

Death and Neurological Devastation From Intrathecal Vinca Alkaloids

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In July 2013, the Institute for Safe Medication Practices (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 United States: the risk of administering vinCRISStine or other vinca alkaloids intrathecally instead of intravenously.

While overall compliance among respondents was high for a risk-reduction strategy associated with labeling containers of vinCRISStine with a prominent warning, implementation was disturbingly low for three key recommendations that ISMP has promoted³ since 2001; the Joint Commission has endorsed⁴ since 2005; and the World Health Organization has recommended⁵ since 2007:

- Dispense intravenous (IV) vinCRISStine in a mini-bag 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 vinCRISStine in areas where intrathecal medications are administered and/or stored.
- Confirm that any prescribed intrathecal medications have been administered before dispensing IV vinCRISStine.

An ISMP survey conducted in 2005⁶ uncovered minimal adoption of these three recommendations among responding hospitals. A follow-up survey in 2008⁷ showed small, incremental improvement, but the risk of making an error remained substantial. More than a decade since the ISMP first published these recommendations, the 2012 oncology self-assessment results suggested that only about half of U.S. oncology practice sites dilute IV vinCRISStine for administration in a small-volume bag or receive confirmation that intrathecal drug administration has been completed before dispensing IV vinCRISStine. Only about two-thirds prohibit IV vinCRISStine in areas where intrathecal medications are stored or administered.¹

Incidence

The first reported case of fatal ascending myeloencephalopathy caused by the intrathecal administration of IV vinCRISStine occurred in the U.S. in 1968.⁸ Between 1968 and 2007, 17 cases in the U.S. plus 49 cases worldwide were reported in the literature.⁹ Nearly 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 vinCRISStine 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 vinCRISStine 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 U.S. hospital after accidental administration of

IV vinCRISStine by the intrathecal route.¹³ The other case report involved a 63-year-old man with lymphoma from Thailand who received vinCRISStine intrathecally.¹⁵

There have also been cases not reported in the literature but gathered from other sources, such as Food and Drug Administration (FDA) MedWatch reports, legal claims, non-U.S. regulatory agencies, media sources, and personal communications. The sum total of cases worldwide is 120, with 44 occurring in the U.S. and Canada.¹⁴ However, the true incidence of intrathecal administration of IV vinCRISStine or other vinca alkaloids is not known. What we do know is that wrong-route vinCRISStine 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 vinCRISStine administration have not been fully described. However, many events appear to be related to mistaking IV vinCRISStine for an intrathecal medication, such as methotrexate, cytarabine, or hydrocortisone.^{6,7,9,11-16} 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.^{6,7,9,11,16,17}

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 mini-bag and then administered intrathecally. Thus, a consensus exists that the most effective strategy available to prevent this tragic and frequently fatal event is to stop dispensing and administering IV vinCRISTine or other vinca alkaloids in syringes.^{6,7,9,16-18} Even dilution and preparation of IV vinCRISTine or vinca alkaloids in large syringes of 10 to 20 mL has resulted in fatal misadministration via the intrathecal route.^{16,18}

This strategy—dispensing and administering IV vinCRISTine and vinca alkaloids in a small-volume mini-bag—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 mini-bag 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 mini-bag to a patient through a spinal needle.¹⁸

Trissel et al. reported that diluted vinCRISTine is stable in larger volumes,¹⁹ so there is no question regarding stability. In 2013, the FDA approved an addition to vinCRISTine labeling that states: **“To reduce the potential for fatal medication errors due to incorrect route of administration, vinCRISTine 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 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 mini-bags, not syringes.

Very Low Extravasation Risk

Some practitioners have expressed concern that administering diluted IV vinCRISTine via a mini-bag might increase the risk of extravasation and subsequent injury. However, data suggest 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 mini-bag to adult and pediatric patients and found that the extravasation rates were similar and low—0.03% with syringes and 0.04% with mini-bags.²⁰ Another study conducted in children and adults found no cases of extravasation during administration in mini-bags.²¹ These data strongly support the safe use of mini-bags in adults and children.²² 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.

Conclusion

Patient safety has been at the forefront of many international, national, state, and local health care 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 mini-bag, and although vinCRISTine in a mini-bag 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 raise the urgency with

which organizations pursue eradication of this rare but fatal and preventable error.

