

Intravenous dihydroergotamine for inpatient management of refractory primary headaches



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ABSTRACT

Objective: To determine dosing and side effects of dihydroergotamine as they affect outcomes in primary headache disorders.

Methods: We audited our use of dihydroergotamine for inpatient management of disabling primary headache, focusing on the commonly treated problems.

Results: Of patients interviewed, 114 had chronic migraine, 38 had cluster headache, and 11 had new daily persistent headache (NDPH). The mean time to follow-up for the entire cohort was 11 months. The data suggest that IV dihydroergotamine given over 5 days produces improvement in headache and disability in patients with migraine more than shorter courses. It does so with a cumulative effect after discharge up to a month. Giving more dihydroergotamine predicts a greater pain-free rate. Patients with cluster headache benefit from IV dihydroergotamine. In patients with NDPH, only those with migrainous symptoms responded and in that group the response was less robust compared with that seen in the chronic migraine cohort.

Conclusions: Intravenous dihydroergotamine is well-tolerated, and longer treatments produce a better outcome. Nausea is the most common adverse effect, and its control is associated with a better outcome. *Neurology*® 2011;77:1827-1832

GLOSSARY

DHE = dihydroergotamine; **ICHD-II** = *International Classification of Headache Disorders, 2nd edition*; **NDPH** = new daily persistent headache; **VAS** = verbal assessment scale.

Migraine¹ is a disabling brain disorder² with high prevalence.³ The inpatient use of IV dihydroergotamine (DHE)⁴ is regarded widely as a landmark advance in the management of patients with refractory migraine. Here we describe an evolution based on the emerging pharmacology and experimental science regarding DHE in the subsequent quarter century.

To mitigate the vascular effects of ergotamine, DHE was synthesized⁵ and began to be used in the mid-20th century.^{6,7} The optimal current route of administration of DHE is parenteral.^{8,9} A controlled trial in the emergency room demonstrated the utility of DHE in acute migraine.¹⁰ Contemporaneously, Raskin⁴ demonstrated that a 2-day course of IV DHE could terminate persistent migraine in the majority of patients. Such patients would probably now be classified as having chronic migraine,¹¹ and many had medication overuse. Subsequent large case series have confirmed the observation that repetitive administration of DHE is helpful in clinical practice.¹²⁻¹⁴ However, longer administration times than those initially proposed have not been explored in systematic observations on DHE administration alone.

We reasoned, based on laboratory data,^{15,16} that routinely using courses of DHE longer than 2 days would drive more into the brain and provide a more reliable outcome. We thus audited our experience with IV DHE over a 2-year period as dosing days varied to test these questions.

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Supplemental Data



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METHODS From 2001 until 2006, a total of 446 patients were admitted to the National Hospital for Neurology and Neurosurgery, London, for IV DHE. In the previous decade one of us (P.J.G.) had observed clinical responses and outcomes to DHE to evolve the regimen herein described.

Standard protocol approvals, registrations, and patient consents. The study was done as an audit of clinical practice in the United Kingdom and as such did not require ethics approval.

Patient contact and clinical diagnoses. To facilitate contacting patients to confirm the clinical data, the subpopulation of 163 patients were interviewed. These patients had been admitted for IV DHE in 2003–2004. Patients were contacted by one of us (A.J.N.) to review the data by telephone.

Diagnoses were assigned according to the *International Classification of Headache Disorders, 2nd edition* (ICHD-II).¹ The relevant revisions were incorporated for the final report,^{11,17} except for the new daily persistent headache (NDPH) syndrome, for which a syndromic approach was used.¹⁸ To assess outcomes, we asked patients to provide an overall assessment of the therapy's benefit as mild, moderate, or excellent.

The DHE protocol we have evolved is reported in the appendix at the end of this article and in appendix e-1 (on the Neurology® Web site at www.neurology.org).

Analysis. Data were collected for descriptive statistics. We had noted that nausea tended to be associated with a poorer outcome, so this hypothesis was tested using a generalized linear model approach (SPSS) to determine whether the presence of nausea, considered to be non-normal, and rated as absent, minimal, significant, or sufficient to cause the treatment to be stopped, influenced whether the patients became pain-free with treatment. We mirrored pain-free to treatment failure and treated this as a binary outcome with a binomial distribution, using a logit link function. To test whether there was a dose-response effect of DHE, pain-free as the dependent variable was analyzed with the dose of drug in a binary logistic model. Effects were considered significant if $p < 0.05$.

