Ergotamine Tartrate and Dihydroergotamine Mesylate: Safety Profiles

Richard B. Lipton, MD

Ergotamine tartrate (ET) and dihydroergotamine mesylate (DHE) have been widely and effectively used in the treatment of migraine for many decades, although few randomized, controlled clinical trials have been conducted with these compounds. To compare their safety profiles, the world literature on the two agents was surveyed. The results are summarized, along with a critical analysis of the strengths and limitations of the various sources of safety data (in vitro research, animal studies, Phase I and II studies, controlled clinical trials, and postmarketing surveillance).

Significant pharmacologic and safety differences exist between ET and DHE. Dihydroergotamine mesylate is a less potent arterial vasoconstrictor than ET, although nearly equipotent as a venoconstrictor. It is a more potent α-adrenergic antagonist, but is much less emetic, has less effect on the uterus, and is not associated with rebound headache. Adverse effects associated with ET (which are often due to excessive dosage and/or chronic usage) include nausea, acroparesthesia, ischemia, habituation and overuse headache, and, rarely, overt ergotism.

Reports of serious adverse effects following recommended doses of DHE are rare. As with most antimigraine drugs, the most frequent adverse effect with intravenous (IV) DHE is nausea; however, following intramuscular (IM) or intranasal (IN) administration, the incidence of nausea is low and concomitant administration of an antiemetic is not needed. In patients without contraindications, both DHE and ET are safe and effective when used in recommended doses. Nearly 50 years of clinical experience without major safety problems allows a high level of confidence in their clinical use.

Key words: dihydroergotamine mesylate (DHE), ergotamine tartrate (ET), migraine, nausea, safety

Abbreviations: AAN American Academy of Neurology, CCT controlled clinical trial, DES diethylstilbestrol, DHE dihydroergotamine, ET ergotamine tartrate, FDA Food and Drug Administration, QSS Quality Standards Subcommittee

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Ergotamine tartrate (ET) was introduced in the 1920s and dihydroergotamine mesylate (DHE) in 1946. There have been few randomized, controlled clinical trials (CCTs) with these compounds.[1,2] Despite years of clinical experience, these medications are often misused, in part because of uncertainty about their proper use and appropriate dose limits.[3] Much of the evidence about the safety of these compounds is derived from expert opinion, studies using nonrandomized historical controls, case reports, and surveillance data. An objective comparison of the safety of ET and DHE requires a clear understanding of the strengths and limitations of each type of data source.

This article reviews the safety data for ET and DHE starting with a general discussion of the sources of information about safety. The strengths and limitations of in vitro research, animal studies, open-label safety and dose-finding studies, CCTs, and postmarketing surveillance are reviewed. The existing safety information on ET and DHE in each category is then reviewed, and the two agents are compared.

DEFINITION AND TYPES OF ADVERSE EVENTS

An adverse event is defined as any undesirable effect produced by a drug (with the proviso that temporal association does not necessarily imply causation).[4] Adverse events are often categorized as dose dependent and idiosyncratic; in general, dose-dependent effects become more likely as the dose is increased, and are fairly predictable in that they are consistent with the known pharmacology of the drug. In contrast, idiosyncratic events are rare, unpredictable, and not dose related; they are based less on the known pharmacology of the drug than on individual reaction to it.[4]

SOURCES OF SAFETY DATA

The various types of safety data available on a compound correspond roughly to the stages of new drug development (Figure 1),[4] beginning with chemical investigation and animal research and progressing to clinical trials in humans: open-

From Montefiore Medical Center, Bronx, NY.

Address all correspondence to Dr. Richard B. Lipton, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467.

