 3.—Receptor Types and Subclasses Affected by Ergotamine and Dihydroergotamine[10]

Serotonin Receptors	Adrenergic Receptors	Dopamine Receptors
5-HT_{1A}	Alpha_1	DA_1
5-HT_{1B}	Alpha_2	DA_2
5-HT_{1D}	Beta	
5-HT_{1F}, 5-HT_{2A}, 5-HT_{2C}	(Alpha_1, Alpha_2, > Beta)	($\text{DA}_2 > \text{DA}_1$)

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Table 4.—Clinical Comparison of DHE and ET

Safety/Efficacy Measure	DHE	ET
5-HT activity	++	++
Arterial vasoconstriction	+	+++
Venoconstriction	++	++
Alpha-adrenergic antagonist activity	++	+
Nausea/vomiting	+	+++
Uterotonic effects	+	++
Pain relief	+++	+++
Headache recurrence	+/0	++
Medication-overuse headache	0	++

0 = none; + = mild; ++ = moderate; +++ = prominent.

DHE is 8′-hydroxyl-DHE. Its pharmacologic activity is similar to that of DHE, but the metabolite occurs in concentrations 5 to 7 times those of the parent compound.[17,20,21]

DHE interacts with multiple receptors with varying degrees of affinity and resultant biologic activity. Its efficacy is a function of its ability to gain access to key receptor sites, which is system and organ specific. The fact that DHE is structurally related to the biogenic amines explains its affinity for norepinephrine, epinephrine, dopamine, and serotonin receptors (Table 3).[10] Although the antimigraine effects of DHE and other ergot alkaloids are presumably related to their activity at 1 or more types of these biogenic amine receptors, the precise mechanisms of action are not known. It is believed that, as with the triptans, agonist activity at 5-HT_{1D} receptors plays an important role, but this is likely only part of the clinically meaningful spectrum of activity of the parent drug and its active metabolites.[4,19,21] Thus, unlike the narrow spectrum of effect of the triptans, DHE provides a broad spectrum of potentially relevant receptor influence.

Comparison with ET.—DHE and ET are both effective treatments for migraine pain, but they have several clinically relevant pharmacodynamic differences (Table 4).[2] First, ET is more likely than DHE to cause medication-overuse headache (commonly termed "rebound" headache).[7,22,23] In vulnerable patients, abrupt withdrawal of ET can induce severe headache and associated symptoms even after limited use of the drug—only 1 or 2 days per week.[24] In contrast, medication-overuse headaches have never been reported with DHE.[22,23] This is an important distinction, since headaches induced by ET withdrawal are considered quite challenging headaches to treat by standard treatment measures.[24] (See also the article by Dr. Dodick in this supplement.) Also of importance is the very low rate of headache recurrence seen with DHE, relative to ET, although the reason for this crucial clinical difference is not known.[22] (See also the article by Dr. Silberstein in this supplement.)

Other Pharmacologic Differences Between DHE and ET.—The vascular effects of DHE are of historical interest, since vasoconstriction of the extracranial vascular bed was thought to account for its therapeutic effect in the treatment of migraine.[25] The vascular effects of DHE depend on drug dose and vasomotor tone. DHE is a far more potent constrictor of venous capacitance vessels than of arteries (Table 5).[10] DHE has strong alpha-adrenergic antagonist activity[22] and weak uterotonic activity.[19]

ET is a more potent arterioconstrictor than is DHE,[2,22] but it equals DHE in venoconstriction (Table 5).[7,22,23] DHE is somewhat less likely than ET to cause nausea and vomiting. Although intravenous DHE is routinely administered with an antiemetic, the co-administration of antiemetic drugs with intramuscular DHE is often not necessary.[26-28] ET is a more potent uterotonic agent than DHE (Table 4).[10]

