Death and neurological devastation from intrathecal vinca alkaloids: Prepared in syringes = 120; Prepared in minibags = 0

In July, ISMP Canada published selected findings from the 2012 ISMP International Medication Safety Self Assessment for Oncology.¹ The assessment, which was funded by the International Society of Oncology Pharmacy Practitioners (ISOPP), was developed by ISMP and ISMP Canada with help from an international panel of oncology and safety experts.² From April to October 2012, more than 350 oncology practice sites from 13 countries submitted results for analysis. This analysis uncovered a particularly troubling risk that appears to be weakly addressed, especially in the US: the risk of administering vinCRIStine or another vinca alkaloid intrathecally instead of intravenously.

While overall compliance among respondents was high for a risk-reduction strategy associated with labeling containers of vinCRIStine with a prominent warning, implementation was disturbingly low for three key recommendations (Table 1) that ISMP has promoted since 2001, The Joint Commission has endorsed since 2005, and the World Health Organization has recommended since 2007:

- Dispense intravenous (IV) vinCRIStine in a minibag of a compatible solution (e.g., 25 mL for pediatric patients and 50 mL for adults) and never dispense and/or administer the drug using a syringe.
- Prohibit IV vinCRIStine in areas where intrathecal medications are administered and/or stored.
- Confirm that any prescribed intrathecal medications have been administered before dispensing IV vinCRIStine.

An ISMP survey conducted in 2005³ uncovered minimal adoption of these three recommendations among responding hospitals. A follow-up survey in 2008⁴ showed small, incremental improvement, but the risk of making an error remained substantial. Now, more than a decade later:

### Table 1. VinCRIStine Safety Strategies (% Full Implementation)

<table>
<thead>
<tr>
<th>Assessment Item</th>
<th>2005 Survey¹</th>
<th>2008 Survey²</th>
<th>2012 Self Assessment³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VinCRIStine is dispensed with a prominent warning label that reads: FOR INTRAVENOUS USE ONLY—FATAL IF GIVEN BY OTHER ROUTES.</td>
<td>93%</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>92%</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>VinCRIStine is dispensed in a minibag of a compatible solution (e.g., 25 mL for pediatric patients and 50 mL for adults). VinCRIStine doses are never dispensed and/or administered using a syringe.</td>
<td>23%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>27%</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td>The presence of vinCRIStine is prohibited in areas where intrathecal medications are administered and/or stored.</td>
<td>38%</td>
<td>55%</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>53%</td>
<td>64%</td>
<td>65%</td>
</tr>
<tr>
<td>Confirmation that the administration of any prescribed intrathecal medications has been completed is required before dispensing vinCRIStine.</td>
<td>42%</td>
<td>51%</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>48%</td>
<td>54%</td>
<td>54%</td>
</tr>
</tbody>
</table>

¹Survey conducted by ISMP⁵
²Survey conducted by ISMP, Hematology Oncology Pharmacy Association (HOPA), and the International Society of Pharmacy Practitioners (ISOPP)⁷
³Assessment conducted by ISMP and ISMP Canada²
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and the bag was dispensed to the NICU. The nurse happened to scan the label on the bag that stated 120 units in 0.49% sodium chloride and thought she had confirmed the correct product, never noticing the heparin 25,000 units/250 mL in 5% dextrose pharmacy label on the other side of the bag. She prepared the bag for infusion and then asked another nurse to independently check the product. The second nurse read the patient-specific label that stated heparin 120 units/250 mL and verified the patient and drug. The usual checking process did not include looking at both sides of the IV bag. Fortunately, the bag swung around as the nurse went to begin the infusion, during which she noticed the second label, and the error was captured before the drug reached the patient. Along with providing staff with education and awareness about the event, the hospital where the error occurred decided to affix yellow auxiliary warning labels to both sides of compounded bags of heparin 25,000 units/250 mL to promote recognition of their contents. We would also suggest a thorough review of pharmacy compounding workflow—including label sorting, verification, and application. Some organizations also print duplicate labels to affix to both sides of a bag or bottle, taking care not to cover important manufacturers’ label information. Likewise, we have long recommended to manufacturers to print labels on both sides of bags or bottles, but so far, only Hospira has done this for just sterile compounding can also be found at: www.ismp.org/sc?id=243.