RESULTS The cohort consisted of 110 women and 52 men with a mean age of 45 years (SD 12 years). Of patients interviewed, 114 had chronic migraine, of whom 42 had had migraine with aura, 38 had cluster headache, and 11 had NDPH. One patient had migraine with aura and NDPH; both phenotypes were clear and we have included the patient for completeness in both groups, so the groups add to 163 patients. From an headache frequency viewpoint, all patients had headache on 15 days or more a month for the preceding 3 months; thus, most patients fulfilled the generic rubric of chronic daily headache.¹⁹ Not all patients gave us all information in all categories so the denominator is specified for the results reported in the sections below. During the same period, 4 patients with other primary headaches, notably one each of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, short-lasting unilateral neuralgiform headache attacks with cranial anatomic features,²⁰ chronic paroxysmal hemicrania,²¹ and

hemicrania continua,²² were admitted for DHE and are reported as cited.

DHE total dosage ranged from 8.25 to 11.25 mg over the admission, varying with side effects, logistics of admissions, and responses.

Migraine. For the patients with migraine ($n = 114$) the follow-up was 11 ± 2 months (mean \pm SEM). Of these patients, 84 of 113 (74%) reported at least some subjective benefit with half reporting moderate or excellent overall benefit. It is noteworthy that the mean duration of frequent migraine (15 days or more a month) was 21 ± 16 years in this group of patients who had had migraine for 26 ± 15 years, and their average attack frequency was 4 migraine days per week before treatment. Patients in this cohort had medically refractory migraine.²³

Efficacy. Of 114 patients, 76 (67%) reported headache attack freedom during treatment, and 85 (75%) reported headache freedom within 1 month of treatment completion. The effect lasted for an average of 28 days with an average reduction on their verbal assessment scale (VAS) pain score from 9 to 7 and a reduction in headache worsening from 4 to 2 per week. Of patients whose attacks returned to their original frequency or intensity ($n = 34$), this occurred in a mean of 61 ± 61 days. In contrast to those with worsening, background pain was eliminated in only 44 patients.

Disability. Of 114 patients, 29 reported less time off sick after treatment, whereas 57 reported increased activity. Of the cohort, 68 reported an increase in their sense of well-being after the treatment.

Medication changes. All patients admitted for DHE had any medication overuse stopped. Of 114 patients treated with DHE, preventive treatments were started in 81 at or, typically, about 1 week after discharge, the latter to avoid confusion with side effects associated with the hospitalization. The medicines used were amitriptyline ($n = 3$), flunarizine ($n = 19$), valproate ($n = 14$), topiramate ($n = 20$), gabapentin ($n = 13$), propranolol ($n = 6$), methysergide ($n = 5$), or phenelzine ($n = 1$).

Migraine with aura. There were no notable differences in the patients who had migraine with aura. Of the 42 patients, 29 (69%) who had had migraine with aura reported benefit from DHE, with 35 (83%) reporting headache freedom at 1 month. Similarly, adverse event patterns were no different in this group and are collated below.

Cluster headache. Of 38 patients admitted for DHE, 26 were men with a mean of 27 attacks per week before treatment. Four had episodic cluster headache and the remainder had chronic cluster headache.¹ Each patient had medically refractory cluster headache.²³ Six of the cohort had experienced migraine at other times, and this was not the disorder either ac-

tive or being treated by the admission. Of the cohort, 29 (76%) felt that the DHE had been beneficial overall, with half of that group regarding it as moderately beneficial or excellent.

Efficacy. Of the 38 patients, 32 reported headache freedom during treatment with DHE. This effect was seen during the stay. The mean time to return of attacks was 17 days with a mean reduction in VAS of 1 point and an essentially unchanged headache frequency when attacks returned, although the time to return of the pretreatment frequency was a mean of 66 days, ranging from 1 day at a minimum to 12 months ongoing at the time of audit.

Disability. Of the 38 patients, 10 reported reduced time off sick, whereas 18 had increased activity and 22 reported an increase in their sense of well-being.

Medication changes. Of the 38 patients, 17 were started on a cluster headache preventive treatment at discharge based on their history of chronicity and wish to do so. The medications used were verapamil ($n = 5$), methysergide ($n = 3$), lithium ($n = 3$), melatonin ($n = 2$), and topiramate ($n = 4$).