Sustained, frequent use of ET has been associated with multiple case reports of fibrosis involving the pericardium, coronary ostia and valves, pulmonary tissue, and retroperitoneum. These are presumed to be serotonergic-related idiosyncratic events. The chronic use of rectal formulations of ET has also been

Table 5.—Comparative Vascular Effects of DHE and ET[10]

	DHE	ET
Arteries		
Resistance vessels		
Peripheral	• Mild arterioconstriction • Variable effect on blood pressure* • Inhibition of norepinephrine-induced vasoconstriction	• Arterioconstriction • Increased blood pressure* • Inhibition of norepinephrine-induced vasoconstriction
Cerebral	• Constriction of larger (capacitance) cranial arteries • Inhibition of norepinephrine-induced vasoconstriction • Negligible effect on resistance vessels • No change in cerebral blood flow • Closure of arteriovenous anastomoses	• Constriction of larger (capacitance) cranial arteries • Increase? in norepinephrine-induced vasoconstriction • Negligible effect on resistance vessels • No change in cerebral blood flow • Closure of arteriovenous anastomoses
Veins		
Capacitance vessels	• Venoconstriction	• Venoconstriction
Resistance vessels	• Negligible effect	• Negligible effect

*Dependent upon initial vasomotor tone.
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associated with rectal fibrosis.[29] An increased risk of vasospasm has been reported with the concomitant use of ET and triptans.[30] There have also been sporadic case reports of fibrosis involving DHE, but these are far less common,[31] and case reports of vasospastic adverse events associated with the use of DHE have been rare.[32]

ET is contraindicated in patients with prolonged aura or vertebrobasilar migraine, because of the possibility of migrainous infarction.[33] Case reports in uncontrolled studies also suggest that ET may lengthen or aggravate the aura in individuals with prolonged aura.[22] DHE, on the other hand, has not been reported to lengthen or aggravate the aura, and it can be administered during the aura if clinically indicated.[19]

DHE: CLINICAL TRIAL DATA

In 1995, an expert advisory panel, appointed by the Quality Standards Subcommittee of the American Academy of Neurology (AAN), reviewed the clinical literature on DHE.[22] The advisory panel was composed of experts from the Headache and Facial Pain Section of the AAN. On the basis of this review of the literature, the AAN Practice Parameter on the use of DHE and ET in the treatment of migraine and status migrainosus was developed.[34] Most of the 21 clinical studies involving DHE that were reviewed as the basis for this Practice Parameter were uncontrolled, open-label, and unblinded investigations, the primary objective of which was to evaluate the efficacy of DHE. Although data on safety and adverse events were not always collected systematically, the Quality Standards Subcommittee concluded that, based upon the available data, DHE was effective in the treatment of migraine headache and was not usually associated with significant side effects.[34] The following discussion summarizes the safety and efficacy data from these clinical trials, according to route of administration.

Intravenous DHE.—The results of an open-label trial comparing repetitive intravenous DHE with intravenous diazepam for the treatment of chronic intractable migraine, published in 1986,[8] reported impressive efficacy and tolerability for DHE. In this trial, intravenous DHE 1 mg was given every 8 hours, in conjunction with metoclopramide (an antiemetic). Of the 55 patients who received intravenous DHE, 66% (36/55) were considered to be overusing ergotamine, analgesics, diazepam, or corticosteroids. The intravenous diazepam group consisted of 54 age-matched patients, 70% (38/54) of whom were medication overusers. The primary outcome measure was complete headache relief. This endpoint was achieved by 89% of patients (49/55) from the intravenous DHE group by 48 hours, versus 24% of patients (13/54) from the intravenous diazepam group. The patients who received intravenous DHE maintained better long-term improvement; specifically, 80% of the responders (39/55) sustained therapeutic benefit over a 16-month follow-up period (maintenance treatment regimen not specified). Adverse events related to DHE (lower-extremity muscular pain, nausea, and diarrhea)

occurred infrequently and were managed by dose adjustment.

