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Intravenous Dihydroergotamine (DHE) for the Treatment of Refractory Migraines

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Migraine headaches are reported to occur in 3 to 10% of older children and adolescents. They may interfere with school, work, or extra-curricular activities. Management of migraines generally includes nonpharmacologic measures to reduce stress and medications for both prophylaxis and treatment. Several recent reviews have addressed drug selection for routine prophylaxis and treatment of migraines in children.[1,2] Prophylaxis may include the use of non-steroidal anti-inflammatory agents, tricyclic antidepressants, antiepileptics (e.g., valproic acid, gabapentin, topiramate, levetiracetam, or zonisamide), antihypertensives, or antihistamines such as cyproheptadine. Treatment often incorporates multiple agents, such as analgesics, the triptans (sumatriptan, rizatriptan), prochlorperazine, or intranasal dihydroergotamine (DHE).

In adolescents and adults who fail to respond to traditional choices, intravenous DHE may provide relief. A 2000 practice parameter from the Quality Standards Subcommittee of the American Academy of Neurology recommends the use of DHE for acute treatment of moderate or severe migraine or mild-to-moderate headaches that have not responded to other therapies.[3] This issue of *Pediatric Pharmacotherapy* will review the pharmacology of dihydroergotamine and the steps to administering it in adolescents admitted with refractory migraines.

Mechanism of Action

Dihydroergotamine mesylate is one of the ergot alkaloids. It was synthesized from ergotamine tartrate in 1943. Although the precise mechanism of action of DHE is not well understood, its therapeutic effects are believed to result from its binding to serotonin 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors. Binding at these receptors produces the meningeal vasoconstriction and trigeminal inhibition of pro-inflammatory neuropeptide release which may lead to migraine resolution. Unlike other ergot alkaloids, DHE produces significantly greater constriction of venous capacitance vessels than of arteries. Dihydroergotamine also binds to a number of other receptors, including 5-HT_{1B} and 5-HT_{1F} receptors, which may augment its efficacy in migraines. It also binds at 5-HT_{1A} and 5-HT_{2A} receptors, as well as alpha and beta adrenergic receptors and dopaminergic receptors. Binding at these latter sites is responsible for many of the adverse effects observed after DHE administration.[4-7]

Clinical Experience

A number of studies have been conducted in adults to demonstrate the efficacy and safety of intravenous DHE. The current method of using repeated intravenous doses of DHE to treat severe migraines was introduced by Raskin in 1986.[8] Since that time, two placebo-controlled trials have been published using parenteral DHE, as well as comparison studies with butorphanol, chlorpromazine, dexamethasone, diazepam, ketorolac, lidocaine, meperidine, sumatriptan, and valproic acid.[7-9] Additional studies have demonstrated the benefit of parenteral or intranasal DHE in the management of menstrual migraine, migraine with cutaneous allodynia, medication-overuse headache, and migraine recurrence, and status migrainosus (a migraine lasting more than 3 days).[10]

In their 2005 review of the literature, Colman and colleagues evaluated 11 randomized controlled trials of parenteral DHE for the treatment of acute migraines in adults.[9] A DHE dose of 1 mg was used in all studies, administered by either an intravenous (IV), intramuscular (IM), or subcutaneous (SC) route. When administered with an antiemetic, DHE produced a better or comparable level of relief of headache pain, less need for rescue medication, and less nausea than comparison treatments in most studies. In the single study evaluating complete pain relief, the combination of DHE and metoclopramide was less effective than the combination of butorphanol, meperidine, and hydroxyzine. However, the combination of DHE and hydroxyzine or metoclopramide was

significantly better than other agents (ketorolac, meperidine with hydroxyzine, or valproate) in preventing migraine relapse within 48 hours.

While DHE has not been extensively studied in adolescents, its use is described in two studies and several recent reviews.[2,11-13] In 1994, Linder conducted a retrospective review of 30 children and young adults treated with intravenous DHE and oral metoclopramide for refractory migraines.[12] The children included in the study ranged in age from 8 to 22 years. Patients between 6 and 9 years of age were treated with DHE doses of 0.1 mg, while patients between 9 and 12 years received doses of 0.15 mg, and older children received 0.2 mg, with subsequent adjustment based on clinical response. All patients were given oral metoclopramide at a dose of 0.2 mg/kg (to a maximum of 20 mg) 30 minutes prior to each DHE dose. Doses were administered every 6 hours for a maximum of eight doses. Once the migraine resolved, patients were given one additional dose to prevent recurrence. The author reported an 80% response rate with minimal adverse effects. Effective DHE doses ranged from 0.1 to 0.5 mg. An average of five doses was needed to achieve migraine resolution (range 5-8).

