

This series brings you up-to-date information about medication safety issues and strategies to prevent medication errors. It draws on Australian incidents and US experience, including (with permission) material from ISMP Medication Safety Alert! a bulletin published by the Institute for Safe Medication Practices, USA <www.ismp.org>. This series is coordinated through the Committee of Specialty Practice in Medication Safety (Chair, Rosemary Burke, Director of Pharmacy, Concord Hospital, NSW). Australian incidents are collated and editorial recommendations made by Penny Thornton (Federal Councillor, SHPA, and Pharmacy Services Manager, The Children's Hospital, NSW; e-mail: pennyt2@chw.edu.au).

AUSTRALIAN INCIDENTS

Rotarix—an ORAL vaccine in a syringe!

A female born 22 June 2006 was going to get her first oral rotavirus vaccination (Rotarix) on 23 August 2006. The vaccine kit contains an oral applicator with diluent and a vial with the antigen. The diluent is transferred from the applicator into the vial with the antigen, then the oral applicator is filled again with the vaccine and given via the oral route. However, the GP transferred the diluent into the vial, but then took a needle with syringe and injected the vaccine in the gluteus maximus. This was clearly an application error. On the package the oral applicator is described as a syringe and there is a vial with the antigen. A vaccinologist saw the patient on 24 August 2006 and advised the parents to cancel proposed travel abroad and for their child to stay in the clinic with RV-PCR monitoring (stool and blood). In addition, IV immunoglobulin was suggested (extra-intestinal sites of viral replication exist, immunoglobulin could inhibit viral replication). The parents wanted a second opinion. The next day the child was well but then contact was lost. GSK has advised that to date 11 such incidents have been reported and that this product is clearly labelled for oral use.

Recommendation: The package and the leaflet and SPC should be changed. The word syringe must be avoided. Instead it is proposed the word oral applicator is used. In addition red text should be printed on the package 'For oral use only'.

[Australian Incident 54, September 2006]

Look-alike and sound-alike—a recipe for mis-dispensing

Xalacom (latanoprost+timolol) eye drops has recently been given marketing approval in Australia. It has a very similar name and look-alike packaging to Xalatan (latanoprost) eye drops. There have been reports of near misses over confusion in dispensing these two products. It is vital when a new product of similar labelling and brand name comes onto the market, that staff are made aware of it. At first glance it may be assumed to be just new packaging of the same product (mainly due to similar name) as they both have same few letters.

[Australian Incident 55, November 2006]

Another mis-dispensing incident waiting to happen involves the new combination product—Caduet (amlodipine+atorvastatin). We are told that it is to come in 5 or 10 mg doses of amlodipine combined with 10 mg, 20 mg, 40 mg or 80 mg doses of atorvastatin. This means, 8 different look-alike products to sit together on the shelf. Now one might ask, how could the company have best identified these products for clarity? We believe they have done the best they can through similar brand labelling and clear identification of the combination strengths. Given that we may have 8 different new products together on the shelf, it is up to us to ensure that we enhance our storage and checking procedures to ensure we do not mis-dispense these products.

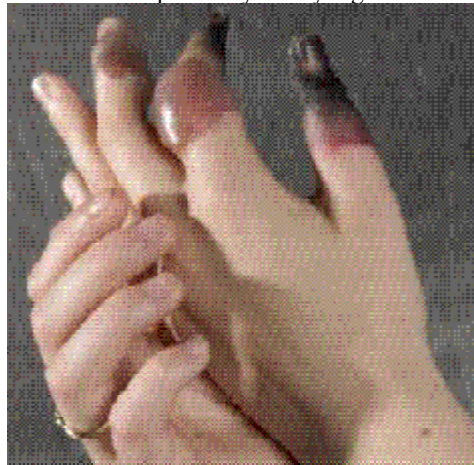
Recommendation: Most hospitals require generic prescribing for a number of good safety reasons. However, do we prescribe combination products by brand name? We are aware that this is widely practised to uniquely specify the particular combination. This may prevent confusion in dispensing of these two products.