Following this report, Callaham and Raskin conducted a double-blind, placebo-controlled, crossover study of intravenous DHE for the treatment of acute migraine pain in an emergency room setting (N = 37).[9] DHE 0.75 mg or placebo was administered intravenously 15 minutes after infusion of prochlorperazine (an antiemetic), and the crossover treatment was given after 30 minutes. Headache pain was rated serially every 30 minutes on a 10-point Likert scale. At 1 hour, the mean pain rating in patients who initially received DHE was 2.5 (compared with 6.3 at baseline, a 60% reduction), and it was 4.7 (a 25% reduction) in those who received DHE at 30 minutes. Although DHE was not significantly better than placebo at 30 minutes post infusion, this may have been because the dose of DHE was too low (standard dosing of intravenous DHE is 1 mg, not 0.75 mg). Adverse events were mild and transient and did not necessitate withdrawal of therapy. No cardiovascular side effects were reported. Nausea was reported in 7 DHE patients (versus 1 placebo patient), and vomiting occurred in 3 DHE patients.

Silberstein and colleagues conducted a retrospective review of data from 300 patients who had received repetitive doses of intravenous DHE for chronic daily headache, short-duration headache, or cluster headache.[35] The patients had been withdrawn from any overused medications and were treated with intravenous DHE, metoclopramide, and other prophylactic medications. With DHE treatment, 91% of the patients became headache free, most within 2 to 3 days. Reported adverse events included nausea (increased over baseline) (32%), chest tightness and mild systemic burning (8%), leg cramps (7%), vomiting (6%), and increased blood pressure (5%). Most side effects resolved spontaneously or with minor adjustments of the medication dosage. Only 2 patients discontinued therapy because of an adverse event (1 patient with drug-related claudication, 1 patient with an unspecified somatic complaint). The possible pain control contribution of the neuroleptic antiemetic remains uncertain.

Intramuscular Injection of DHE.—Winner and associates conducted a large, prospective, open-label trial (N = 311; 274 women; mean age, 39 years) of intramuscular DHE in acute migraine.[26] Dosing was 1 mg initially, followed by 1 mg at 60 minutes if needed. Rescue therapy, at the investigator's discretion, could be given at 60 or 120 minutes. Primary efficacy measures were headache relief (by patient self-assessment on a 4-point Likert scale) at 30, 60, 90, and 120 minutes and 24 hours postdose; secondary measures included use of rescue medication and rate of headache recurrence.

At baseline, 95% of patients rated the severity of headache pain as moderate or severe. By 30 minutes, 56% of patients who received only a single injection (n = 220) rated their headache pain as mild or none, and by 60 minutes 88% did so. Among those who received a second injection (n = 88), 58% reported mild or no headache pain at 90 minutes, and 70% reported this degree of relief at 120 minutes. Only 34 patients (11%) were given rescue medication, and the same percentage experienced headache recurrence, defined as the return of moderate or severe pain after having experienced mild or no pain. Comparable improvement was seen in patient-rated functional ability over the course of the study (Figures 3 and 4).

The incidence of nausea was also carefully observed in this study. At baseline, 62% of the patients reported nausea; this proportion dropped to 40% by 30 minutes and to 30% by 60 minutes after treatment. At the discretion of the investigator, an antiemetic could be administered to patients before treatment. A total

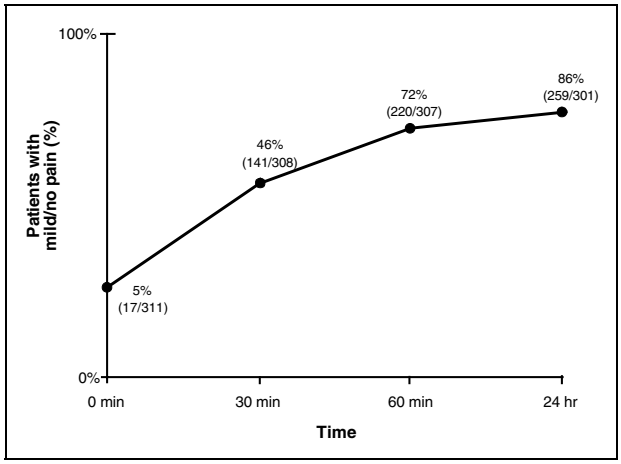

Fig 3.—Mild/no head pain over 24 hours among patients receiving 1 or 2 injections of DHE 1 mg intramuscularly.[26] Used with permission.