In 2005, Charles and Jotkowitz reported the use of parenteral DHE in ten patients, seven adolescents and three adults, with chronic migraines.[13] The patients were treated with DHE, dexamethasone, and hydroxyzine once a week for three weeks. All seven adolescents experienced termination of their chronic migraine by the end of the treatment period. None of the three adults responded to treatment. The patients were followed for a period of 5 days to 4 years, depending on response. All of the adolescents converted to benign episodic migraines which did not require daily preventative therapy, termed a "carry-over effect" of their DHE treatment. The authors suggested that this regimen be considered in younger migraine patients as a potential means of avoiding long-term oral preventative therapy.

Pharmacokinetics

Dihydroergotamine may be administered intranasally, IV, IM, or SC. It is 93% protein bound, with an apparent steady-state volume of distribution of approximately 800 L in adults. Dihydroergotamine is metabolized by hepatic cytochrome P450 3A4 (CYP3A4) enzymes. Among the metabolites identified are several which are pharmacologically active. The major metabolite, 8'-hydroxydihydroergotamine, has a level of receptor affinity similar to that of the parent compound. The primary route of excretion is via the bile, with a clearance rate of 1.5 L/min. Less than 10% of a dose is excreted renally. Dihydroergotamine has a biphasic elimination pattern. The terminal elimination half-life in adults is approximately 10-13 hours, reflecting the slow disassociation of both parent drug and metabolites from their target receptors.[4-6]

Drug Interactions

As a result of its metabolism through CYP3A4, DHE may be subject to drug interactions resulting from inhibition of these enzymes. Clarithromycin, erythromycin, and troleandomycin, as well as protease inhibitors (e.g., indinavir, nelfinavir, and ritonavir), and azole antifungals such as ketoconazole and itraconazole may impair the metabolism of DHE, resulting in increased serum concentrations and a greater risk for toxicity. Less potent CYP3A4 inhibitors, such as clotrimazole, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, nefazodone, saquinavir, and zileuton, should be used with caution.[4,5]

Because of their potentially additive effects, DHE should not be administered with peripheral or central vasoconstrictors, beta blocking agents, or nicotine. In addition, it is recommended that DHE not be administered within 24 hours of sumatriptan or other ergot compounds, to avoid an additive risk for coronary artery vasospasm. Co-administration of DHE and selective serotonin reuptake inhibitors (SSRIs) may produce weakness, hyper-reflexia, and incoordination.[4-6]

Contraindications and Precautions

The use of DHE is contraindicated in patients with ischemic heart disease, coronary artery vasospasm, hypertension, sepsis, vascular disease, and severe renal or hepatic dysfunction. It should not be administered to patients with hemiplegic or basilar migraines. Based on evidence of intrauterine growth retardation and skeletal ossification in animal models, as well as the risk for fetal hypoxia associated with its oxytocic effects, the use of DHE is contraindicated during pregnancy. Women requiring intravenous DHE should be aware of the need to avoid pregnancy and should receive a pregnancy test prior to dose administration.[4,5,13]

Adverse Effects

The most common adverse effects associated with intravenous DHE administration are nausea and emesis, occurring in 10-70% of patients, diarrhea in 2-30%, muscle cramps in 5-20%, dizziness in 10-30%, and worsening or continued headache in 10-40%. Although common, these

adverse effects tend to decrease with subsequent dosing and only rarely result in the need to discontinue therapy.[14]

In their review, Colman and colleagues found a significantly greater incidence of nausea with DHE, even when administered with an antiemetic, than with comparison treatments. Other adverse effects associated with DHE administration include anxiety, dyspnea, flushing, rash, and diaphoresis. Additional symptoms of DHE-induced vasospasm, including numbness, coldness, pallor and cyanosis of the digits, may also occur. Discontinuation of therapy may be necessary in patients experiencing vasospastic adverse effects.[4,5]

Other consequences of severe dihydroergotamine-induced vasoconstriction, including intestinal and colonic ischemia, have been reported in pediatric patients as well as in adults.[4,15] In 2006, Padon and colleagues described intestinal ischemia in a 4 year old child who had been treated with DHE for cyclic vomiting syndrome.[15] Following an episode of vomiting, the patient was admitted and treated with 1 mg intravenous DHE every 8 hours, according to protocol. After 2 days, the patient developed worsening abdominal pain and hematochezia. Dihydroergotamine was discontinued on the 3rd hospital day, after 8 doses. On the following day, the patient developed signs of sepsis. Subsequent biopsy during colonoscopy revealed histiologic evidence of ischemic enteritis. The patient recovered without sequelae.

