

Pegaspargase, a chemotherapy drug known to improve survival outcomes in acute lymphoblastic leukemia, is associated with a risk for hypersensitivity reactions. At a children's hospital in the midwestern United States, two patients developed unusual reactions consisting of disseminated urticaria about two weeks after their second dose of pegaspargase. Both patients then proceeded to have severe anaphylaxis with the third dose of pegaspargase. These cases highlight the importance of advanced practice nurses being alert for the occurrence of unusual and delayed reactions to chemotherapy administration.

AT A GLANCE

- Pegaspargase is linked to hypersensitivity reaction risk; hypersensitivity reactions typically occur within a few minutes to hours of the infusion.
- Disseminated urticaria, appearing about two weeks after a second infusion of pegaspargase, preceded anaphylactic reactions to a third infusion in two patients with acute lymphoblastic leukemia.
- Advanced practice nurses should be alert for delayed and unusual reactions to pegaspargase and consider the risks of hypersensitivity reaction in all patients.

KEYWORDS

pegaspargase; urticaria; hypersensitivity; pediatric; acute lymphoblastic leukemia

DIGITAL OBJECT

IDENTIFIER

10.1188/21.CJON.511-513

Pegaspargase

Two pediatric case studies of delayed urticaria preceding anaphylactic reactions postadministration

Kathleen R. Busack, MSN, RN, CPNP-PC, CPHON®

Asparaginase is a standard chemotherapy treatment for pediatric acute lymphoblastic leukemia (ALL) (Heo et al., 2019; Marini et al., 2019). Administration is associated with risk of hypersensitivity reactions (HSRs), including anaphylaxis, angioedema, cough, and local or diffuse erythema and urticaria (Burke & Rheingold, 2017; Pidaparti & Bostrom, 2012). These reactions occur in 3%–41% of patients receiving asparaginase (Burke et al., 2018). Reactions may be immediate or delayed and can vary in severity in relation to both patient- and treatment-related factors. Although anaphylactic reactions typically occur within minutes to hours, delayed reactions have been reported within a few days of administration (Burke & Rheingold, 2017).

There are five formulations of asparaginase: *Escherichia coli* (*E. coli*)–derived, pegylated (pegaspargase), *Erwinia*, calaspargase, and recombinant crisantaspase (Jazz Pharmaceuticals, 2019; Marini et al., 2019). Pegaspargase was created to decrease the incidence of HSRs, the development of neutralizing antibodies, and the frequency of administration (Heo et al., 2019). Known hypersensitivity to *E. coli* asparaginase increases the risk of pegaspargase reactions (Burke et al., 2018). Pegaspargase can administered by intramuscular or IV routes; both are associated with HSR risk (Beaupin et al., 2017; Burke et al., 2018; Hasan et al., 2017). Differences in reaction definitions, reporting, and patient risk may contribute to variations in reported reaction rates. In addition, reactions

occurring outside the healthcare setting and those that are self-managed may be underreported (Beaupin et al., 2017).

At a children's hospital in the midwestern United States, two patients experienced disseminated urticaria about two weeks after their second dose of IV pegaspargase. Both patients subsequently developed anaphylaxis with the third pegaspargase infusion. Remaining alert for the occurrence of unusual and delayed reactions to pegaspargase is important as advanced practice nurses consider individualized reaction risk.

Case Study 1

Patient A is a two-year-old male diagnosed with very high-risk pre-B-cell ALL treated on the Children's Oncology Group protocol AALL1131. This protocol entails about three and half years of therapy for males, with phases including induction, consolidation, interim maintenance I, delayed intensification, and maintenance (Burke et al., 2019). Very high-risk patients also undergo a second interim maintenance phase. Pegaspargase is given once in induction, twice in consolidation, twice in delayed intensification, and twice in interim maintenance II (Burke et al., 2019). Patient A tolerated the first dose of IV pegaspargase without reaction. The second infusion was paused twice for a total of eight minutes, once for two short coughing episodes and once for sudden restlessness and irritability. He recovered quickly with each pause. The infusion was completed without additional issues or need for medications, but persistent vomiting and decreased intake developed soon after discharge. This

continued for more than a week, prompting an overnight admission 11 days after pegaspargase administration. Inpatient treatment included fluid and electrolyte supplementation, along with scheduled metoclopramide, ondansetron, and ranitidine. His symptoms improved, and he was discharged the next day. His mother called two days later (13 days after his second pegaspargase dose) to report widespread generalized urticaria. Diphenhydramine was prescribed, and the rash resolved in 48 hours.