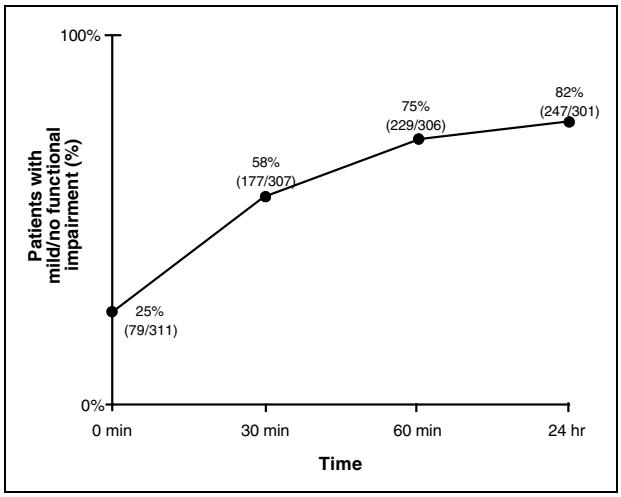

Fig 4.—Mild/no functional impairment over 24 hours among patients receiving 1 or 2 injections of DHE 1 mg intramuscularly.[26] Used with permission.

of 133 patients (43%) received an antiemetic. However, nausea improved in all patients following DHE administration (Figure 5), indicating that premedication with an antiemetic was not necessary. This was an important finding at the time, because prophylactic antiemetics are generally required when DHE is administered intravenously. Adverse events, including injection site pain and leg cramps, occurred in less than 10% of patients and generally remitted within 1 hour.

Weisz et al reported results of a study involving 29 patients who self-administered intramuscular DHE.[36] These patients all had acute migraine headache unresponsive to conventional therapies. The initial DHE dose was 0.5 mg, which could be followed by an additional 0.5 mg if necessary. Among the 20 patients who were followed up, 9 patients (45%) experienced at least 50% relief of headache pain and continued to use the drug. Initial response to treatment was predictive of continued use of DHE. Patients who had more severe headaches showed a greater response to the DHE treatment.

In an open-label, comparative trial of intravenous valproate versus intramuscular DHE in acute migraine (N = 40), patients received either intravenous valproate 500 mg or intramuscular DHE 1 mg.[37] At 4 hours posttreatment, relief of headache pain was comparable in the 2 groups. However, at 24 hours, relief was superior in the DHE group: the proportion of patients reporting improvement in pain from "moderate or severe" to "none or mild" was 90% for the DHE group, versus 60% for valproate. No side effects were reported in the valproate group, but 15% of the DHE patents reported nausea or diarrhea within the first 4 hours after treatment.

On the basis of these studies, it was determined that DHE could be administered by the intramuscular