Although there have been no reports to date with intravenous DHE, administration of excessive doses of ergot alkaloids may lead to ergotism, a syndrome of pronounced nausea, emesis, severe paresthesias and muscle pain, severe cyanosis of the extremities with diminished or absent peripheral pulses, blood pressure changes, respiratory depression, and altered mental status. Dihydroergotamine should be stopped immediately if ergotism is suspected, and supportive care should be initiated.[4,5]

Dosing Recommendations

At the University of Virginia Children's Hospital, administration of intravenous DHE is done according to a protocol developed by the Neurology service.[8] In order to be eligible for treatment, patients must weight at least 40 kg and have failed traditional therapies. After evaluation to exclude contraindications, patients are evaluated for baseline vital signs and pain score. Premedication with haloperidol, lorazepam, acetaminophen, and diphenhydramine is recommended to reduce adverse effects. The patient's environment, including the bed position, lighting, and room temperature, are adjusted to his or her preference.

Dihydroergotamine is administered as an initial 0.5 mg dose given slow IV push over 2 to 3 minutes. If the patient responds, treatment may be repeated at 8-hour intervals. In patients who do not respond, the dose may be increased to 1 mg. Once the headache is improving, DHE dosing may be tapered to a 12-hour interval and continued for 2 to 3 more doses until full headache resolution.

Vital signs and pain scores are monitored every 10 minutes for the first 30 minutes after each DHE dose. The dose is held and the prescriber contacted for changes in blood pressure, chest pain, severe nausea, or emesis. A normal saline bolus is given in patients who develop mild hypotension with or without reflex tachycardia. The combination diphenoxylate and atropine (Lomotil®) is recommended for patients who develop DHE-induced diarrhea.

Availability and Cost

Dihydroergotamine mesylate injection (1 mg/mL, 1 mL vials or ampules) is available from several manufacturers. It should be stored at room temperature in a light-resistant container. The solution should only be administered if it is clear and colorless; it does not require further dilution.[4] The acquisition cost for parenteral DHE is approximately $35.00 per single vial or ampule.[16]

Summary

Intravenous DHE is a useful alternative for the treatment of patients with refractory migraines. Careful patient selection, close monitoring, and administration of a prophylactic antiemetic, such as lorazepam, can significantly reduce the adverse effects associated with its use.

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Pharmacology Literature Review

Cefepime in cerebrospinal fluid (CSF)

This study evaluated cefepime CSF concentrations in nine neonates (2 preterm, 7 term) being treated for suspected bacterial meningitis during a nosocomial outbreak of *Klebsiella pneumoniae*. There was no difference in mean serum trough concentrations between the preterm and term groups (32.2 mcg/mL and 35.3 mcg/mL, respectively). As in previous studies, the trough concentrations in these patients were substantially higher than those observed in older children and adults, suggesting increased crossing of drug into the CSF in neonates. Based on their results, the authors agree with the recommendation made by other investigators for a lower (30 mg/kg) cefepime dose for neonates. Ellis JM, Rivera L, Reyes G, et al. Cefepime cerebrospinal fluid concentrations in neonatal bacterial meningitis. **Ann Pharmacother 2007;41:900-1.**

Ganciclovir kinetics in neonates

The pharmacokinetic profile of intravenous ganciclovir and oral valganciclovir were evaluated in 24 neonates receiving a six week treatment course for symptomatic congenital cytomegalovirus infection. Using NONMEM techniques based on a one-compartment model, the authors developed the following parameter estimates: volume of distribution 1.15 L/kg, bioavailability 0.536, and terminal clearance 1.68 L/hr. It appears that this preliminary pharmacokinetic information will be used to develop a commercially-available oral valganciclovir solution. Acosta EP, Brundage RC, King JR, et al. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. **Clin Pharmacol Ther 2007;81:867-72.**

Top 200 drugs of 2006

The annual assessment of prescription drug sales has recently been published. The 10 most frequently prescribed products of the year were: atorvastatin (Lipitor®), two generic brands of hydrocodone/acetaminophen, extended-release metoprolol (Toprol-XL®), amlodipine (Norvasc®), generic amoxicillin, levothyroxine (Synthroid®), esomeprazole (Nexium®), escitalopram (Lexapro®) and generic albuterol. The top 10 products in terms of sales included atorvastatin (Lipitor®), esomeprazole (Nexium®), fluticasone/salmeterol (Advair Diskus®), darbepoetin (Aranesp®), lansoprazole (Prevacid®), epoetin (Epogen®), simvastatin (Zocor®), etanercept (Enbrel®), quetiapine (Seroquel®), and montelukast (Singulair®). Lamb E. Top 200 prescription drugs of 2006. **Pharmacy Times 2006;73(5):34-7.**

Treatment of cholestatic pruritus

The authors of this review discuss the available options for treatment of cholestatic pruritus in children. They include not only traditional agents, such as rifampin, phenobarbital, ursodiol, and bile-binding resins, but also potential future therapies. Cies JJ, Giamalis JN. Treatment of cholestatic pruritus in children. **Am J Health-Syst Pharm 2007;54:1157-62.**

Formulary Update

The Pharmacy and Therapeutics Committee did not meet in June. Meetings will resume in July.

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