NDPH. Of 11 patients with NDPH, 7 had attack features that would in isolation fulfill the ICHD-II criteria for migraine, whereas 4 did not. All patients had primary NDPH, having had secondary causes, such as altered CSF pressure, excluded by history, physical examination, and extensive investigations including MRI with gadolinium and, where appropriate, lumbar puncture.¹⁸

Efficacy. Two of the 11 patients reported only mild benefit with DHE, and both of these had ICHD-II features of migraine in terms of their headache worsening. One felt that his overall well-being had been improved by the DHE. For both patients, the effects were seen within 4 weeks of treatment and lasted 21 and 30 days, respectively. Neither patient who benefited was started on a new preventive treatment at discharge.

Predictors of response. Considering pain-free as a binary dependent outcome, increasing the DHE dose was significant in a logistic model (Wald test, $\chi^2 = 16.0$, $p = 0.001$). Nausea rated at none, minimal, significant, or sufficient to stop treatment was a significant predictor of failure to become pain-free (Wald test, $\chi^2 = 12.6$, $p = 0.002$).

Adverse events. A range of side effects were reported in patients. None were particular to the underlying diagnosis. Nausea was the most commonly reported side effect in 94 patients and caused cessation of DHE in 6 patients. It was described as significant in a further 30 patients and minimal in 58 patients. No other side effect caused treatment to be stopped. The next most common adverse events were leg cramp in

46 patients and re-siting of the IV cannula in 46 patients. Limb pain with infusion was reported in 26 patients, and chest tightness was reported in 5. None of these latter patients and no other patients reported here had cardiac problems. The EKGs in patients with chest discomfort were unchanged. Diarrhea in 19 patients, constipation in 5 patients, and abdominal cramps in 16 patients were the important gastrointestinal adverse events. Two patients described shortness of breath that resolved spontaneously. Other side effects included eye pain, burning sensations in the head, lightheadedness, transient worsening of headache, belching, an abnormal sweet taste, insomnia, diarrhea, which was best not treated and settled quickly, and paresthesia. No side effects prolonged hospital stay, and none were life-threatening.

DISCUSSION The data support the notion that repetitive IV DHE is both effective and well-tolerated for the inpatient management of medically refractory primary headache. The data suggest that patients with chronic migraine, whether they have had migraine with aura or migraine without aura, will do equally well. Accompanying the efficacy in headache, there is an improvement in general indicators of disability. There are 3 relatively novel findings of this study. First, there is a delayed component to the improvement in migraine. This occurs too soon after discharge to be entirely accounted for by other medication changes, and it is also seen in patients in whom there was no medication change. Second, the data demonstrate a strong predictive effect of good control of nausea, highlighting a practical aspect of management. Third, the data support increasing the dose of DHE to 11.25 mg over 5 days based on increased pain-free responses. For cluster headache, DHE can provide a relative holiday in some patients,²⁴ and this can be used to initiate new preventive therapies. For NDPH, the outcome is less encouraging, and this is particularly true for nonmigrainous primary NDPH that remains a very significant management challenge. Finally, IV DHE is well tolerated with transient side effects that generally (except for nausea) do not stop treatment and in no cases lead to serious adverse events. The data support 5-day courses of IV DHE for the management of chronic migraine and cluster headache.

DHE has complex pharmacology⁵ and poor bioavailability.^{8,9} It has a long action in vitro²⁵ with high affinity for serotonin receptors and slow dissociation.²⁶ It was said not to enter the brain.²⁷ However, clinical experience in terms of side effects and its duration of action in some patients²⁸ led to detailed studies of its distribution in vivo using autoradiographic methods. These studies showed highly local-

ized binding of [³H]DHE in the brainstem.¹⁵ Furthermore, DHE when administered IV inhibits nociceptive trigeminovascular activation in vivo, although this action takes some time for onset.¹⁶ Taken together, these data suggested to us that a more substantial dose of DHE would render a better outcome. Moreover, given the complex pharmacology, its use as a single agent seemed important to evaluate.