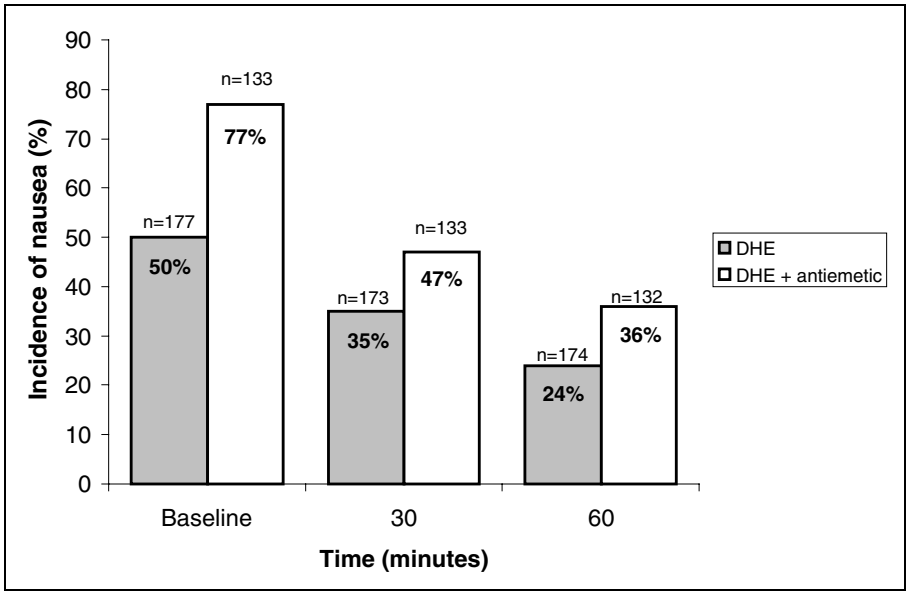

Fig 5.—Nausea among patients who did and did not receive an antiemetic.[26] Used with permission.

route in the office setting[26,28,38,39] or by patients themselves following proper training. The typical intramuscular dose of DHE is 1 mg, and the dose may be repeated after 60 minutes, if needed. The maximum recommended dose per attack is 3 mg, with a weekly maximum of 20 mg.[22] Anecdotal reports suggest that mixing DHE with saline solution may reduce injection site pain. There are no clinical studies of long-term intramuscular administration of DHE.[34]

Subcutaneous Injection of DHE.—A randomized, cross-over study in 30 healthy male volunteers demonstrated bioequivalence of subcutaneous and intramuscular DHE.[12] However, there are no published, placebo-controlled studies examining this route of delivery of DHE. A retrospective case series of 51 patients treated with 1 mg SC DHE by self-injection for acute headache pain, of whom 21 had episodic migraine and 27 had transformed migraine, reported a "good to excellent" response in 53% of cases, with 65% continuing to use this treatment modality after an average follow-up of 21 weeks.[40]

Intranasal DHE.—A total of 7 placebo-controlled clinical trials of intranasal DHE were published between 1985 and 1996; all of these reported a statistically significant advantage for intranasal DHE in the relief of migraine pain.[41-47] In the largest and most recent trial,[42] patients (n = 348) were randomized to receive either intranasal DHE (2 or 3 mg) or placebo as treatment for 2 episodes of migraine pain that were at least moderately severe. Resolution of pain by 4 hours was recorded in 70% of patients treated with intranasal DHE ($P < .05$ vs placebo), with a recurrence rate at 24 hours of 14% (vs 33% for placebo). No serious adverse events were noted in either group.

Two other multicenter, double-blind, parallel-group studies comparing the efficacy and safety of intranasal DHE with placebo during the first 4 hours of a migraine headache yielded similar findings.[41,43] In each of these comparably designed studies, patients self-administered intranasal DHE (0.5 mg per nostril at the onset of pain and 15 minutes thereafter) and then recorded symptom severity hourly for 4 hours on a 4-point Likert scale. Intranasal DHE was significantly superior to placebo for relief of headache pain at 1 hour ($P < .05$) and at 4 hours ($P < .01$) in both studies. Reduction in nausea was also significant by 2 hours in both studies ($P < .05$). Adverse events were limited and localized to the nasopharynx.

