

## Safety in Using Promethazine (Phenergan)

First approved by the U.S. Food and Drug Administration (FDA) in 1951, promethazine (Phenergan) is a medication in common use today. However, despite its familiarity, its use is not without risks. In particular, reports submitted to PA-PSRS illustrate that patients in Pennsylvania are being harmed when promethazine is prescribed intravenously.

### The Drug

Promethazine is a phenothiazine derivative that possesses histamine H1-blocking, anti-muscarinic, sedative, anti-motion sickness, anti-emetic and anticholinergic effects. Indications for promethazine include the amelioration of allergic reactions to blood or plasma or, after acute symptoms have been controlled, as an adjunct to epinephrine and other standard measures in anaphylaxis. Other uses include sedation, relief of apprehension, active treatment of motion sickness, and prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery. It is also used in surgical situations (e.g., repeated bronchoscopy, ophthalmic surgery) with reduced amounts of meperidine or other narcotic analgesic as an adjunct to anesthesia and analgesia. Its clinical effects are apparent within five minutes of an intravenous (IV) injection.<sup>1,2</sup> The duration of action is 4 to 6 hours, although effects may persist up to 12 hours.

Promethazine is formulated with phenol and has a pH between 4 and 5.5.<sup>3</sup> Although manufacturers' product labeling refers to promethazine as an irritant drug, some sources consider it a lesser-known vesicant that can be highly caustic to the intima of blood vessels and surrounding tissue.<sup>2,4-7</sup> Although deep intramuscular injection into a large muscle is the preferred parenteral route of administration, promethazine's product labeling states that it may be given by slow IV push, which is the typical method of administration in most hospitals.<sup>8</sup>

### The Risks

Because of its longstanding use, clinicians have grown comfortable with promethazine despite its serious risks.<sup>3</sup> There have been numerous reports submitted to PA-PSRS regarding severe, tragic or local injuries after infiltration or inadvertent intra-arterial injection. These types of injuries include the following: tenderness at intravenous site, burning, erythema, pain, induration, edema, severe spasm of

vessels, venous thrombosis, nerve damage, paralysis, abscess, tissue necrosis, and gangrene.<sup>5</sup> Use of promethazine can result in severe tissue damage, regardless of the route of parenteral administration, although IV and inadvertent intra-arterial or subcutaneous administration results in more significant complications, including arteriospasm and the potential for gangrene.<sup>8</sup> There have been cases that required surgical intervention, including fasciotomy, skin graft, and even amputation.

While the extent of this problem is unknown, numerous reports submitted to PA-PSRS and the United States Pharmacopeia-Institute for Safe Medication Practices (ISMP) Medication Errors Reporting Program (MERP); articles in professional literature; news of lawsuits in the media; and communications on various Internet listservs and message boards suggest that patient harm may be occurring more frequently than previously recognized.<sup>8</sup> Three examples from PA-PSRS include the following:

*Following a dose of Phenergan for nausea, the patient voiced complaints of IV site pain, which was red upon inspection and very tender to touch. The follow-up call, one week after discharge, revealed continued pain at the site with darker discoloration and difficulty holding onto things.*

*One hour following an IV injection of Phenergan, the patient stated her left arm felt tight. Upon inspection, the patient's left hand was larger than the right, and swelling and small blisters were noted on her hand seven hours later. The following morning, her entire arm was swollen. Patient was discharged but was readmitted three days later with edema*

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## Safety in Using Promethazine (Phenergan) (Continued)

*and pain in her left arm and with blackened fingertips. Her treatment is ongoing.*

*A postoperative patient returned to the inpatient unit with left-hand discoloration and complaints of tingling in her arm; her fingers and palm became purple and cool to touch, shortly after receiving Phenergan IV in the recovery room. Several days later, the hand*



Figure 1. Woman Develops Gangrene after Receiving Phenergan IV. Image provided courtesy of ISMP.