[Australian Incident 57, November 2006]

US SAFETY BRIEFS

Prevent serious tissue injury with IV promethazine

Promethazine (Phenergan) injection is commonly used and has antihistamine, sedative, antimotion sickness, and antiemetic effects. Promethazine, a known vesicant is highly caustic to the intima of blood vessels and surrounding tissue. Formulated with phenol, promethazine has a pH between 4 and 5.5. Although deep IM injection into a large muscle is the preferred parenteral route of administration, product labelling states that the drug may also be given by slow IV push. Severe tissue damage can occur regardless of the route of administration, although IV and intra-arterial or SC use results in more significant complications, such as burning, erythema, pain, swelling, thrombophlebitis, venous thrombosis, nerve damage, paralysis, abscess, tissue necrosis, and gangrene. Sometimes surgical intervention has been required, including fasciotomy, skin graft, and even amputation. The true extent of this problem may be unknown. Scores of submitted reports; literature articles; lawsuits; and communications on Internet listservs and message boards suggest that patient harm may be occurring more frequently than recognised. 1) In 2005, a 19-year-old woman went to the ED with flu-like symptoms and received Phenergan IV. During the injection, she yelled out in pain and was tempted to pull out her IV line. After the injection, she told the nurse that her arm was still in significant pain and that she felt 'something was wrong'. The nurse reassured the patient and left the room. The patient's arm and fingers became purple and blotchy. She remained in hospital for 30 days, during which she watched her previously healthy fingers turn black and shrivel.



Her thumb, index finger, and top of her middle finger had to be amputated. 2) In 2005, a patient received IV promethazine 12.5 mg into an IV site in the hand. During the injection, he complained of extreme burning, but the nurse did not stop. He developed an area of necrosis on his hand, eventually requiring skin grafting and physical rehabilitation. 3) In 2005, a physician intern posted the following request on a message board: 'I am currently doing a rheumatology consult and saw a patient who presented with a history of an intra-arterial injection of Phenergan, likely causing her extreme pain throughout the arm and gangrenous first two digits, which will most likely be amputated. I am hoping anyone who reads this with experience handling this problem or knows of a possible reversal please contact me ASAP. From what I have been able to gather, there is no current published treatment protocol. The patient will likely have her two fingers amputated, and in my opinion, could require more and suffer from lifelong chronic pain.' 4) In 2004, a professional guitar player was awarded \$2.4 million for her past and future medical expenses and \$5 million for her pain and suffering after she endured two amputations following accidental intra-arterial injection of Phenergan. Suffering from a migraine, she had gone to the ED, and received inadvertent intra-arterial Phenergan. She developed circulatory problems and then progressive gangrene which led to amputation of her arm in stages. According to the package insert: 'Proper IV administration of this product is well tolerated, but use of this route is not without some hazards.' To reduce the risk of these hazards, the manufacturer recommends: give the drug in concentrations no greater than 25 mg/mL; administer at a rate no greater than 25 mg/min; inject the drug through the tubing of an infusion set that is running and known to be functioning; and stop the injection if the patient reports burning to evaluate possible arterial placement or perivascular extravasation. In the 1970s, after numerous reports of infiltration and inadvertent intra-arterial injection of hydroxyzine, FDA asked the manufacturer to revise the label and remove IV as an approved route. Today hydroxyzine is only indicated for IM or oral use. Similarly, FDA should investigate promethazine to determine if labelling changes are warranted, including removal of approval for IV use.

Recommendation: The following strategies along with the manufacturer's recommendations, should be considered to prevent/minimise tissue damage when giving IV promethazine.

Limit concentration. As 25 mg/mL is the highest strength of promethazine that can be given IV, only stock this concentration.

Limit dose. Consider 6.25 to 12.5 mg of promethazine as the starting IV dose, especially for the elderly. Hospitals have reported that these smaller doses have proven effective.

Dilute drug. Require further dilution of the 25 mg/mL strength to reduce vesicant effects and enable slow administration. For example, dilute the drug in 10 to 20 mL of normal saline to be administered via a running IV, or prepare it in minibags containing normal saline. Extravasation can also be recognised more quickly when promethazine is diluted than if it is given in a smaller volume.

Use large patent veins. Give it only through a large-bore vein (preferably a central venous access site, but absolutely no hand or wrist veins). **Check patency of the access site before administration.** According to the package insert, aspiration of dark blood does not preclude intra-arterial placement of the needle because blood can become discoloured 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.

Inject into the furthest port. Administer IV promethazine through a running IV line at the port furthest from the patient's vein. **Administer slowly.** Consider administering IV promethazine over 10 to 15 minutes. **Revise orders.** Revise preprinted order forms to ensure orders for promethazine reflect the safety measures listed above. **Educate patients.** Before

administration of the drug, tell patients to let you know immediately if burning or pain occurs during or after the injection.