Two of the earlier trials used a crossover design and analyzed the data by treated episodes (n = 318[44] and n = 126[47]). DHE doses ranged from 0.9 to 2.0 mg per treatment episode. The primary endpoint in the larger study was complete headache relief at 2 hours. This was attained in 37% of DHE-treated episodes versus 20% of placebo-treated episodes ($P < .01$). The primary endpoint in the smaller study was mean pain relief, as measured on a 5-point Likert scale. Results in the smaller study also significantly favored DHE (Wilcoxon signed rank test, $P < .05$).

Comparative Studies.—Comparative data on the efficacy of DHE versus the triptans or any other treatments for migraine headache are limited. The only published study was a double-blind, randomized, parallel-group trial of subcutaneous DHE 1 mg versus subcutaneous sumatriptan succinate 6 mg in the treatment of moderate or severe acute migraine.[48] Patients rated headache pain, functional ability, and nausea and vomiting at baseline and at 0.5, 1, 2, 4, and 24 hours after treatment. Evaluations were based on data from 295 patients. At the 2-hour postdosing time point, 73.1% of the DHE-treated patients experienced relief of headache pain, versus 85.1% of the sumatriptan-treated patients ($P = .02$ favoring sumatriptan). At 4 hours postdosing, the headache relief rates for DHE and sumatriptan were 85.5% and 83.5%, respectively. By the 24-hour postdosing time point, 89.7% of DHE patients versus 76.7% of sumatriptan patients reported pain relief ($P = .004$ favoring DHE). Rates of headache recurrence within 24 hours of treatment were 17.7% for DHE and 45% for sumatriptan ($P \leq .001$ favoring DHE). Thus, although sumatriptan was superior to DHE in the acute relief of migraine headache pain, headache recurrence was twice as likely with sumatriptan.

Adverse Events.—Overall, nausea is the most common adverse event experienced with the use of DHE, particularly when it is administered intravenously. Therefore, a prophylactic antiemetic, usually metoclopramide, is routinely given with intravenous DHE. A prospective study in 72 patients treated with repetitive intravenous DHE in an inpatient setting showed

Table 6.—Adverse Events in Clinical Trials of Intranasal DHE (Incidence ≥2% and Occurring More Frequently Than Placebo)[49]

	Intranasal DHE N = 597 (%)	Placebo N = 631 (%)
Rhinitis	26	7
Nausea	10	4
Altered sense of taste	8	1
Application site reaction	6	2
Vomiting	4	1
Pharyngitis	3	1

that transient adverse events of mild to moderate intensity were common, including nausea (72%), lightheadedness (33%), and leg cramps (23%). No patients required discontinuation of DHE therapy due to adverse events, and the dose was decreased in only 4 patients.[30] Other common side effects (>10% incidence) are rhinitis (intranasal formulation, Table 6)[49] and transient pain at the injection site (intramuscular and subcutaneous formulations).[26,36]

At recommended dosages, by any route of administration, DHE has not been associated with serious cardiovascular adverse events. However, because of its known potential for arterioconstriction and uterine contraction, DHE is contraindicated in pregnancy and in patients with coronary, cerebral, and peripheral vascular disease, as well as in those with uncontrolled hypertension. Other contraindications include melanoma or a history of melanoma, renal or hepatic failure, history of hypersensitivity to DHE or other ergotamine compounds, and age <12 years.[7,34,49]

SUMMARY

DHE, the last of the ergot alkaloids to be synthesized and introduced to the pharmacologic armamentarium of antimigraine agents, has numerous pharmacokinetic and pharmacodynamic advantages in the treatment of migraine. Among these are its biphasic elimination and its associated long duration of pharmacologic activity, which significantly reduce the rate of headache recurrence and which seem to essentially eliminate the risk of medication-overuse headache. DHE's favorable adverse event profile compared with that of ET substantially increases the safety and tolerability of DHE, allowing for treatment with higher serum levels and less associated nausea. Results from published clinical trials and case series have demonstrated that DHE, administered by the intravenous, intramuscular, subcutaneous, or intranasal route, is effective and well tolerated in the treatment of migraine headache.

Conflict of Interest: None declared

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