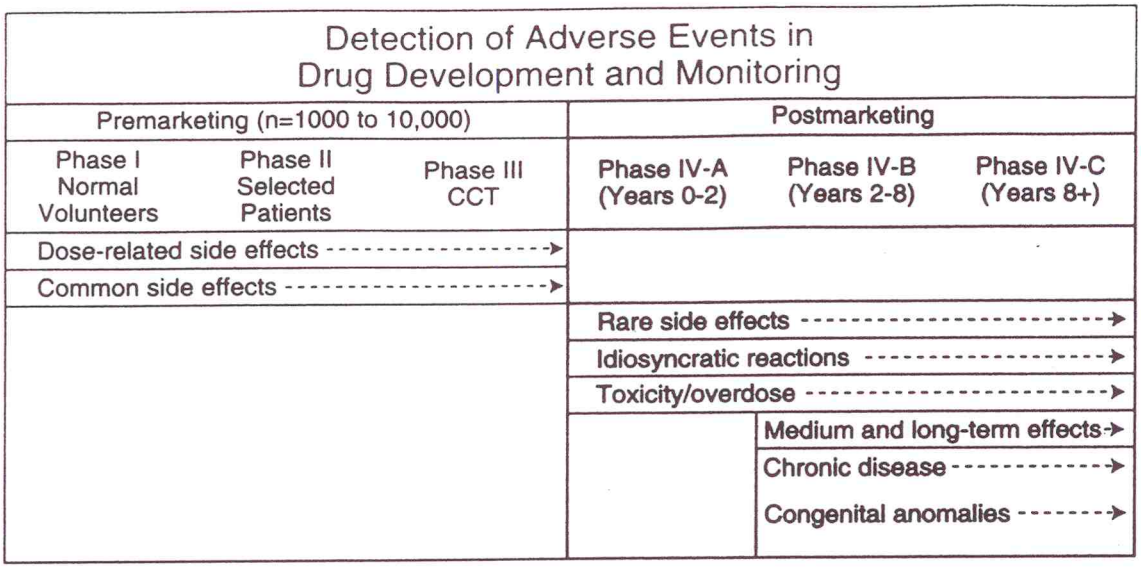

Fig 1.—Detection of adverse events in drug development and marketing. In the premarketing phase, the probability of detecting common and dose-related adverse events is highest. During later phases, the probability increases that rare adverse events, idiosyncratic reactions, and toxicity due to overdose or inappropriate use will be observed. From Rogers.[4]

label safety studies (Phase I), dose-finding trials (Phase II), CCTs (Phase III), and postmarketing surveillance (Phase IV). Some preliminary safety information is suggested by in vitro research into the drug's mechanism of action or interactions with various receptor types, although chemical activities seldom offer a complete picture of the clinical effects a drug may exhibit.

Animal Studies.—Animal research on drug safety is based on the assumption that adverse events in humans can be predicted from adverse events in animals, with no risk to patients. The limitations are twofold: first, the assumption is never fully verified, because drugs that are shown to be toxic in animals are rarely tested in humans. There may be compounds that are safe in humans but toxic in nonhuman systems that go untested. Second, in animal toxicology studies, negative findings cannot guarantee safety; no amount of experience with animals can ensure complete safety in humans.[4]

Open-Label Safety and Dose-Finding Studies.—In new drug development, animal studies are followed by open-label safety (Phase I) and dose-finding (Phase II) trials in humans. The strength of these studies is their ability to define safe dose levels, as they often follow a systematic dose-escalation algorithm. In addition, early studies are sometimes conducted without a placebo group. As a consequence, intensive inpatient monitoring characteristic of this type of research is used efficiently. The lack of a placebo group is, of course, also a limitation, as the contribution of placebo effects to reported adverse events cannot be measured. Phase I and II trials also share some of the same limitations as CCTs.

Controlled Clinical Trials.—The principal strengths of Phase III protocols include the incorporation of a placebo-treated group and a substantial increase in sample size. By comparing subjects who receive active agent with those treated with placebo, one can more clearly identify drug-attributable adverse effects. If an adverse effect occurs with equal frequency in groups treated with active drug and placebo, the adverse effect is not drug attributable. When the differences in frequency of adverse effects between groups are statistically significant, the causal inferences are extremely strong. In addition, well-designed CCTs use randomization to assure comparability of the treatment groups and double-blinding to minimize clinician and patient bias in assessing a drug's benefits and side effects.

