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Promethazine: Recommendations for Safe Use in Children

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Promethazine was developed in 1946 and approved for use by the Food and Drug Administration (FDA) on March 29, 1951.¹ It is indicated for the treatment of allergic reactions, as an adjunct to epinephrine in patients with anaphylaxis, for sedation, for the treatment of nausea and vomiting from motion sickness or anesthesia, and as an adjunctive therapy to analgesics.^{1,2} Once widely used as a sedative in children, reports of promethazine-induced respiratory depression and apnea led to a gradual decline in its use and the eventual addition of a black box warning to its labeling in 2004.³ More recently, promethazine has been in the news after publication of several cases involving severe extravasation injury after intravenous (IV) and inadvertent intra-arterial injection. These cases led the FDA to add a second black box warning to its labeling in 2009.⁴ As a result, health care providers are once again faced with determining how to best utilize this medication in their practice. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of promethazine, as well as reports of toxicity associated with its administration, and describe measures to maximize its safe use in children.

Mechanism of Action

Promethazine is a phenothiazine antihistamine with sedative, antiemetic, and anticholinergic effects. It is a competitive histamine (H₁) and alpha-adrenergic receptor antagonist. Unlike other phenothiazine derivatives such as chlorpromazine, promethazine has limited effects at dopaminergic (D₂) receptors. It produces antiemetic effects but is not useful as an antipsychotic.^{1,2}

Pharmacokinetics and Pharmacodynamics

Approximately 80 to 90% of an oral promethazine dose is absorbed from the gastrointestinal tract. It undergoes significant first-pass metabolism, however, resulting in an absolute bioavailability of only 25%. In a study conducted in 37 adults, the average maximum plasma concentration after a 50 mg dose of oral promethazine syrup was 19.3 ng/mL and the time

to reach the maximum concentration was 4.4 hours.⁵ In contrast, rectal suppositories produced a lower maximum concentration, 9 ng/mL, with a longer time to reach the maximum, 6.7-8.6 hours. Promethazine is metabolized by hepatic cytochrome P450 enzymes (CYP2D6 and CYP2B6) to N-desmethylpromethazine. Both the parent compound and metabolite undergo further conversion to sulfoxide compounds. These metabolites are eliminated in the urine. The elimination half-life of promethazine in adults ranges from 9-16 hours after IV or intramuscular (IM) administration and 16-19 hours after oral or rectal administration. The wide range of half-lives reflects the differences in metabolic rate among CYP2D6 genotypes, ranging from ultrarapid to poor metabolizers.^{1,2,6}

The clinical effects of promethazine generally occur within 5 minutes after an IV dose and 20 minutes after an IM dose in adults. The average duration of action is 4 to 6 hours, but effects may persist for up to 12 hours.^{1,2} The pharmacokinetics and pharmacodynamics of promethazine have not been studied in children.

Use in Children

The use of promethazine as a sedative agent spread rapidly after its approval. In children, the combination of meperidine (Demerol®), promethazine (Phenergan®), and chlorpromazine (Thorazine®), commonly referred to as DPT or the lytic cocktail, became popular in the 1970s for procedural sedation. While often producing a satisfactory level of sedation, the combination was associated with respiratory depression, hypotension, extrapyramidal effects, and prolonged recovery times. Growing concerns over the toxicity of the three drugs and the availability of shorter-acting sedatives, led the American Academy of Pediatrics to publish a statement in 1995 discouraging the use of these agents as sedatives in children.⁷

While its use as a sedative has declined, promethazine remains one of the most widely used antiemetics in the United States. Although

the FDA recommends that promethazine **not** be used for the management of uncomplicated vomiting in children, it is frequently used in the outpatient setting.^{1,2} In a retrospective study of prescriptions written for pediatric patients with presumed infectious gastroenteritis during 2005, Pfeil and colleagues found that promethazine was the most frequently prescribed antiemetic in the United States.⁸ In this analysis of over 2 million prescriptions written for children < 10 years of age, 23% received a prescription for an antiemetic, with over 90% written for promethazine. In comparison, ondansetron, a safer alternative, was prescribed for only 3%.

Contraindications and Precautions

Respiratory Depression and Apnea

The potential for promethazine to produce severe respiratory depression and apnea in infants was first suggested by Khan and Blum in 1979.⁹ After seeing four victims of sudden infant death syndrome (SIDS) who had received promethazine, the authors evaluated 52 more SIDS cases, finding that 23% of the SIDS victims and 22% of near-miss SIDS patients had received a phenothiazine prior to the event.¹⁰ Additional cases were gradually added to the literature confirming the relationship between phenothiazines and respiratory adverse effects in infants. In 1991, Buck and Blumer described promethazine-induced apnea in a 2-month-old girl.¹¹ Upon taking a medication history from the mother, the authors identified an episode of apnea related to DPT in one of her siblings.