An important in principle difference among current protocols and our newly reported protocol is the inherent purpose behind it. The aim of the Raskin protocol⁴ was to treat a patient for 2 days with IV DHE to render the patient headache-free before switching to rectal DHE and adding propranolol as a preventive treatment. Although this is an effective approach, as evidenced by its widespread adoption, censoring the IV administration to 2 days may have limited overall efficacy. We have prospectively tested this hypothesis and found that increasing the dose correlated with a greater likelihood of being pain-free. Moreover, the aim for pain-free status as part of the treatment, as echoed in other protocols,¹² belies the important pathophysiologic question of whether DHE can have modulatory effects in the medium term. Our current protocol emphasizes the use of a single active agent, DHE, to both minimize side effects and provide clarity of outcome. The new protocol is constructed as a treatment in its own right with the aim of the admission being DHE administration; reducing headache severity during inpatient status is a bonus but not the sole purpose. From a practical viewpoint, this approach relieves the clinician of the goal of pain freedom with the realistic expectation at discharge that improvement will continue.

The data demonstrate that nausea is the most common side effect, reported twice as often as leg cramps, and the most important because it predicts outcome. Nausea is probably a dopaminergic effect of dihydroergotamine. Various approaches have been used to treat nausea including prochlorperazine, metoclopramide, promethazine, domperidone, and 5-HT₃ receptor antagonists, such as ondansetron and granisetron. Of these, a curious issue is the use of domperidone, which is widespread in Europe and limited in the United States because of concerns about breast-feeding women using it in high dose to increase lactation. The US Food and Drug Administration is apparently concerned about the use of IV domperidone and its risk of cardiac mortality. It is a significant limitation to US practice that oral or suppository domperidone is not readily available for use in migraine. We observed no side effects of note with the use of domperidone in our cohort or indeed more broadly in a decade of previous practice with its use (P.J.G.). Our data emphasize the importance of good

control of nausea whereas treating with IV dihydroergotamine both for patient comfort and to ensure an optimal outcome. An important issue of note in the use of DHE is it can be somewhat troublesome in terms of being harsh on peripheral veins. This drawback often necessitates more than one IV access site per course of treatment. A further issue is transient worsening of headache. This is seen with triptans.²⁹ Remarkably, it often settles on the next infusion and can be mitigated generally by slowing the next infusion.

A significant issue from the first description of the use of repetitive IV dihydroergotamine in the hospital⁴ has been commencing another therapy or in later years the coadministration of other medicines. Treatments such as IV sodium valproate^{30,31} and IV corticosteroids,³² the latter being of limited value,^{33,34} are used sometimes with or soon after DHE. Indeed, given the issue of nausea, medicines used for that indication are a complication. The mainstay of therapy for nausea in the cohort we report has been domperidone and either ondansetron or granisetron, none of which has proven efficacy in migraine.^{35,36} Of the cohort of migraineurs treated in our group, preventive therapy was started in 81 (71%) usually about 7–10 days later. The delayed strategy was used to avoid mixing late side effects of hospital treatment with early side effects of the preventive treatment. The extent to which the delayed effect of improvement in headache we report is due to initiation of a preventive medicine is unsettled, although there was no obvious difference in this respect between those who commenced therapy and those who did not start a preventive therapy.

There are a number of caveats. There is no placebo control arm. It seems clear from studies of intranasal DHE³⁷ and inhaled DHE³⁸ that it is effective in migraine, and IM DHE is comparable to subcutaneous sumatriptan.³⁹ It seems unlikely that 80% of a cohort of long duration chronic migraine would improve within a month of treatment by chance alone. Second, the waiting time until treatment commenced exceeded the time until improvement occurred by a factor of 4–6. Nevertheless, some part of the improvement is the combination of regulation of medicines and the inpatient environment. Regarding disability, a limit of this report is that we could not systematically locate disability tools, notably Migraine Disability Assessment,⁴⁰ in the notes. We are left with the patient descriptions of well-being. Last, we cannot be sure the delayed effect is one of DHE or of the other medicines used.

We have audited our use of IV DHE for the inpatient treatment of patients with medically refractory primary headache disorders. The data suggest that IV

DHE given over 5 days produces improvements in headache and disability in migraine patients more than is seen with shorter admissions. The effect is dose-dependent, and there is a cumulative effect after discharge. Patients with cluster headache benefit from IV DHE. IV DHE is a valuable component of comprehensive headache management. After 60 years of use, understanding its mechanism of action will yield important insights into both migraine and cluster headache.

AUTHOR CONTRIBUTIONS

Dr. Nagy: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Gandhi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Ms. Bhola: drafting/revising the manuscript, acquisition of data. Dr. Goadsby: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision.