Patient A returned for the second part of the consolidation phase, including his third dose of pegaspargase, six weeks later. As per protocol at the time, no standard HSR premedications were administered. Eight minutes after the infusion started, he developed severe anaphylaxis, exhibiting coughing, gagging, and perioral and periorbital swelling. He subsequently developed laryngeal edema; his blood pressure and oxygen saturation declined; and he required intubation with intensive care management. The patient recovered with scheduled steroids and diphenhydramine. He was extubated within 24 hours and discharged to home on the second day of hospitalization.

Case Study 2

Patient B is a three-year-old male with high-risk pre-B-cell ALL, also treated on Children's Oncology Group protocol AALL1131. His first dose of IV pegaspargase was completed without reaction. He received his second dose in the consolidation phase. About 10 minutes into the infusion, he began coughing, developed audible wheezing, and complained of lower abdominal pain. The infusion was paused for five minutes, IV diphenhydramine was given, symptoms improved, and the infusion was restarted at a slower rate. Nausea and lower abdominal pain returned at completion of the infusion, prompting an overnight admission and scheduled diphenhydramine. He was discharged in the morning without any additional symptoms. However, 11 days postpegaspargase infusion, Patient B presented to the emergency department with

complaints of fever, vague abdominal pain, and decreased appetite. He received antibiotics and was discharged. He returned for scheduled chemotherapy 14 days after the second dose of pegaspargase. On admission to the clinic and prior to receiving any medications, disseminated urticaria of unknown etiology was noted. Diphenhydramine was initiated in the

infusion rate adjustments. The urticarial rash emerged 13–14 days after the second dose of pegaspargase. Patient B's urticaria had no suspected etiology, whereas Patient A's urticaria was initially attributed to medications or oral supplementation received while hospitalized. Both patients experienced immediate and severe reactions to the subsequent pegaspargase

"Remaining alert for the occurrence of unusual and delayed reactions to pegaspargase is important as advanced practice nurses consider individualized risk."

clinic and prescribed for home. The rash resolved within 24 hours.

Patient B received his third pegaspargase infusion four weeks after the second dose. At this time, new premedication guidelines had been implemented, including administration of diphenhydramine, ondansetron, and hydrocortisone, and standard infusion time was lengthened from one to two hours. He had received less than 2 ml of pegaspargase when he developed shortness of breath, facial edema, decreased oxygen saturations, and hypotension. He was admitted for intensive care management with fluids, diphenhydramine, steroids, and albuterol. Intubation was not required, and he was discharged two days later.

Discussion

HSR is a known risk of asparaginase administration (Marini et al., 2019). The presentation of delayed urticaria preceding anaphylaxis with the next dose of pegaspargase, as described in these case studies, is unique to the literature. Both patients experienced nonspecific abdominal pain and irritability during their second doses, but they were able to complete the full infusion with dose pause and

dose. In hindsight, the similarities of both patients' rashes suggest the possibility of delayed pegaspargase reactions.

According to the available literature, urticaria usually develops during or within a few hours of asparaginase, whether administered via IV or intramuscular routes (Burke & Rheingold, 2017). Several published reports highlight this expected time frame for both IV and intramuscular pegaspargase, as well as other asparaginase formulations. In a retrospective review of 492 patients with ALL receiving IV pegaspargase, 63 patients experienced HSRs ranging from mild rash and flushing to life-threatening anaphylaxis (Browne et al., 2018). All but one reaction occurred during the 60-minute infusion; a single delayed reaction occurred 199 minutes after completion of the infusion (Browne et al., 2018).