While the strength of CCTs is their ability to support strong inferences about drug-attributable effects, a limitation is that they are insensitive to rare events.[4] Serious or life-threatening adverse effects may occur in only one person in 10 000 or even one person per million. To detect differences between an active agent and placebo in the rates of occurrence of such rare events, tens of thousands of subjects are required. Most clinical trials are too small to detect significant but rare adverse events.

Other limitations are inherent to the design of these trials. In order to optimize study rigor and safety, patients who have concurrent diseases or who are taking other medications are often ineli-

gible for study entry. Consequently, information about potential interactions between the study drug and other drugs or diseases is limited.[4] Restricted entry criteria also mean that the study results may not be generalizable to the total population that will use the drug. Acute treatment trials often examine one or several drug administrations; safety after multiple exposures requires more extended designs. In addition, CCTs are likely to be time-limited so that little can be learned about adverse events that occur after a long latency such as obstetrical effects or cancer.[4]

Postmarketing Surveillance.—The observation of adverse events after a drug is marketed (Phase IV data) falls into three categories: (1) spontaneous, voluntary reporting of events to the Food and Drug Administration (FDA) by physicians; (2) systematic monitoring via the collection of data on the nature, incidence, and severity of adverse events from panels of patients receiving the drug; and (3) hypothesis-driven monitoring.[4] The first two types of surveillance are undertaken to identify a broad range of adverse events, as a matter of routine, in new drug development. The third type of surveillance usually addresses specific causal hypotheses generated from case reports; these studies systematically capture particular kinds of adverse events in defined subgroups of treated patients (eg, those taking the study agent and another drug concurrently).

Postmarketing surveillance offers a number of unique advantages over the other forms of adverse event reporting. Because it reflects real-world drug usage patterns, previously unrecognized modifiers of drug efficacy and toxicity can be identified. Furthermore, it is the best method for identifying rare events, events that occur with long latency, and events that result from long-term or chronic drug administration. Because some adverse effects, such as the second-generation risk of cervical cancer due to diethylstilbestrol (DES), do not become apparent for very long periods, compounds that have been used safely for many years offer an extra degree of confidence.

Reporting bias is one important limitation of postmarketing safety data. With the spontaneous reporting system, the paperwork can be time-consuming. Health-care practitioners may not extend the effort to file a report, especially if the adverse event is not life-threatening.[5] Thus, minor adverse events are generally underreported, while serious events may be proportionally overreported.

A further drawback of postmarketing adverse event reporting lies in the weakness of the causal inferences. An unrelated effect may be wrongly attributed to a drug, or an adverse effect may not be recognized as being drug related.[5] In a clinical trial, the placebo group provides a useful method for estimating the background rate of adverse events in the absence of the study treatment. It is difficult to estimate background rates for postmarketing surveillance data. In addition, the reports that are submitted tend to be biased toward short-latency events, since the potential causal relationship to the drug is more readily identified.

Classification of Evidence on Safety.—A variety of systems have been utilized to evaluate the strength of scientific data and published reports. In the recently published American Academy of Neurology (AAN) Practice Parameter on the safety and efficacy of ET and DHE,[3,6] the published data on ET and DHE were evaluated and ranked according to predefined evidence classes (eg, Class I, Class II, Class III) (Table 1).[7] Though this classification of evidence is usually applied to efficacy data, it also applies to safety data.

Class I evidence is derived from one or more randomized CCTs and is usually required to support *practice standards* (generally accepted principles for patient management that reflect a high degree of clinical certainty).

Class II evidence is derived from well-designed observational research, such as case-control or

Table 1.—Levels of Evidence for Evaluating Safety and Efficacy

Level of Evidence	Nature of Evidence	Practice Parameter
Class I	Randomized, controlled clinical trials	Standards
Class II	Well-designed observational studies	Guidelines
Class III	Expert opinion, nonrandomized historical controls, individual case reports, surveillance data	Options

From Silberstein and Young.[3]

cohort studies and is provided by one or more such studies. Again, the role of drug in the development of an adverse event can be evaluated relative to a control group, although the lack of randomization leaves open the possibility that systematic differences in groups (confounding or bias) may influence study results. Class II evidence usually supports *practice guidelines* (recommendations for patient management that reflect moderate clinical certainty), but may support *practice standards* if the evidence is overwhelming and circumstances preclude randomized clinical trials.