Figure 2. Promethazine Extravasation Causes Gangrene in Man's Fingers. Image provided courtesy of ISMP.

*swelling subsided; the hand was less tender, without tingling, and the patient improved.*

Similar cases have also been reported to MERP. In one example, a 19-year-old woman went to the emergency department (ED) with flu-like symptoms and received the branded drug Phenergan IV. During the injection, she complained of pain in the arm that received the medication, and was tempted to pull out her IV line. After the injection, she continued to experience arm pain and said that "something was wrong." Later, the patient's arm and fingers became purple and mottled (see Figure 1). The patient remained in the hospital for 30 days, during which she developed gangrene and required the amputation of several fingers.<sup>8,9</sup>

Another patient received 12.5 mg of promethazine into an IV site in the hand. During the injection, the patient complained of extreme burning, but the nurse continued administering the medication. The patient developed an area of necrosis on his hand, eventually requiring skin grafting and physical rehabilitation.<sup>10</sup> (See Figure 2.)

### Safe Practice Strategies

According to the promethazine package insert, "Proper IV administration of this product is well tolerated, but use of this route is not without some hazards."<sup>4,10</sup> It should be administered cautiously and it requires monitoring as some of its side effects may not be apparent for several days. To reduce the risk of these hazards, manufacturer labeling recommends the following:

- Give the drug in concentrations no greater than 25 mg/mL.
- Administer the drug at a rate no greater than 25 mg/minute.
- Inject the drug through the tubing of an infusion set that is running and known to be functioning satisfactorily.
- If the patient reports burning at the injection site, stop the IV immediately to evaluate for possible arterial placement or perivascular extravasation.

In April 2006, FDA issued an alert and black box warning for use of promethazine in children younger than two years of age, as it has been associated with cases of breathing problems, which sometimes resulted in death.<sup>11</sup> In addition, caution should be

## Safety in Using Promethazine (Phenergan) (Continued)

exercised in giving promethazine in any form to children age two and older. The labeling on all brand name and generic products has been changed to reflect these strengthened warnings. Promethazine is also contraindicated for patients in comatose states and those who have demonstrated an idiosyncratic reaction or hypersensitivity to promethazine or other phenothiazines.

Sharing the following safe practices in using promethazine with physicians, pharmacists, and nurses may facilitate discussion. While these suggestions may not be feasible in every facility, they can assist with the evaluation of current practices. Along with the manufacturer recommendations, the following strategies may help to prevent or minimize tissue damage when giving IV promethazine:<sup>1,4,5,8,9-13</sup>

- Do not stock promethazine in concentrations greater than 25 mg/mL, because this is the highest concentration of promethazine recommended by the manufacturer to be given IV.
- Limit the dose, especially for elderly patients, and consider 6.25 to 12.5 mg of promethazine as the starting IV dose. Hospitals have reported that these smaller doses have proven quite effective.
- During preparation, dilute the 25 mg/mL concentration to reduce promethazine's vesicant effects and enable slow administration. For example, dilute the drug in 10 to 20 mL of normal saline if it will be administered via a running IV, or prepare the medication in minibags containing normal saline if there is time for pharmacy to dispense them as needed for individual patients. Extravasation can also be recognized more quickly when promethazine is diluted than if the drug is given in a smaller volume.
- Administer the medication through large patent veins (i.e., preferably via a central venous access site, absolutely no hand or wrist veins).
- Check the means of administration. According to the package insert, aspiration of dark blood does not preclude intra-arterial placement of the needle because blood can become discolored upon contact with promethazine. Use of syringes with rigid plungers or small bore needles might obscure

typical arterial backflow if this is relied upon alone.

- Administer IV promethazine slowly over 10 to 15 minutes.
- Revise preprinted order forms to ensure orders for promethazine reflect the safety measures listed above.
- Educate patients before administration of the drug. Request patients to immediately alert caregivers to burning or pain sensations during or after the injection.