In another retrospective review, 79 of 615 patients receiving intramuscular pegaspargase according to AALL2008, a Nordic Society of Pediatric Hematology and Oncology protocol, experienced HSRs (Henriksen et al., 2015). All reactions occurred within one hour and 50 minutes of the injection, with the most delayed reactions developing 24–36 hours

after administration (Henriksen et al., 2015).

A case report published by Spiegel et al. (1980) reviewed three separate patients who had hypersensitivity reactions to intramuscular *E. coli* asparaginase. Patients experienced restlessness, periorbital swelling, urticaria, and generalized rashes or pruritus 1.5–48 hours after administration (Spiegel et al., 1980).

Kloos et al. (2016) reviewed reactions to IV asparaginase in patients treated on three Dutch Childhood Oncology Group protocols: ALL-11, ALL-10, and CoALL 08–09. The ALL-11 and CoALL 08–09 protocols included pegaspargase throughout all phases of treatment, whereas the ALL-10 protocol contained *E. coli* asparaginase in the first phase and pegaspargase in the remaining phases (Kloos et al., 2016). Of the 24 patients who developed reactions, 83% reacted to pegaspargase (Kloos et al., 2016). Most reactions occurred within 60 minutes of the infusion; the most delayed reactions occurred within 24 hours of the pegaspargase infusion start time and consisted of rash, urticaria, or fever (Kloos et al., 2016).

Petersen et al. (2014) evaluated patients with ALL who received IV or intramuscular pegaspargase. Reactions were reported in 48 of 318 patients. Twenty-eight reactions occurred within 30 minutes, with 23 of those occurring within the first 10 minutes (Petersen et al., 2014). The most delayed reactions were described as occurring “several hours” later or the “next day” (Petersen et al., 2014, p. 314).

Conclusion

Delayed urticaria occurring about two weeks after pegaspargase has not previously been reported and may be a parameter to consider in treatment planning and patient assessment. Delayed reactions, such as urticarial rashes, occurring weeks after pegaspargase infusion may occur while patients are at home. If patients are not under direct clinical observation, the potential for self-treatment and underreporting to and among the healthcare team is possible. Greater attention and observation, as

well as additional research, are needed to draw any conclusions. This article hopes to inform clinicians of the importance of remaining alert for potential delayed and unusual reactions. Evidence continues to evolve in practice, and observations may contribute information to treatment planning, patient monitoring, and education. Informing patients and families of symptoms to watch for and the duration of time that reactions are possible is imperative (Woods et al., 2017).

Kathleen R. Busack, MSN, RN, CPNP-PC, CPHON®

is a clinical beacon analyst at Nationwide Children's Hospital in Columbus, OH. Busack can be reached at kathleen.busack@nationwidechildrens.org, with copy to CJONEditor@ons.org.

The author takes full responsibility for this content and did not receive honoraria or disclose any relevant financial relationships.