DISCLOSURE

Dr. Nagy and Dr. Gandhi report no disclosures. Ms. Bhola serves as a consultant for Neuralie Inc. Dr. Goadsby has served as a consultant for or served on a scientific advisory board for Advanced Bionics, Allergan, Inc., Almirall, Amgen, ATI, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, CoLucid Pharmaceuticals, Coherex Medical, Inc., Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson, Medtronic, Inc., MAP Pharmaceuticals, Inc. (makers of an inhaled form of DHE; this consultation period postdates the period of audit, the period of data collection and initial analysis), Minster Pharmaceuticals plc, Merck & Co., Inc., Neuralie Inc., NeurAxon Inc., NeuroTherapeutics Pharma, and Pfizer Inc.; receives royalties from the publication of *Mechanism and Management of Headache, 7th ed.* (Elsevier, 2005); and has received research support from GlaxoSmithKline, Neuralie Inc., Merck & Co., Inc., Johnson & Johnson, and MAP Pharmaceuticals, Inc.

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APPENDIX

Intravenous dihydroergotamine protocol

Generic name: Dihydroergotamine (DHE)

Available dosage form: 1 mg/1 mL

Indication/procedure: DHE is used in the treatment of medically refractory migraine and cluster headache

Admission

- Check any complicating medicines, such as triptans, 5-HT_{1B/1D} receptor agonists, have been discontinued
- Vital sign recording: heart rate, blood pressure, respiratory rate, temperature, oxygen saturation, upon admission and then prior to each DHE dose

Baseline

- EKG
- Weight
- Laboratory tests: complete blood count with differential, sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphate, prothrombin time, partial thromboplastin time, international normalized ratio
- Urine: for pregnancy (if female) and toxicology screen

Potential side effects/adverse events

- Nausea and vomiting, leg cramps, limb pain, chest discomfort, abdominal cramps, diarrhea, paresthesias
- Cardiovascular effects: vasospasms, tachycardia, bradycardia, hypertension
- Coldness of the skin and/or numbness and tingling of the extremities may indicate ergotism, which can include gangrene

Contraindications/warnings

- Peripheral vascular disease, coronary heart disease, history of cerebrovascular event, severe or poorly controlled hypertension
- Impaired liver or renal function
- Pregnancy

Adult dosing: intermittent IV infusion of DHE for patients older than 16 years or weighing more than 50 kg (it is essential to control nausea during

the use of dihydroergotamine; dose and rate of infusion may need to be adjusted as described below)

- The patient should be pretreated with ondansetron (ondansetron may be substituted for granisetron or other appropriate antiemetic drugs based on local clinical practice or particular clinical settings; the key practice point is to strive to minimize nausea) 4 mg IV every 8 hours, 30 minutes before each DHE infusion.
- If the patient has baseline nausea, consider using 8 mg ondansetron as premedication.
- When available, domperidone 10–20 mg orally or by suppository may be used.

Day 1: First dose: 0.5 mg in 100 mL of normal saline over 1 hour

If well tolerated, escalate dosing as follows:

Second dose, 8 hours later: 0.75 mg in 250 mL of normal saline over 1 hour

Day 2–5: Third and subsequent doses: 1 mg in 250 mL of normal saline over 1 hour every 8 hours for 10 doses with the goal of a cumulative total dosage of 11.25 mg (\pm 1 mg)

Pediatric dosing: weight-based dosing recommendations

Dosing should be adjusted and may require some individualization:

$$\text{Dose (mg)} = (\text{adult dose in mg}) \times (\text{patient weight in kg}) \times (0.014 \text{ mg})$$

Side effect management

- If the patient has moderate or severe nausea, even with the routine premedication with ondansetron, consider:
 1. Increasing the ondansetron dose, either by increasing the standing order to 8 mg every 8 hours or by adding 4 mg as an every 8 hour PRN dose to the 4 mg every 8 hours routine, standing order.
 2. Add in another antiemetic such as promethazine 12.5–25 mg IV every 12 hours as needed.
 3. Slowing the rate of infusion to over 2 or 3 hours.
 4. Not escalating the dose or if already at 1 mg, consider reducing the dose to the highest that the patient can tolerate.
- For muscle cramping or joint pain, consider naproxen 500 mg every 12 hours as needed