Class III evidence is drawn from expert opinion, nonrandomized historical controls, individual case reports, and surveillance data. This type of evidence is the least reliable and usually supports *practice options or advisories* (other strategies for patient management for which the clinical utility is uncertain); in order to support *practice guidelines*, there must be a strong consensus of this type of evidence.[3]

Drug-Attributable Nausea in Migraine.—In the case of migraine, where certain adverse effects of the available drugs (particularly nausea) can mimic the signs or symptoms of the illness, it is critical to distinguish drug-attributable effects (eg, drug-attributable relief of nausea or drug-induced nausea) from disease-attributable effects (eg, disease-related nausea). Nausea is a very common symptom of migraine, occurring in from 60% to 90% of migraine sufferers,[8-11] and is moderate to severe in nature in many patients,[9,10] contributing to disability. Nausea begins with or after the onset of pain in most migraineurs and interferes with the ability to take oral medications.[9] In this discussion, exacerbation of nausea refers to either the development of new nausea or a measurable worsening of nausea (eg, from mild to severe). In studies that include a placebo group, drug-attributable nausea can be defined as the proportion of patients in the active treatment group whose nausea is exacerbated after treatment minus the proportion of patients in the placebo group whose nausea is exacerbated after treatment. Similarly, drug-attributable relief of nausea can be defined as the proportion of patients on active treatment whose nausea improves minus the proportion of patients on placebo whose nausea improves.

Summary.—The types of adverse events detected at each stage of drug development and marketing are summarized in Figure 1. The most rigorous information about drug-attributable adverse events comes from randomized CCTs, primarily because the randomized design ensures that the treatment groups and ascertainment methods are equivalent. Thus, if an adverse event occurs at an increased rate in the active treatment group, a causal role for the drug is strongly supported.

CLINICAL SAFETY EXPERIENCE WITH DIHYDROERGOTAMINE MESYLATE

In developing the AAN Practice Parameter,[3] the Quality Standards Subcommittee (QSS) of the Academy appointed an advisory committee of experts from the Headache and Facial Pain Section. This advisory committee reviewed the literature on both DHE and ET.[3] Of the 21 clinical studies involving DHE, few were controlled clinical trials (Class I); many were open-label and unblinded, and most did not compare DHE to placebo. The majority were conducted prior to the publication of the International Headache Society classification of migraine. Because many of the studies included in this review focused on efficacy issues, adverse effects were often not documented systematically.

There were no clinical studies of long-term intramuscular (IM) administration, and only a small number assessed repetitive intravenous (IV) administration (in the hospital setting, usually for the treatment of refractory migraine). Based on the existing data, it was concluded that "significant side effects were usually not present. The most common side effects [of IV DHE] were nausea and muscle cramps."[3] It was noted that nausea associated with intravenous DHE may be related to the rate of administration. Finally, though there is clinical experience with repetitive parenteral DHE, the advisory committee and the QSS of the AAN note that without close medical supervision, safety has not been established.

Studies in various animal species demonstrate that DHE is a more potent α-adrenergic blocker than ET, but much less potent in terms of uterotonic and emetic activity.[12] The peripheral vasoconstrictor effect of DHE is considerably weaker than that of ET; thus, it is difficult to induce experimental gangrene in the rat's tail with high doses of DHE, but easy with high doses of ET.[3,12] Animal toxicology studies also show that LD_{50} values are substantially higher for DHE than for ET,[13] indicating that DHE has a greater margin of safety. In addition, DHE exhibits a significantly weaker emetic effect than ET in dogs.[12]

The following summary reviews the published safety data on IM, IV, and intranasal (IN) administration of DHE.

