Dihydroergotamine (DHE) Critically Appraised Topic (CAT)

PICOT Question:
In the pediatric patient diagnosed with a refractory migraine, does dihydroergotamine (DHE) vs. meperidine (IM); or DHE nasal spray; or IV valproate acid vs. IM DHE and Metoclopramide decrease migraine pain or cure the migraine?

Clinical bottom line based on literature appraisal below:
Dihydroergotamine (DHE) is an ergot alkaloid which has been studied in the treatment of pediatric migraine headache. The safety and efficacy of DHE has been described in the pediatric and adult literature (Carleton et al., 1998; Edwards, Norton, Behnke, 2001; Fisher, Gosy, Heary, & Shaw, 2007). DHE is most effective for the refractory migraine headache which has failed other medications and interventions (Carleton et al, 1998; Edwards, Norton, Behnke, 2001; Fisher, Gosy, Heary, & Shaw, 2007).

All patients must be pre-treated with metoclopramide (Reglan) at a dose 0.15 mg/kg (maximum 10 mg) 10 minutes prior to DHE infusion. DHE is dosed as an intravenous infusion at an initial dose of 0.25 mg IV over 5-10 minutes (in children> 40 kg). If this dose is tolerated, a second dose of 0.5 mg should be infused over 5-10 minutes (Ogden, 2010).

Common side effects of DHE infusion include burning at the site of infusion, leg cramps, nausea, and vomiting. All female patients receiving DHE require an evaluation for pregnancy (beta-HCG). Limitations to DHE use include the following: uncontrolled hypertension, chest pain, basilar migraine, or use of monoamine-oxidase inhibitors (MAOI’s). DHE should not be used concomitantly (or within 24 hours) with “triptans” or cytochrome P-450 inhibiting (CYP450-3A4) medications (Gunn & Nechyba, 2002).

For further guidance regarding DHE use in pediatric migraine, please consult the on-call pediatric neurologist.

[GRADE = Strong recommendation / Low-quality evidence]

Search strategy implemented:

Search outcome:
7 papers were found. Of the studies found the following studies were not included in this review: LeJuenne et al. (1998) and Pradalier et al. (2004) compared DHE to medications not approved in the US; Ford and Ford (1996) was a case review; and Rapoport and Winner (2006) was a literature review but it was not systematic in nature. Of the three remaining studies, one included 14 yoa and greater and the others treated adults with migraine.

Synthesis of relevant studies:

<table>
<thead>
<tr>
<th>Author, date, country, and industry of funding</th>
<th>Patient Group</th>
<th>Level of Evidence (Oxford) / Strength of Evidence (GRADE)</th>
<th>Research design</th>
<th>Significant results</th>
<th>Limitations</th>
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IV Valporate acid vs. IM DHE and Metoclopramide

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
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| Edwards, K.R., Norton, J., Behnke, M. (2001). | Randomized Control Trial | Patients (N=40) with an International Headache Society (IHS) defined acute migraine (14 – 74 yoa) with or without aura | Intravenous valproate (Valproate) 500 mg over 15-30 minute infusion (n=20) or IM MCLP (Metoclopramide) 10 mg followed by IM DHE (Dihydroergotamine) 1 mg (n=20) in an alternating fashion. Patients receiving a triptan within 12 hours of presenting to the clinic were excluded from the study. | No dropouts were identified. Headache severity (0-3 scale, 0=no headache, 1=mild, 2=moderate, 3=severe) and associated symptomatology (photophobia, phonophobia, and/or nausea) were rated at baseline, and 15, 30, 45 minutes and 1, 2, 4, and 24 hours. The researchers included the 24 hour time point from the analysis but did not believe it to accurately reflected the effects of the treatment. It did not appear there was any significant difference between the two interventions:
- presence of a moderate-to severe headache at four hours was \( p = 0.36 \);
- nausea \( p = 0.26 \);
- photophobia \( p = 0.53 \);
- phonophobia \( p = 0.76 \).
- The recurrence of migraine headache pain and symptomatology at 24 hours was higher in the VPA group than the DHE/MCLP group however a \( p \) value was not reported. |

DHE vs. Meperidine

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<tbody>
<tr>
<td>Carleton SC, Shesser RF, Pietrzak MP, Chudnofsky CR, Starkman S, Morris DL, Johnson G, Rhee KJ, Barton CW, Chelly JE, Rosenberg J, Van Valen MK. (1998).</td>
<td>Prospective, multicenter, double-blind, convenience study sample occurring between 11/91 – 8/92.</td>
<td>156 adult patients (18 – 60 yoa) with at least one prior experience of a migraine H/A with or without an aura; patients had to have at least 4 vascular symptoms</td>
<td>Intramuscular dihydroergotamine (DHE) 1 mg IM or Meperidine 1.5 mg/kg and Hydroxyzine .70mg/kg IM was administered to both arms.</td>
<td>Compared the efficacy and safety of DHE and meperidine (MEP) using appropriate dosages, given IM to patients presenting to an ED with a CC of acute migraine headaches; a second dose of the same medication was given 60 minutes after the first dose if required. There was no significant difference between the two therapies at 30 and 60 minutes after medication administration. Nor were there any significant differences between the adverse events associated with the either therapy. This study raises the potential for not administering opioid medications in the treatment of migraines.</td>
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</table>

Pediatric patients were not included in this study. Presenting patients when study personnel were not in the ED were not approached. Study patients who were approached but declined study enrollment were not kept. The vascular scoring measure scale is not a validated measure. Physician rated drug effectiveness however patients were not asked to rate study effectiveness.
### DHE nasal spray


<table>
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<tr>
<th>Patients receiving DHE nasal spray (2.0 mg per H/A) between 1/1/2000 – 12/31/04 whose H/A did not respond to one or more triptan formulations</th>
<th>Oxford 4 GRADE: weak recommendation to use DHE</th>
<th>Retrospective chart review</th>
<th>For patients’ refractory to one triptan n=50; response to DHE treatment: complete 16; partial response 8; unresponsive 17; lost 9. 13 patients were lost to follow-up; however, these patients are included in the DHE response to DHE treatment. For patients’ refractory to two triptans n=25; response to DHE treatment: complete 9; partial response 2; unresponsive 11; lost 3. For patients’ refractory to three triptans n=22; response to DHE treatment: complete 8; partial response 3; unresponsive 10; lost 1.</th>
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**Study design.** The rationale for this study is due to the lack of data regarding the effects of DHE in patients who are refractory to triptan treatment. Patient response was based on patient recollection of how their headache responded to the DHE within the 4 week period. Across all levels of patients’ refractory to triptan therapy only 47% had a positive response to the therapy (complete or partial response); 39% had no response.

**Literature synthesized by:**
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**Clinical Bottom Line developed by Migraine CPG team.**

**Date created:**
05/09

**References:**