Create alerts. 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, reminding them that the drug is a vesicant and should be diluted and administered slowly through a running IV. **Treat.** The manufacturer notes there is no proven successful management of unintentional intra-arterial injection or perivascular extravasation. However, sympathetic block and heparinisation have been employed during acute management of promethazine extravasations. **Use alternatives.** Consider safer alternatives, e.g. 5-HT₃ receptor antagonists, may be used for prophylaxis and as rescue antiemetics. Also ensure that appropriate surgical patients are receiving a 5-HT₃ receptor antagonist for prophylaxis and are well hydrated to reduce the risk of postoperative nausea and vomiting and, thus, the need for a rescue antiemetic. **Remove from formulary.** Hospitals that have continued to experience adverse outcomes despite safety measures have removed promethazine from their formulary or banned its IV use.

Promethazine conundrum: IV can hurt more than IM!

The discussion (above) on the caustic effects of promethazine injection evoked considerable response from the readers and media who contacted us with comments about our recommendations along with troubling stories of their own about serious injuries from promethazine extravasations. In response to this heightened attention, we invited readers to participate in a survey to learn more about the scope of the problem and to prioritise our injury prevention strategies. From the nearly 1000 responses and many additional unsolicited comments we received, two things were abundantly clear: promethazine extravasations that result in serious tissue damage are not rare; and 1 in 5 respondents reported awareness of such an occurrence in their facility within the past 5 years. While health professionals are frustrated with this longstanding problem for which there is no easy solution, many have been inspired to revisit the issue and take new measures to reduce the risk of injury from IV promethazine. Among the recommendations we suggested in our survey to reduce the risk of tissue injuries, most were deemed to be of great value by respondents, particularly: diluting the drug; limiting the concentration and initial dose; providing alerts on MARs and automated dispensing cabinet screens; injecting the drug into a running IV using the port furthest from the patient's vein; and advising patients to report any IV site discomfort. Yet, implementation of these recommendations was much lower than expected, considering their perceived value. While two-thirds of respondents limit promethazine concentration to 25 mg/mL, only half dilute the drug in 10 to 20 mL of normal saline, inject it through a running line, and advise patients to report IV site discomfort. Only a quarter limit the starting dose, provide alerts on MARs, and use the furthest port when injecting the drug. Even more surprising, just one-third of respondents expect staff to remain with the patient during administration to assess the IV site, and only one-quarter require slow administration over 10 minutes, although two-thirds clearly felt these actions were valuable. About half the respondents agreed that IV promethazine should never be administered via hand or wrist veins, but just 10% reported following such a policy. Recommendations that would eliminate the use of IV promethazine and remove it from the formulary received the lowest scores for both perceived value and current implementation, perhaps because there are so few alternatives as effective as IV promethazine. This survey and responses to our initial article brought to light some concerns about our recommendations, as well as new ideas for managing

the risk of tissue injury. Several practitioners expressed concern about our reference to promethazine as a 'known vesicant'. While other credible sources have also suggested that the drug is a vesicant, the package insert for Phenergan and promethazine refers to the drug as an irritant. Thus, we agree that vesicant may have been used inappropriately to describe promethazine. However, some hospitals have added promethazine to their list of vesicants, primarily to promote awareness and facilitate proper risk reduction efforts. Several practitioners were also concerned that preparing promethazine in a normal saline bag and administering it over 10 minutes or more, would require the use of an infusion pump, potentially leading staff to believe they do not need to remain at the bedside to observe the IV site. Thus, current policies on the use of infusion pumps and conditions that require constant monitoring may need revisions to promote safe administration of IV promethazine. While the rate of infusion may not be directly associated with the tissue damage that results from extravasation, a dilute drug administered very slowly allows for quick discontinuation of the injection if the patient complains of pain. Very slow administration also reduces the risk of extravasation in small, fragile veins. Another pharmacist questioned the use of 5-HT₃ receptor antagonists as an alternative to IV promethazine as a rescue antiemetic. These drugs are typically used to prevent nausea and vomiting during chemotherapy or radiation therapy. During such treatments, serotonin (5-HT) is released from the gastrointestinal tract, which stimulates vagal neurons to transmit a signal to the vomiting centre in the brain. 5-HT₃ receptor antagonists bind to the vagal neuron receptors, thus blocking the signal to vomit. These drugs are most effective if they are given before treatment, or before the patient becomes nauseous, and thus may not be effective as rescue antiemetics. The pharmacist also pointed out that higher doses of 5-HT₃ receptor antagonists can increase the QT interval and cause cardiac arrhythmias.