Intramuscular Dihydroergotamine Mesylate.—*Open Trials.*—The use of intramuscular DHE to treat acute migraine in the office setting was investigated in an open trial of 24 patients.[14] No adverse

events were reported in any subject; in fact, among the 20 patients admitted with nausea, 17 (85%) experienced complete relief within 45 minutes of treatment, including 8 of 9 patients with moderate nausea. New-onset nausea was not reported.

A larger open trial of intramuscular DHE for this indication showed a dramatic reduction in nausea in the first hour following treatment.[11,15] At baseline, 62% of the 311 subjects reported nausea; this proportion decreased to 40% at 30 minutes and 30% at 60 minutes. Almost half the patients (both with and without baseline nausea) received an antiemetic at the study outset at the discretion of the treating physician. The higher proportion of patients with nausea at baseline in the group treated with antiemetics most likely reflects the fact that physicians were more likely to give antimetics to nauseated patients. Nausea improved both in patients who did and in those who did not receive an antiemetic (Figure 2). Adverse reactions such as pain at the injection site and leg cramps were experienced by less than 10% of patients; side effects remitted within 1 hour in all patients.

Intravenous Dihydroergotamine Mesylate.—*Controlled Clinical Trials.*—The most common adverse effect with intravenous DHE is nausea; however, again, drug-attributable effects should be distinguished from disease-attributable effects where possible. The incidence and severity of nausea with intravenous DHE may be related to the rate of administration and even to the type of headache treated. In a prospective, double-blind, crossover study, intravenous DHE was compared to placebo in 37 patients.[16] Although minor adverse effects were common, they tended to subside within 15 minutes. No serious adverse effects such as tachycardia, bradycardia, or peripheral vasospasm were reported. Despite prophylactic treatment with prochlorperazine, the most common adverse effects were nausea (7 patients following DHE and 1 patient following placebo) and vomiting (3 patients following DHE and none following placebo). In another prospective, randomized, double-blind trial comparing intravenous DHE plus metoclopramide with IM meperidine plus promethazine, adverse effects were infrequent in the DHE treatment group, consisting of a few patients with nausea, lethargy, or orthostasis; no patient experienced increased nausea.[17]

Open Trials.—While occasional reports of leg pain and paresthesias have appeared in the literature, as well as a few cases of angina and ergotism, they are very rare.[2] The predominant adverse effect reported in open trials is nausea.[18] This was confirmed in an open study of repetitive intravenous DHE use[19] in which nausea was the most common complaint, affecting 96 of 300 patients (32%). This figure represents only those patients whose nausea was increased over baseline levels. Other adverse effects included a feeling of chest tight-