Alternatives	
Ondansetron (Zofran)	an antiemetic, 5HT3 receptor antagonist
Prochlorperazine (Compazine)	an antiemetic, phenothiazine
Metoclopramide (Reglan)	GI stimulant, an antiemetic
Dolasetron (Anzemet)	an antiemetic, 5 HT3 receptor antagonist
Granisetron (Kytril)	an antiemetic, 5HT3 receptor antagonist
Droperidol (Inapsine)	an antiemetic, anesthesia adjunct
Trimethobenzamide (Tigan)	an antiemetic
Alternative route of promethazine	i.e., suppository, IM, compounded topical gel
Diphenhydramine (Bendaryl)	an antihistamine, antidyskinetic, antiemetic, sedative-hypnotic
Hydroxyzine (Vistaril)	an antihistamine
Dexamethasone (Decadron)	an anti-inflammatory, antiemetic, immunosuppressant
H2-receptor antagonists	i.e., ranitidine (Zantac), famotidine (Pepcid)
Lorazepam (Ativan)	a benzodiazepine, sedative-hypnotic, antianxiety, antiemetic
Haloperidol (Haldol)	an antipsychotic, antiemetic
Nalbuphine (Nubain)	a narcotic analgesic, anesthesia adjunct
Zolmitriptan (Zomig)	an antimigraine, Serotonin Receptor Agonist, 5HT1

**Table 1. Alternatives to IV Promethazine.** The table lists alternatives to IV promethazine, in descending order of frequency, used by respondents to an Institute for Safe Medication Practices survey.<sup>10</sup>

## Safety in Using Promethazine (Phenergan) (Continued)

### Self-Assessment Questions

The following questions about this article may be useful for internal education and assessment. You may use the following examples or come up with your own.

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1. What is the maximum concentration that should be used when injecting promethazine?
  - A. No greater than 25 mg/mL
  - B. 6.25 to 12.5 mg/ml
  - C. 50 mg/mL
  - D. 10 to 20 mg/mL
2. In what age population is the use of all forms of promethazine contraindicated?
  - A. The elderly
  - B. Over 2 years of age
  - C. Under 2 years of age
  - D. 21 year olds with diabetes
3. All patients who experience local injury from IV promethazine infusions will have burning at the time of infusion.
  - A. True
  - B. False
4. Safe practices that may be considered to prevent or minimize tissue damage when giving IV promethazine include all EXCEPT which one of the following?
  - A. Dilute the drug of the 25 mg/mL strength to reduce vesicants effects.
  - B. Use large patent veins to administer IV promethazine.
  - C. Consider safer alternatives.
  - D. Dilute in bicarbonate.
  - E. Consider administering IV promethazine slowly over 10 to 15 minutes.

- Build an alert to appear on computer-generated medication administration records (MARs), electronic MARs, and on automated dispensing cabinet screens for nurses to view each time they access and administer a dose of promethazine. This alert would serve to remind nurses that the drug is an irritant (lesser-known vesicant) and should be diluted and administered slowly through a running IV.
- Treat all promethazine extravasations and although the manufacturer notes there is no proven successful management of

unintentional intra-arterial injection or perivascular extravasation, sympathetic block and heparinization have been employed during acute management of promethazine extravasations.

- Consider using safer alternatives with fewer drug interactions for the various conditions treated with IV promethazine. For example, 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) receptor antagonists may be used for both prophylaxis and as a rescue antiemetic. See "Table 1. Alternatives for IV Promethazine."

### Conclusion

While all medications have risks and benefits, the safety of using promethazine must be considered. It should be administered and closely monitored for immediate and delayed side effects, which may not be visible for several days. It is very important that physicians, pharmacists, and nurses understand promethazine's risks because complications can be identified sooner and averted. Further, remedial interventions can be initiated so the extent of damage can be minimized. Incorporating these safe practice strategies proactively can help to reduce the risk of using promethazine.

### Notes

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## Safety in Using Promethazine (Phenergan) (Continued)

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