### DIHYDROERGOTAMINE (DHE)

<table>
<thead>
<tr>
<th>THERAPEUTICS</th>
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<tbody>
<tr>
<td><strong>Brands</strong></td>
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<tr>
<td>- Migranal, DHE-45, Dihydergot</td>
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<tr>
<td><strong>Generic?</strong></td>
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<tr>
<td>Yes</td>
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<tr>
<td><strong>Class</strong></td>
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<tr>
<td>Ergot</td>
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<tr>
<td><strong>Commonly Prescribed For</strong></td>
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<tr>
<td>(FDA approved in bold)</td>
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<tr>
<td>- Acute migraine</td>
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<tr>
<td>- Acute cluster headache</td>
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<td>- Status migrainosus</td>
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#### How the Drug Works
- Agonism of 5-HT1B and D receptors similar to triptans, but with additional actions at 5-HT1A and 5-HT2A receptors. Also acts at norepinephrine (inhibits reuptake) and dopamine (including D2 and D3) receptors.
- Effectiveness and vasoconstrictive effects are likely related to agonism of 5-HT1B and D receptors. Blocking the transmission of pain signals from the trigeminal nerve to the trigeminal nucleus caudalis and preventing release of inflammatory neuropeptides is more likely the reason for effectiveness rather than vasoconstriction.

#### How Long until It Works
- Migraine/cluster: within 1–2 hours

#### If It Works
- Continue to take as needed. Patients taking acute treatment more than 2 days/week are at risk for medication-overuse headache, especially if they have migraine.

#### If It Doesn’t Work
- Treat early in the attack (before severe pain)
- Change to another agent

#### Best Augmenting Combos for Partial Response or Treatment-Resistance
- Migraine: nonsteroidal anti-inflammatory drugs (NSAIDs) or antiemetics are often used to augment response
- Cluster: oxygen (high-flow)
- Status migrainosus: combine with neuroleptics, ketorolac, diphenhydramine, intravenous valproate, intravenous magnesium, hydrate, and start preventive treatment

#### Tests
- Monitor blood pressure, especially after intravenous administration

### ADVERSE EFFECTS (AEs)

#### How Drug Causes AEs
- Actions on serotonin receptors cause vasoconstriction, nausea

#### Notable AEs
- Nausea, dizziness, paresthesias, chest or throat tightness
- Muscle pains, coldness, pallor, and cyanosis of digits
- Hypertension
- Altered taste, rhinitis (nasal spray), injection site reaction (IM)

#### Life-Threatening or Dangerous AEs
- Ergotism, cardiac (acute myocardial infarction, arrhythmia) or cerebrovascular events (hemorrhagic or ischemic stroke) are all rare

#### Weight Gain
- Unusual

#### Sedation
- Not unusual

#### What to Do about AEs
- Lower dose for nausea, stop for serious AEs

#### Best Augmenting Agents for AEs
- Pretreat before using (especially IV) with antiemetics
**DOSING AND USE**

**Usual Dosage Range**
- IV/IM up to 3 mg/day
- Nasal spray: up to 2 kits (4 mg each)/day

**Dosage Forms**
- Nasal spray: 4 mg/mL
- Injection: 1 mg/mL

**How to Dose**
- IV: give 0.1–1 mg 3–4 times daily as needed, usually for status migrainosus. Start with a test dose of 0.5 mg in adults. Reduce dose for significant nausea (more than 10 minutes) after dose. If tolerated and pain not relieved, increase to 1 mg dose. Give a maximum 3 mg/day. Give up to 21 mg for status migrainosus over 7 days.
- IM: give 0.5–1 mg as needed, up to 3 mg/day
- Nasal spray: give 1 spray (0.5 mg) in each nostril, repeat in 10–15 minutes up to twice a day

**Dosing Tips**
- Push IV form slowly over 3 or more minutes to avoid nausea
- Pretreatment with antiemetics is recommended for IV administration, but may not be necessary with IM or nasal spray. Pretreat with antiemetics (metoclopramide, droperidol, prochlorperazine) 30 minutes before DHE
- In patients with risk factors for coronary artery disease, give the first dose in a medical setting

**Overdose**
- Ergotamine poisoning may cause abdominal pain, nausea, vomiting, paresthesias, edema, muscle pain, cold hands and feet, and hypertension or hypotension. Confusion, depression, convulsions and gangrene may occur. Unclear if DHE poses similar risks

**Long-Term Use**
- Appears safe, but monitor blood pressure and vascular risk factors with extended use

**Habit Forming**
- No

**How to Stop**
- No need to taper

**Pharmacokinetics**
- Very low oral bioavailability (about 1%). Nasal spray has 40% bioavailability. Peak plasma level 30 minutes after IM injection, 45 minutes after SC injection, and less than 1 hour after intranasal use. Hepatic metabolism, mostly excreted in bile

**Drug Interactions**
- Use with caution with other vasoconstrictive agents, such as other ergot alkaloids or triptans
- Do not administer with potent CYP3A4 inhibitors, including macrolide antibiotics (erythromycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (delavirdine, ritonavir, nelfinavir, indinavir), or azole antifungals (ketoconazole, itraconazole, voriconazole). Less potent CYP3A4 inhibitors include saquinavir, nefazodone, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, and clotrimazole
- Nicotine may predispose to vasoconstriction
- May decrease effectiveness of nitrates

**Do Not Use**
- Uncontrolled hypertension, coronary artery vasospasm (Prinzmetal angina), pregnancy, breast-feeding, coronary arterial disease, or hypersensitivity to ergots

**SPECIAL POPULATIONS**

**Renal Impairment**
- Risks unknown. May be prone to hypertension and cardiac AEs

**Hepatic Impairment**
- Safety and effect of significant disease on drug metabolism unknown. Avoid in patients with severe disease

**Cardiac Impairment**
- Do not use in patients with hypertension or coronary artery disease
Elderly
- No known effects, but ensure safety before use (normal blood pressure, no coronary artery disease)

Children and Adolescents
- Not studied in children but likely safe

Pregnancy
- Category X. Associated with developmental toxicity and has oxytocic properties

Breast-Feeding
- Likely excreted in breast milk. Do not breast-feed after using

THE ART OF PAIN PHARMACOLOGY

Potential Advantages
- Effective in status migrainosus, with low risk for medication overuse and fewer AEs than ergotamine
- Effective in preventing migraine recurrence

Potential Disadvantages
- Compared to triptans: not available as oral form, as effective in episodic migraine and acute

Primary Target Symptoms
- Headache pain, nausea, photo- and phonophobia

Pearls
- An ergotamine derivative with better safety profile than other ergots: less arterial constriction, less nausea and emesis, less oxytocic, and less likely to produce ergotism and gangrene
- Safety with other potentially vasoconstrictive drugs (e.g. triptans) is unknown. In general do not use within 24 hours of triptans
- Compared with sumatriptan injection, less effective for cluster headache and less rapid onset of action, but with lower rates of headache recurrence
- May be useful in the setting of acute medication overuse. Medication overuse from opioids, barbiturates, or triptans can lead to treatment refractoriness
- An orally inhaled DHE (Levadex) may soon be available for acute migraine with efficacy comparable to IV treatment

Suggested Reading