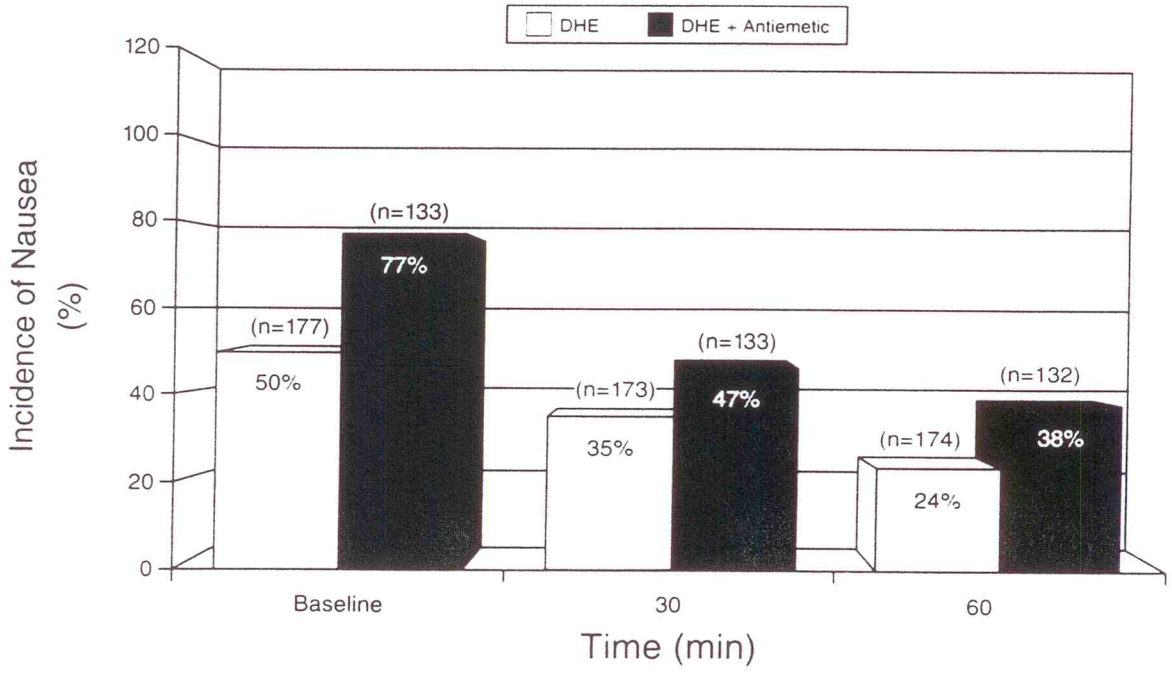

Fig 2.—Change (Δ) in nausea incidence as a function of the addition of a concomitant antiemetic to dihydroergotamine mesylate. Nausea improved both in patients who did and those who did not receive an antiemetic. From Winner et al.[11]

ness or a mild systemic burning sensation (8%), leg cramps (7%), vomiting (6%), and increased blood pressure (5%).

In general, other open trials have demonstrated few adverse effects; those reported occasionally include diarrhea, leg pain, and abdominal discomfort.[20]

Postmarketing Surveillance.—In recent years, spontaneous reports of adverse events possibly related to DHE use have included isolated cases of ischemic complications, nausea/vomiting, seizures, cardiac and noncardiac vascular disorders (vasospasm and infarction), parosmia, liver abnormalities, leg pain, chest pain, hypertensive crisis, injection site reactions, head and shoulder pain, and paresthesia.[21]

Intranasal Dihydroergotamine Mesylate.—*Controlled Clinical Trials.*—Worldwide experience indicates that intranasal DHE is well tolerated. The most frequent adverse effects are localized to the site of administration, the nasopharynx.[21-23] Adverse events reported in 1% or more of patients receiving intranasal DHE or placebo in double-blind clinical studies are shown in Table 2.[21] Most adverse events were transient, self-limiting, and did not require discontinuation of therapy.

Nausea and vomiting were recorded and classified as either a migraine-related phenomenon or treatment-related (DHE or placebo), as stipulated in individual study protocols. Both of these effects were reported in 4% or less of patients receiving intranasal DHE or placebo in clinical studies; there was no evidence that nausea or vomiting were exacerbated by intranasal DHE.[22,23] In the study of Ziegler et al,[23] nausea was significantly improved by intranasal DHE therapy.

Table 2.—Adverse Events Reported in 1% or More of Patients in Double-Blind, Placebo-Controlled Studies of Intranasal Dihydroergotamine Mesylate (DHE)

Body System/ Adverse Event	No. (%) of Patients Given Intranasal DHE, N=364	No. (%) of Patients Given Placebo N=371
Respiratory		
Nasal congestion	36 (10)	8 (2)
Throat discomfort	9 (2)	0
Nasal irritation	7 (2)	2 (<1)
Rhinorrhea	5 (1)	4 (1)
Gastrointestinal		
Nausea	14 (4)	5 (1)
Bitter/abnormal taste	9 (2)	0
Vomiting	5 (1)	3 (<1)
CNS		
Dizziness	3 (<1)	3 (<1)
Musculoskeletal		
Muscle pain	2 (<1)	0

From Sandoz Pharmaceuticals Corporation.[21]

Bitter or abnormal taste was reported in 2% of patients receiving intranasal DHE, but not in placebo-treated patients. Dizziness and muscle pain were reported in less than 1% of patients, regardless of treatment.