Recommendations. Some facilities reported additional strategies not mentioned in our survey or article. One pharmacist reported that he now dispenses each vial of promethazine in a ziplock bag with an insert that contains instructions for safe administration along with a photo of actual tissue damage. Although the pharmacy also prints alert messages on MARs, these warnings are not available to all staff, so the attention-grabbing photo and information in the bag are the primary means of communicating precautions. Another hospital reported that, in addition to prohibiting administration of promethazine through IV sites in the hand and wrist, nurses no longer give the drug through an IV in the antecubital space, where nerves, arteries, and veins are very close. Whenever possible, they use an IV site on the back of the arm unless the patient has a central line. Several hospitals have told us about nausea and vomiting prevention protocols they use to reduce the use of IV promethazine, e.g. patients receive ranitidine and dexamethasone preoperatively, and dolasetron 30 minutes before the end of surgery, and promethazine IV is used only as a last resort.

Conclusion. Only 24% of respondents believe FDA should withdraw approval for the IV route of administration of promethazine. Health practitioners need to review their current practices associated with the administration of IV promethazine and establish safeguards to prevent inadvertent arterial injection and IV extravasation. An ED physician aptly affirmed both the desire to preserve IV use of promethazine and the need to address its risks in the following message: 'For 27 years, I have used IV promethazine 2 to 3 times every shift I work. I have personally never seen serious tissue damage or other major problems with this medication, aside from rare instances of local phlebitis that have resolved without incident. This is not to underestimate the serious risks of using this medication, mostly associated with inadvertent intra-arterial injection or tissue

infiltration, but to underscore the fact that all medications have risks/benefits. In my opinion, the benefits far outweigh the risks with IV promethazine. . . I have seen many good drugs go out of favour because of reported problems, which have almost always been disproportionate to their benefits. Most of these have been related to improper use or administration. Let's face it: life decisions in general, and the practice of medicine in particular, always involves risks and benefits. Let's not ignore the risks, but let us also keep the benefits in perspective!'

[Medication Safety Alert! November 2, 2006]

Sodium bicarbonate extravasation

Repeated doses of undiluted IV sodium bicarbonate delivered to an elderly hospitalised man with statin-induced rhabdomyolysis resulted in a serious infiltration at the peripheral IV access site. On admission to the ED, the patient's potassium level was 8.2 mEq/L. He was treated for hyperkalaemia with regular insulin, glucose 50%, and sodium bicarbonate 50 mEq via slow IV push. In ICU, he received 3 more doses of sodium bicarbonate 50 mEq, 2 hours apart, via slow IV push into an IV site through which normal saline had been infusing at 125 mL/h. Before the third and final dose, he complained of pain at the IV site, which was swollen and beginning to turn purple. However, the nurse continued to administer this dose into the existing IV site and, afterwards, changed the site to the right hand. His left hand continued to swell and became a dusky purple for 2 more days, after which healing was very slow. Inadvertent extravasation of hypertonic solutions of sodium bicarbonate has reportedly caused chemical cellulitis due to its alkalinity, resulting in tissue necrosis, ulceration, and/or sloughing at the injection site. Although not recommended for routine use during CPR, sodium bicarbonate is sometimes given if other efforts have been ineffective. For administration in non-emergent situations through peripheral lines, diluting the drug to a 1:1 concentration with water for injection, and infusing it over a longer period of time (1 to 8 hours) can reduce the risk of serious harm in the event of extravasation. Review your guidelines for IV sodium bicarbonate and make changes to avoid the risk of extravasation.

[Medication Safety Alert! August 10, 2006]

Infant heparin flush overdose

Recently three premature infants died at a Midwestern hospital after receiving an overdose of heparin. Apparently, 1 mL heparin 10 000 units/mL vials were placed incorrectly into an automated dispensing cabinet where 1 mL, 10 units/mL vials were normally kept. The vials looked very similar. Several nurses requested 10 units/mL vials to prepare an umbilical line flush and were directed to that drawer, but did not notice that the vials contained the wrong concentration. Please take a close look at your own restocking processes. Having a double-check of items before they leave the pharmacy is an important way to prevent mistakes, but even that is not foolproof. Where possible, hospitals should avoid stocking items on nursing units that require further preparation by nurses before administration. As you examine your own practices, pay special attention to cabinets that are used for neonates and paediatric patients. For example, assess the medications and strengths that are stocked in cabinets. Perhaps this is time for you, too, to consider what might be removed for safety sake. Although not a factor in this case, this is also a good time to examine which medications are being removed from the cabinet without a pharmacist's review. Also, even with the perceived safety of automated dispensing cabinets, hospitals should take steps to minimise look-alike packages and labels. Finally, if you are not discussing bar coding at your location, it is time to do so. Bar coding is valuable for bedside scanning to confirm the accuracy of the patient, drug and dose. But even

without bedside scanning, cabinet vendors also provide bar code systems for assuring proper medications are stocked. We do not profess to know the easy answers, but this tragic case brings to light a serious problem about which all should be concerned.