Several mechanisms have been suggested for promethazine-induced apnea including a direct central respiratory depressant effect, antagonism of central dopaminergic receptors resulting in increased levels of endogenous opioids capable of producing respiratory depression, or potentiation of the respiratory depressant effects of concomitantly administered opioids. Respiratory depression may be more pronounced in infants, particularly premature neonates, who may not be able to metabolize promethazine as well as older children and adults due to lower levels of CYP2D6 activity or reduced sulfur stores.¹¹

In 2000, the FDA strengthened the warning section of the prescribing information for promethazine to state that it should not be used in children less than 2 years of age.³ In spite of this warning, cases of severe respiratory depression continued to be reported. In an evaluation of cases reported to the FDA between 1969 and 2003, there were 22 cases of respiratory depression reported in this age group, including 7 deaths. As a result, the FDA added a black box warning to promethazine in November 2004, making use in children less than 2 years a contraindication.

Tissue Injury from Parenteral Administration

Promethazine injection has a pH of 4 to 5.5 and IV administration may lead to severe injection site reactions. These range from burning, pain, and erythema at the site of injection to thrombophlebitis, venous thrombosis, abscess formation, tissue necrosis, and gangrene. Nerve injury, including paralysis, has been reported after parenteral administration into or near a nerve. Subcutaneous (SC) administration has also resulted in chemical irritation of the tissues with subsequent necrosis. The SC route is now contraindicated.^{2,3,13,14}

Inadvertent intra-arterial injection, when IV administration was intended, has resulted in severe tissue injury resulting in the need for fasciotomies, debridement, skin grafting, and amputation of digits or limbs. Initial reports of this adverse effect date back to the late 1960s, but only recently have garnered wider attention. On August 10, 2006, the Institute for Safe Medication Practices (ISMP) published a report entitled "Action needed to prevent serious tissue injury with IV promethazine."¹² This report described 4 cases of severe tissue injury, including a case from 2004 of a professional guitar player whose arm had to be amputated after inadvertent intra-arterial injection of promethazine.¹³ To further disseminate this information, the FDA circulated the ISMP report, including its recommendations for safe promethazine administration, in December 2006 and again in February 2008.¹⁴

On March 4, 2009, the US Supreme Court upheld an earlier ruling that Wyeth, one of the manufacturers of promethazine, provided inadequate warnings of this risk and awarded \$6.7 million in damages to the guitar player described in the ISMP report. Writing for the majority, Associate Justice John Paul Stevens noted that these risks had been known to the company since 1967 and should have resulted in stronger warnings and a contraindication for IV push administration.¹⁵

In spite of these reports and attempts to educate health care providers through changes in product labeling, patients continue to be injured by unintentional intra-arterial administration. In the May-June 2009 issue of *The Journal of Hand Surgery*, Foret and colleagues described two cases of women given promethazine in the Emergency Department.¹³ One was treated for emesis related to gastroenteritis and the other for pain and nausea during treatment for sickle cell crisis. In both cases, promethazine was injected into a line believed to be a peripheral IV. In one case, the drug was injected into the brachial artery and in the other, the radial artery. The first patient required amputation of all 5 digits of the affected hand. The second patient required

amputation of the index finger. Although the authors underscore the lack of established treatment guidelines, based on their cases and a review of the literature, they suggest immediate consultation with a hand surgeon, anticoagulation with heparin, elevation of the extremity, and consideration of a stellate ganglion blockade. Relief of arterial spasm with calcium channel blockers, papaverine, or local anesthetics is also recommended, as well as thrombolytics for cases with impaired blood flow.

On September 16, 2009, the FDA notified health care providers that manufacturers of promethazine injection would be required to modify the drug's prescribing information to include a black box warning highlighting the risk for serious tissue injury with incorrect administration.⁴ In addition, the Dosage and Administration section of the prescribing information would have been modified to include the ISMP recommendations.

Other Adverse Effects

In clinical trials of promethazine in adults and children, the most frequently observed adverse effects are sedation, somnolence, blurred vision, dry mouth, and confusion. Extrapyramidal adverse effects may present as oculogyric crisis, torticollis, and tongue protrusion. These effects are typically the result of an acute overdose, but may occur after therapeutic doses. Other adverse CNS effects include tinnitus, akathisia, ataxia, fatigue, altered mental status, diplopia, insomnia, tremors, seizures, paradoxical agitation, and hallucinations. Promethazine may produce alterations in heart rate or blood pressure, dermatitis, photosensitivity, leukopenia, thrombocytopenia, and agranulocytosis. Jaundice and angioedema have also been reported with promethazine.^{1,2,16}

Like other agents in its class, promethazine has been associated with neuroleptic malignant syndrome (NMS), when administered as a single agent or in combination with antipsychotic agents. It is a rare adverse effect, but has been reported in children. Brown and colleagues described NMS in a 7 year old girl given three 12.5 mg doses of rectal promethazine given in the postoperative setting.¹⁷ Symptoms developed within 4 hours of the second dose and included agitation, disorientation, hyperpyrexia, tachycardia, tachypnea, abnormal jaw movements, and muscle rigidity. She recovered after a prolonged hospital admission. Patients and their families should be aware of the symptoms of NMS and the need to seek immediate medical attention.