Only 1.3% of 1181 patients receiving intranasal DHE in worldwide clinical studies discontinued therapy due to adverse effects, and only 0.6% discontinued therapy due to local symptoms (nasal congestion, irritation, secretions, and/or obstruction).[21]

Summary.—Controlled clinical trials and open-label studies show that serious adverse effects following recommended doses of DHE are extremely rare, regardless of the route of administration.[3]

CLINICAL SAFETY EXPERIENCE WITH ERGOTAMINE TARTRATE

The AAN advisory committee review included 64 published reports on the adverse effects of ET, all of which consisted of Class III evidence, mostly anecdotal reports of only one or two patients.[3] The most common adverse effect was ischemia of the extremities, and there were several reports of anal or rectal ulcers reported with rectal suppository use. Most of the adverse events were associated with excessive dosage and/or long-term administration.

Acute Adverse Effects.—*Animal Studies.*—Studies in various animal species demonstrate that ET is a less potent α-adrenergic blocker than DHE, but much more potent in terms of uterotonic and emetic activity.[12] The peripheral vasoconstrictor effect of ET is considerably stronger than that of DHE; thus, it is easy to induce experimental gangrene in the rat's tail with high doses of ET, but difficult with high doses of DHE.[3,12] Animal toxicology studies also show that LD_{50} values are substantially lower for ET than for DHE,[13] indicating that ET has a lower margin of safety.

Controlled Clinical Trials.—In a review of several placebo-controlled trials, Dahlöf found that treatment with ET alone or in combination with caffeine was associated with increased severity of nausea and vomiting compared to placebo in five studies and was equal to placebo in one study.[24] Other reports confirm that nausea is among the most prominent acute adverse effects of ET: one controlled trial found that 20 of 48 patients (42%) treated with oral ET experienced worsening of baseline nausea or new nausea, compared to only 8 of 48 (17%) treated with placebo.[25] These data are consistent with the clinical observation that

nausea is usually the principal adverse effect limiting the use of ET.[1]

Single-Case Reports.—Other adverse effects are less common. Abdominal discomfort, acroparesthesias, ischemic complications, swollen fingers, and leg cramps have all been associated with acute administration of ET, but only in individual case reports.[1,3,26]

Chronic Adverse Effects.—*Animal Studies.*—The principal effect of chronic administration of ET in animals is peripheral ischemia due to vasoconstriction. In general, the dihydrogenated derivatives are less toxic than the original alkaloids in this regard; in fact, DHE exerts some protection against the vasoconstrictive effects of ET.[13] The other major adverse effect described after chronic administration of ET to animals is emesis.[13] In dogs, ET exhibits approximately 12-fold greater emetic activity than DHE.[12]

Single-Case Reports.—As noted above, most of the chronic adverse effects that have been reported in association with ET are due to excessive dosage or long-term administration. They include nausea, acroparesthesia, ischemic neuropathy, and anorectal ulcers following rectal suppository use.[1] Again, the evidence consists predominantly of single-case reports.

In addition, chronic daily intake can result in habituation and overuse headaches.[1,27,28] In this condition, regular doses of ET (two to three times per week) induce a physiologic and psychologic dependency, leading to a persistent, self-sustaining cycle of headaches and ergotamine intake.[3] A few instances of overt ergotism have also been reported,[1] manifesting as vasoconstrictive complications, ischemic symptoms such as tingling and numbness in the extremities, and occasionally as changes in mental status.

DIHYDROERGOTAMINE MESYLATE AND EGOTAMINE TARTRATE: PHARMACOLOGIC AND SAFETY PROFILES

While both DHE and ET effectively relieve the pain of migraine, a review of their published pharmacologic and safety data shows significant clinical differences between the two (Table 3). Ergotamine tartrate is a much stronger arterial vasoconstrictor than DHE, although the two agents are nearly equipotent as venoconstrictors.[3,28,29] However, DHE has somewhat stronger α-adrenergic antagonist activity.[3] Ergotamine tartrate is much more likely to produce nausea and vomiting, uterine effects, and rebound headache.[3,28,29] Coadministration of antiemetics with intramuscular DHE is not necessary, as they do not appear to reduce nausea any more than DHE alone (Figure 2).[11,15,30]

Table 3.—Dihydroergotamine Mesylate (DHE) Versus Ergotamine Tartrate (ET): Clinical Comparison

Safety/Efficacy Measure	DHE	ET
5-HT_1 activity	++	++
Arterial vasoconstriction	+	+++
Venoconstriction	++	++
α-Adrenergic antagonist activity	++	+
Nausea/vomiting	+	+++
Uterotonic effects	+	++
Pain relief	+++	+++
Headache recurrence	+	++
Rebound headache	0	++

0 indicates none, + minimal/mild effect, ++ moderate effect, +++ prominent/marked effect.