REFERENCES

- Beaupin, L.K., Bostrom, B., Barth, M.J., Franklin, I., Jaeger, R., Kamath, P., . . . Bleyer, A. (2017). Pegaspargase hypersensitivity reactions: Intravenous infusion versus intramuscular injection—A review. *Leukemia and Lymphoma*, 58(4), 766–772. <https://doi.org/10.1080/10428194.2016.1218004>
- Browne, E.K., Moore, C., Sykes, A., Lu, Z., Jeha, S.J., & Mandrell, B.N. (2018). Clinical characteristics of intravenous PEG-asparaginase hypersensitivity reactions in patients undergoing treatment for acute lymphoblastic leukemia. *Journal of Pediatric Oncology Nursing*, 35(2), 103–109. <https://doi.org/10.1177/1043454217741868>
- Burke, M.J., Devidas, M., Maloney, K., Angiolillo, A., Schore, R., Dunsmore, K., . . . Bleyer, A. (2018). Severe pegaspargase hypersensitivity reaction rates (grade ≥ 3) with intravenous infusion vs. intramuscular injection: Analysis of 54,280 doses administered to 16,534 patients on children's oncology group (COG) clinical trials. *Leukemia and Lymphoma*, 59(7), 1624–1633. <https://doi.org/10.1080/10428194.2017.1397658>
- Burke, M.J., & Rheingold, S.R. (2017). Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. *Leukemia and Lymphoma*, 58(3), 540–551. <https://doi.org/10.1080/10428194.2016.1213826>
- Burke, M.J., Salzer, W.L., Devidas, M., Dai, Y., Gore, L., Hilden, J.M., . . . Hunger, S.P. (2019). Replacing cyclophosphamide/cytarabine/mercaptopurine with cyclophosphamide/etoposide during consolidation/
- delayed intensification does not improve outcome for pediatric B-cell acute lymphoblastic leukemia: A report from the COG. *Haematologica*, 104(5), 986–992. <https://doi.org/10.3324/haematol.2018.204545>
- Hasan, J., Shaikh, O.M., Rassekh, S.R., Howard, A.F., & Goddard, K. (2017). Comparison of hypersensitivity rates to intravenous and intramuscular PEG-asparaginase in children with acute lymphoblastic leukemia: A meta-analysis and systemic review. *Pediatric Blood and Cancer*, 64(1), 81–88. <https://doi.org/10.1002/pbc.26200>
- Henriksen, L.T., Harila-Saari, A., Rudd, E., Abrahamsson, J., Pruunsild, K., Vaitkeviciene, G., . . . Albertsen, B.K. (2015). PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol. *Pediatric Blood and Cancer*, 62(3), 427–433. <http://doi.org/10.1002/pbc.25319>
- Heo, Y.-A., Syed, Y.Y., & Kearn, S.J. (2019). Pegaspargase: A review in acute lymphoblastic leukaemia. *Drugs*, 79(7), 767–777. <https://doi.org/10.1007/s40265-019-01120-1>
- Jazz Pharmaceuticals. (2019, August 6). *Jazz Pharmaceuticals advances recombinant crisantaspase development program*. <https://bit.ly/37V68Di>
- Kloos, R.Q.H., Pieters, R., Escherich, G., & van der Sluis, I.M. (2016). Allergic-like reactions to asparaginase: Atypical allergies without asparaginase inactivation. *Pediatric Blood and Cancer*, 63(11), 1928–1934.
- Marini, B.L., Brown, J., Benitez, L., Walling, E., Hutchinson, R.J., Mody, R., . . . Perissinotti, A.J. (2019). A single-center multidisciplinary approach to managing the global Erwinia asparaginase shortage. *Leukemia and Lymphoma*, 60(12), 2854–2868.
- Petersen, W.C., Jr., Clark, D., Senn, S.L., Cash, W.T., Gillespie, S.E., McCracken, C.E., . . . Lew, G. (2014). Comparison of allergic reactions to intravenous and intramuscular pegaspargase in children with acute lymphoblastic leukemia. *Pediatric Hematology and Oncology*, 31(4), 311–317.
- Pidaparti, M., & Bostrom, B. (2012). Comparison of allergic reactions to pegaspargase given intravenously versus intramuscularly. *Pediatric Blood and Cancer*, 59(3), 436–439. <https://doi.org/10.1002/pbc.23380>
- Spiegel, R.J., Echelberger, C.K., & Poplack, D.G. (1980). Delayed allergic reactions following intramuscular L-asparaginase. *Medical and Pediatric Oncology*, 8(2), 123–125. <https://doi.org/10.1002/mpo.2950080204>
- Woods, D., Winchester, K., Towerman, A., Gettinger, K., Carey, C., Timmermann, K., . . . Browne, E. (2017). From the Children's Oncology Group: Evidence-based recommendations for PEG-asparaginase nurse monitoring, hypersensitivity reaction management, and patient/family education. *Journal of Pediatric Oncology Nursing*, 34(6), 387–396. <https://doi.org/10.1177/1043454217713455>