REFERENCES

1. ISMP Canada. Preliminary results from the International Medication Safety Self Assessment for Oncology. *ISMP Canada Safety Bulletin* 2013;13(6):1-5.
2. ISMP and ISMP Canada. 2012 ISMP International Medication Safety Self Assessment for Oncology. Available at: https://mssa.ismp-canada.org/data/oncology/mssa_oncology.pdf. Accessed June 20, 2016.
3. ISMP. This month's *Hospital Pharmacy* includes an article that demonstrates vinCRISTine stability. *ISMP Medication Safety Alert* 2001;6(14):2.
4. The Joint Commission. Preventing vincristine administration errors. *Sentinel Event Alert* 2005;34. Available at: www.jointcommission.org/assets/1/18/SEA_34.PDF. Accessed June 20, 2016.
5. World Health Organization. Vincristine (and other vinca alkaloids) should only be given intravenously via a minibag. Information Exchange System, Alert No. 115. July 18, 2007. Available at: www.who.int/patientsafety/highlights/PS_alert_115_vincristine.pdf?ua=1. Accessed June 20, 2016.
6. ISMP. IV vinCRISTine survey shows safety improvements needed. *ISMP Medication Safety Alert* 2006;11(4):1-2.
7. Johnson PE, Chambers CR, Vaida AJ. Oncology medication safety: a 3D status report 2008. *J Oncol Pharm Pract* 2008;14:169-180.
8. Schochet SS, Lampert PW, Earle KM. Neuronal changes induced by intrathecal vincristine sulfate. *J Neuropathol Exp Neurol* 1968;27(4):645-658.
9. Lagman JL, Tighe CC, Trifillio SM, et al. Inadvertent intrathecal administration of vincristine. *Commun Oncol* 2007;4(1):45-46.
10. ISMP. Fatal vindesine event. *ISMP Medication Safety Alert* 2008;13(16):1.
11. ISMP. Worth repeating ... Prevent vinCRISTine wrong route injections. *ISMP Medication Safety Alert* 2010;15(10):3.
12. D'Addario A, Galuppo J, Navari C, et al. Accidental intrathecal administration of vincristine. *Am J Forensic Med Pathol* 2010; 31(1):83-84.
13. Reddy GK, Brown B, Nanda A. Fatal consequences of a simple mistake: How can a patient be saved from inadvertent intrathecal vincristine? *Clin Neurol Neurosurg* 2011;113:68-71.
14. Seger AC. Personal communication from Andrew C. Seger, PharmD. Division of General Medicine and Primary Care. Brigham and Women's Hospital, Boston, Massachusetts. September 3, 2013.
15. Pongudom S, Chinthammitr Y. Inadvertent intrathecal vincristine administration: report of a fatal case despite cerebrospinal fluid lavage and a review of the literature. *J Med Assoc Thai* 2011;94(suppl 1):S258-S263.

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16. Schulmeister L. Preventing vincristine administration errors: does evidence support minibag infusions? *Clin J Oncol Nurs* 2006;10(2):271-273.
17. Gilbar PJ, Dooley MJ. Review of case reports of inadvertent intrathecal administration of vincristine: recommendations to reduce occurrence. *Asia Pac J Clin Oncol* 2007;3(2):59-65.
18. Gilbar P. Inadvertent intrathecal administration of vincristine: has anything changed? *J Oncol Pharm Pract* 2012;18(1):155-157.
19. Trissel AL, Zhang Y, Cohen MR. The stability of diluted vincristine sulfate used as a deterrent to inadvertent intrathecal injection. *Hosp Pharm* 2001;36:740-745.
20. Gilbar PJ, Carrington CV. The incidence of extravasation of vinca alkaloids supplied in syringes or mini-bags. *J Oncol Pharm Pract* 2006;12(2):113-118.
21. Nurgat ZA, Smythe M, Al-Jedai A, et al. Introduction of vincristine mini-bags and an assessment of the subsequent risk of extravasation. *J Oncol Pharm Pract* 2015;21(5):339-347. doi: 10.1177/1078155214531803. Epub 2014 May 12.
22. Gilbar PJ. Accidental administration of vincristine in pediatric patients. *J Pediatr Oncol* 2013;1(1):9-16.

The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the ISMP website (www.ismp.org) or communicated directly to ISMP by calling 1-800-FAIL-SAFE or via email at ismpinfo@ismp.org. ■