There has been some debate about the difference between recurrent and rebound headache. Recurrent headache may be defined as the reappearance or unmasking of ongoing pain when an acute treatment ceases to be effective. Rebound headache may be defined as new headache triggered by a drop in medication levels. Rebound may be related to changes at the molecular level following long-term overuse, and is therefore predictable in individual headache sufferers. Recurrent headache occurs as a less predictable event when the duration of a particular headache exceeds the duration of action of the treatment.

Contraindications.—Contraindications for DHE and ET are a consequence of their adverse effect profiles and include: pregnancy; renal or hepatic failure; coronary, cerebral, and peripheral vascular disease; hypersensitivity reactions; sepsis; and uncontrolled hypertension.[2,28,29,31] These drugs should not be given to patients likely to have asymptomatic coronary artery disease based on their risk factor profiles, without an adequate workup. Caution is advised in patients with basilar or hemiplegic migraine or migraine with prolonged aura. Coadministration of triacetyloleandomycin or erythromycin is also relatively contraindicated, as these antibiotics may decrease the metabolism of DHE or ET and thus increase plasma levels.[1,3,31]

With ET, special caution is suggested regarding concomitant use of methysergide or sumatriptan, based on anecdotal reports of increased risk of arteriospasm.[1,3,26] There is also some theoretical concern that ß-blockers might increase the α-adrenergic vasoconstrictive properties of both DHE and ET[1,3,29,31]; administering them within 24 hours of each other requires caution.

Ergotamine tartrate is also contraindicated in patients with prolonged aura[1] or vertebrobasilar migraine, due to the possibility of frank migrainous infarction. Of course, migraine itself, and especially migraine with prolonged aura, is a risk factor for stroke, particularly in young women, so distinguishing drug-attributable and disease-attributable cerebral infarction may be difficult.[32] A number of case reports in uncontrolled studies suggest that ET may also lengthen or aggravate the aura in individuals with prolonged aura.[3] Dihydroergotamine mesylate has not been reported to lengthen or aggravate the aura and, in fact, can be administered during the aura if necessary.

Ergotamine tartrate is not usually recommended for children; some pediatric neurologists recommend DHE alone or with antiemetics to treat migraine or intractable headache in children and adolescents.[3]

CONCLUSIONS

Both DHE and ET are safe and effective in the treatment of migraine with and without aura when used in recommended doses in adults who have no contraindications. Though both drugs are widely used, they have often been misused.[3] A comparison of their safety profiles reveals important differences that should influence clinical decision-making: DHE causes less arterial vasoconstriction. Indirect comparisons suggest that DHE causes nausea and vomiting much less frequently than ET.

In addition, overutilization of ET can produce chronic daily headaches refractory to usual abortive and preventive treatment. For this reason, the routine use of ET should be restricted to no more than 2 usage days per week; intravenous DHE is safe for repetitive use over 3 to 7 days in an inpatient setting.[3]

Although most of the safety evidence for these two drugs is Class III, nearly 50 years of clinical experience without major safety problems allows a high level of confidence in their clinical use. This review highlights the importance of postmarketing surveillance in accurately establishing a drug's safety profile; experience with other drugs has shown that rare adverse events or events that arise after a long latency period may not be detected by rigorous CCTs. Finally, CCTs may evolve to include endpoints other than pain relief; both therapeutic effects and adverse events may have important influences on the quality of life, ability to return to work, and the cost-effectiveness of treatment; factors which will become increasingly important in the future.[33]

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