Activate this ADC setting. A hospital reported a medication error that could have been prevented with an alert in the automated dispensing cabinet (ADC) that unknowingly was not activated. Before transferring a patient from one unit to another, a nurse quickly removed all the patient’s morning medications from the unit’s ADC and administered them to the patient. Because it was still early in the morning, the nurse on the receiving unit also gave the patient the same morning medications, which she obtained from her unit’s ADC, without checking the patient’s medication administration record (MAR) from the previous unit from which the patient had been transferred. While information regarding the last dose removed for the patient was available on the ADC screen, the information was easily overlooked by the nurse. After the event, the hospital staff realized that the ADC can be set up to provide a pop-up alert that notifies the nurse continued on page 3—Safety Briefs

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since the first time ISMP published these recommendations, the 2012 oncology self-assessment results suggest that only about half of US oncology practice sites dilute IV vinCRIStine for administration in a small volume bag or receive confirmation that intrathecal drug administration has been completed before dispensing IV vinCRIStine. Only about two-thirds prohibit IV vinCRIStine in areas where intrathecal medications are stored or administered (see Table 1, page 1).1

Incidence

The first reported case of fatal ascending myelonecephalopathy caused by the intrathecal administration of IV vinCRIStine occurred in the US in 1968.8 Between 1968 and 2007, 17 cases in the US plus 49 cases worldwide were reported in the literature.9 Practically all of these events resulted in death; the few patients who survived experienced devastating neurological effects including persistent vegetative state and quadriplegia.

In 2008, ISMP reported a fatality in which a 25-year-old woman with non-Hodgkin’s lymphoma received another vinca alkaloid, vindesine, intrathecally.10 In 2010, we wrote about another fatal event in which a young woman was supposed to receive a dose of intracerebroventricular methotrexate but instead received intracerebroventricular vinCRIStine through an Ommaya reservoir.11 Another case was reported in 2010 in which a 33-year-old man with acute lymphocytic leukemia in complete remission accidentally received an intended maintenance dose of IV vinCRIStine via a lumbar puncture and died.12 In 2011, two additional fatalities were reported in the literature. In one, a 38-year-old woman newly diagnosed with Burkitt’s lymphoma died in a US hospital after accidental administration of IV vinCRIStine by the intrathecal route.13 The other case report involved a 63-year-old man with lymphoma from Thailand who received vinCRIStine intrathecally.14

There have also been cases not reported in the literature but gathered from other sources such as FDA MedWatch reports, legal claims, non-US regulatory agencies, media sources, and personal communications; the sum total of cases worldwide is 120, with 44 occurring in the US and Canada.15 However, the true incidence of intrathecal administration of IV vinCRIStine or other vinca alkaloids is not known. What we do know is that wrong route vinCRIStine errors continue to occur, and although they may happen infrequently, they are always excruciatingly painful over days or weeks until almost certain death, and they are always preventable.

Causes

In most cases of published events, the causes of inadvertent intrathecal vinCRIStine administration have not been fully described. However, many events appear to be related to mistaking IV vinCRIStine for an intrathecal medication, such as methotrexate, cytarabine, or hydrocortisone.5,7,9,11-16 Other causes include: the mislabeling of syringes; bringing IV and intrathecal medications into a treatment area together; failing to administer vinca alkaloids in a specialty oncology unit or with only experienced, oriented staff familiar with current operational and clinical standards, procedures, or protocols; administering chemotherapy outside of normal hours; not conducting an independent double check or “time out” before intrathecal medication administration; and incomplete or missing warning labels.5,7,9,11,16,17

Most effective strategy

While further details might be absent about additional underlying causes of these errors, one thing is clear. To the best of our knowledge, every error involving inadvertent intrathecal administration of vinCRIStine or another vinca alkaloid during the past 45 years has involved preparation and administration of the vinca alkaloid in a syringe. We are not aware of a single incident in which IV vinCRIStine or another vinca alkaloid had been prepared in a minibag and then administered intrathecally. Thus, a consensus exists that the most effective strategy currently available to prevent this tragic and frequently fatal event from continued on page 3—VinCRIStine

Please encourage your patients and staff to visit www.consumermedsafety.org often. It may save a life!
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occuring is to stop dispensing and administering IV vinCRIStine or other vinca alkaloids in syringes. Even dilution and preparation of IV vinCRIStine or vinca alkaloids in large syringes of 10-20 mL has resulted in fatal misadministration via the intrathecal route.

This strategy—dispensing and administering IV vinCRIStine and vinca alkaloids in a small-volume minibag—ensures that the drug will look distinctly different than a syringe containing a medication that may be administered via the intrathecal route. It places the drug in a larger volume of fluid and in a different container for drug administration (infusion from a minibag via IV tubing), neither of which lends itself well to intrathecal administration. It would be nearly impossible to administer a vinca alkaloid prepared in a minibag to a patient through a spinal needle.