[Medication Safety Alert! September 21, 2006]

Harmful errors: how will your facility respond?

Previously we reported the tragic story of a 16-year-old woman who died during labour due to accidental IV administration of a bag of epidural analgesia instead of penicillin. According to news reports, the nurse who was caring for the patient no longer works at the hospital. The hospital would not comment whether this was a voluntary or forced termination, but many speculate the latter. We also reported the death of three premature infants from an overdose of heparin after the wrong strength was used to prepare flush solutions. In stark contrast, staff involved in this error were on leave, receiving supportive care until they felt ready to return to work. Furthermore, a letter of public support for the nurses and pharmacy technician involved in the error, along with collective resolve to do more to protect patients, appeared in the local newspaper. The letter was signed by chief nursing officers and nursing deans from more than 20 hospitals and universities around the Indianapolis area where the error occurred. The nursing leaders noted: 'Anger and outrage over the deaths of these three children is understandable. But it's important for all of us to understand that no amount of blaming or finger-pointing will undo the harm or fix the system weaknesses that allowed this medication error to occur in the first place... As we grieve, we must support all the families and friends rocked by this tragedy, including the clinicians and staff involved in the babies' care. This was everyone's worst nightmare.' Why the glaring differences between the two organisations when responding to harmful errors? Certainly, human error—perhaps even at-risk behaviours or policy violations—occurred in both events. Nevertheless, the culture appears to be far more 'just' in dealing with the staff involved in the most recent event. Without minimising the vast importance of a culture that treats the workforce fairly when an error occurs, there is another reason that organisations might respond differently in the wake of an error: the absence or presence of a thoughtful readiness plan to handle medical errors that harm patients before they occur. Organisations should not underestimate the emotional toll that accompanies harmful medical errors. Often, hindsight and external pressure inevitably lead to finger pointing during the immediate analysis of the event. Sadly, this sometimes leads to ill-conceived employment terminations or other unwarranted disciplinary actions which are often later regretted by the organisation. To help guide the most appropriate response to a harmful error, all practice sites should have a well-designed plan that is fully supported by the organisation and that address the following: **Internal notification.** Who needs to be notified about the event internally, such as the physician, manager, senior leaders, board of trustees, risk

management, patient safety officer, director of pharmacy, and professional staff? Who provides that notification? How should staff report a harmful event to risk management? What is the timeline for notification of the event? How will affected staff be notified about the event? How are staff and the board updated about the investigation and action plan? How will internal public relations activities be conducted so that appropriate staff know the story and how it is being addressed? **External notification.** Who will notify external organisations about the event? Who will the organisation voluntarily notify so others can take precautions to prevent like errors? How should information about the causes of the event be handled according to state peer review statutes? How will the organisation accommodate visits from regulatory or investigative bodies? **Disclosure.** What specifically should be disclosed to patients and families (e.g. circumstances of the event, consequences to the patient, plans for investigation, system-based causes)? Who should disclose the information? How should the disclosure happen? Who should be present during the disclosure? Who will be the contact person for follow-up or to answer questions from the patient or family? How is just compensation for injuries determined and offered to the patient or family? Who should inquire about the patient's or family member's desires regarding the level of disclosure to the public, and how will that information be communicated to all who need to know? **Treatment of staff.** How will staff involved in the event be evaluated and treated? How will system-wide accountability be assessed? What forms of support and psychological counselling will be offered to those involved in the event and those affected by the event? How should staff interact with patients and families who have been victims of a harmful error? How should staff interact with other patients who have heard about the event? **Media inquires.** With inquiries from the news media, how can the organisation provide useful and accurate information without breaching patient confidentiality? Who will provide ongoing feedback to the community? How should staff respond to unsolicited media questions? What procedures must be undertaken to safeguard documents and involved containers and equipment for further investigation? How should the immediate internal review and investigation of an event be carried out? How should a more detailed event analysis occur? What criteria will be used to determine whether an independent review of the event by outside experts should be carried out? How will the results of the investigation be communicated to the patient and/or family and to applicable staff and the board (and the public, if appropriate)? **Improvement.** What process(es) will be used to ensure that appropriate immediate and long-term preventive actions are taken. While we are confident that all healthcare providers hope that such a plan will never be needed in their organisation, the insight gleaned from developing the plan and communicating it to the workforce will set the stage for an appropriate response should such an event happen.

[Medication Safety Alert! October 5, 2006]