Promethazine may lower the seizure threshold and should be used with caution in patients with a known seizure disorder or who are receiving

other medications known to increase seizure risk. It may also produce or worsen bone marrow suppression and should be used with caution in patients receiving other agents known to produce this effect. Promethazine injection may contain sodium metabisulfite and should be avoided in patients with known intolerance to sulfites. As with other anticholinergics agents, promethazine should be used with caution in patients with narrow-angle glaucoma.^{1,2}

Drug Interactions

Promethazine may prolong or potentiate the effects of other CNS or respiratory depressants. Concomitant doses of opioids or barbiturates should be decreased by ¼ to ½ of the usual dose to avoid additive effects. Administration with anticholinergics may also produce additive effects. The vasopressor effects of epinephrine may be reversed by promethazine. As a result, patients experiencing promethazine-induced hypotension should be treated with other supportive measures. Administration of drugs which inhibit CYP2D6, including darunavir, monoamine oxidase inhibitors, paroxetine, pramlintide, and sibutramine, may increase promethazine concentrations and lead to an increased risk for extrapyramidal effects. These agents should be used in combination only with close monitoring. Use of drugs known to prolong the QT interval, such as cisapride or a fluoroquinolone, with promethazine may result in cardiac arrhythmias, including torsades de pointes. These combinations should be avoided. The effects of promethazine may be decreased by concomitant use of acetylcholinesterase inhibitors or peginterferon alfa-2b.^{1,2}

Dosing Recommendations

As previously noted, the FDA recommends that promethazine **not** be used for the management of uncomplicated vomiting in children and that it be restricted to use in cases of prolonged emesis where the etiology is known. For patients requiring treatment for vomiting associated with chemotherapy or surgery, a 5-HT₃ receptor antagonist such as ondansetron is preferred. If promethazine is considered necessary, treatment should begin with the lowest dose within the dosing range and titrated based on response.^{1,2}

The recommended pediatric dose of promethazine to provide an antihistamine effect is 0.1 mg/kg (maximum 12.5 mg) given by mouth every 6 hours as needed. A larger 0.5 mg/kg dose may be given at bedtime. The pediatric antiemetic dose is 0.25-1 mg/kg/dose (maximum 25 mg) given PO, IM, IV, or PR every 4 to 6 hours as needed. For activities known to produce motion sickness, a 0.5 mg/kg oral or rectal dose (maximum 25 mg) may be given 30 minutes to 1 hour before the event and then every 12 hours as needed. The pediatric sedative dose

is 0.5 -1 mg/kg (maximum 50 mg) given PO, IM, IV, or PR every 6 hours as needed. Standard adult doses range from 6.25-25 mg.¹⁸

Oral promethazine may be administered with food or milk to decrease stomach upset. For patients who cannot be treated by the oral or rectal route, the preferred method for parenteral administration is deep IM injection.^{1,2} As previously described, IV administration is not recommended. If IV use is necessary, the ISMP recommends that the contents of a 25 mg/mL 1 mL ampule be diluted with 10-20 mL of normal saline to make a 2.5 mg/mL or 1.25 mg/mL concentration for administration.¹² The dose should be infused through a large vein (not in a hand or wrist) into a running IV over 10-15 minutes to minimize the risk for tissue injury. The University of Virginia has adopted all of these safety recommendations.

Availability

Promethazine is available as the brand name product, Phenergan® (Wyeth Labs, marketed by Baxter Healthcare), and as generic products. It comes as 12.5 mg, 25 mg, and 50 mg oral tablets, 12.5 mg, 25 mg and 50 mg rectal suppositories, a 6.25 mg/5 mL (1.25 mg/mL) oral syrup, and 25 mg/mL and 50 mg/mL injection sold in 1 mL ampules. It is recommended that health care providers carefully evaluate the need to stock the 50 mg/mL injection as it has a greater potential for producing severe tissue injury. If the 50 mg/mL product is stocked, it should be restricted to deep IM injection only. Promethazine must be kept in light-resistant containers. The suppositories should be refrigerated; all other forms may be stored at room temperature.^{1,2}

Summary

Promethazine has a long history in pediatric medicine as an antiemetic and sedative. Recent concerns over the continued reports of significant respiratory depression and severe tissue injury with the injection have led many practitioners to reconsider its use. Careful patient selection and attention to administration techniques are important tools to reduce adverse effects. Pediatric health care providers should keep abreast of new information that may further improve the safety of using this drug in children.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/26/10:

1. Rosuvastatin (Crestor®) was added to the Inpatient Formulary.
2. Methocarbamol injection (Robaxin®) and triamcinolone acetonide (Azmecort®) were deleted due to lack of use. Pancrelipase powder (Viokase® powder) was removed because it is no longer being manufactured.

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