Trisell et al. reported that diluted vinCRIStine is stable in larger volumes, so there is no question regarding stability. Earlier this year, the US Food and Drug Administration (FDA) approved an addition to vinCRIStine labeling that states: “To reduce the potential for fatal medication errors due to incorrect route of administration, vinristine sulfate injection should be diluted in a flexible plastic container and prominently labeled as indicated for intravenous use only.” ISMP believes this strategy should be implemented in all hospitals that administer IV vinCRIStine, even if intrathecal medications are not currently prescribed, as practices can change. A unique connector for intrathecal/epidural syringes, a strategy currently under evaluation and development, will help reduce the risk of wrong route errors. But even with this strategy, there is still a small risk that IV vinCRIStine or another vinca alkaloid could be prepared in the wrong type (intrathecal/epidural) of syringe. Thus, ISMP strongly recommends dispensing and administering IV vinCRIStine and other vinca alkaloids in minibags, not syringes.

Some practitioners have expressed concern that administering diluted IV vinCRIStine via a minibag might increase the risk of extravasation and subsequent injury. However, data suggests that the risk of extravasation is very low, regardless of the method used to administer the drug. A study in Australia involving 68 cancer centers evaluated more than 44,000 doses of vinca alkaloids administered via syringe or minibag to adult and pediatric patients and found that the extravasation rates were similar and low—0.03% with syringes and 0.04% with minibags. Preliminary data from another study conducted in children and adults found no cases of extravasation during administration in minibags. These data strongly support the safe use of minibags in adults and children. The risk of extravasation injury is miniscule when compared to the risk of near certain death or severe neurological injury from administering vinca alkaloids intrathecally. Dilution of the vinca alkaloid also reduces the impact of any extravasation that might occur.

Patient safety has been at the forefront of many international, national, state, and local healthcare agendas during the past decade. However, the importance of proactively reducing the risk of tragic medication errors has been minimized too often because the events have occurred infrequently. “Rare” but harmful events should not be discounted simply because of low frequency. Yes, cost and labor may be a little higher to dilute a vinca alkaloid and prepare it in a minibag, and although vinCRIStine in a minibag can be administered at a similar rate as in a syringe, a little more time may be needed to monitor the patient. But we should all commit to making sure that this tragic event never happens again. After all, patients rarely survive after IV vinCRIStine or another vinca alkaloid has been administered intrathecally, and the subsequent decline until death is slow and painful, both emotionally and physically for the patient and their loved ones. No more evidence than this should be needed to prove the importance of proactively reducing the risk of tragic medication errors.

Very low extravasation risk

References on page 4—VinCRIStine
FDA Advise-ERR: Avoiding topotecan 10-fold overdoses

The US Food and Drug Administration (FDA) and ISMP have received reports of medication errors involving 10-fold topotecan overdoses. One error was due to misreading an order caused by omission of the leading zero in the dose. The topotecan dose was written as .7 mg instead of 0.7 mg, and the patient received 7 mg of the drug in error.

Four other 10-fold overdoses have also been reported. None of these reports indicated the root causes. However, the overdoses in three of the cases may have occurred because the decimal point in the dose was overlooked when interpreting the topotecan order. In one case, a patient was prescribed a 2.5 mg dose but received a 25 mg dose. In another, the physician ordered 2.9 mg but the nurse administering the topotecan misread the dose and the patient received 29 mg. Another patient was supposed to receive 2.4 mg of topotecan, but the order was written for a 24 mg dose. In the fourth case, a patient received 40 mg/m² instead of 4 mg/m². This overdose may have stemmed from a dose on an order with a trailing zero.

Recommendations

Considering that the recommended doses for topotecan are 1.5 mg/m² (for the intravenous infusion)¹ and 2.3 mg/m² (for the oral capsules),² healthcare practitioners should heighten their index of suspicion and question any topotecan doses greater than 5 mg.³ We also recommend the following:

1) Always include a leading zero (e.g., topotecan 0.7 mg) and avoid using trailing zeros (e.g., topotecan 2.0 mg) when expressing dosing, as the dose may be misread leading to dosing errors.

2) In addition to the total calculated dose in milligrams based on the patient’s body surface area, prescribers should be encouraged to include the intended dose in mg/m² to allow other healthcare practitioners to verify that the calculated dose is correct.

3) Consideration should be given to using standardized order sets when ordering topotecan to avoid dose confusion.

References


*Editor’s note: Computer alerts for topotecan doses above 5 mg also should be considered.

FDA Advise-ERR was provided by Tingting Guo, PharmD, BCPPS, James Schlick, RPh, MBA, and Todd Bridges, RPh, of FDA’s Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis.

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References

2) ISMP and ISMP Canada. 2012 ISMP International Medication Safety Self Assessment for Oncology.
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