Journal of Human Lactation
http://jhl.sagepub.com/

Duration of Cisplatin Excretion in Breast Milk

Karen E. Hays, Rachel J. Ryu, Elizabeth M. Swisher, Eddie Reed, Terry McManus, Blanche Rybeck, William P. Petros and Mary F. Hebert

J Hum Lact published online 14 March 2013
DOI: 10.1177/0890334413479671

The online version of this article can be found at:
http://jhl.sagepub.com/content/early/2013/03/08/0890334413479671

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
ILCA
International Lactation Consultant Association

Case Report

International Lactation Consultant Association
A Worldwide Network of Lactation Professionals

Journal of Human Lactation
XX(X) 1–4

DOI: 10.1177/0890334413479671
jhl.sagepub.com
SAGE

Duration of Cisplatin Excretion in Breast Milk

Karen E. Hays, DNP, CNM, ARNP[1,2], Rachel J. Ryu, PharmD[1], Elizabeth M. Swisher, MD[3], Eddie Reed, MD[4], Terry McManus, PhD[4], Blanche Rybeck, BSN, RN[4], William P. Petros, PharmD, FCCP[4], and Mary F. Hebert, PharmD, FCCP[1,3]

Abstract

Cisplatin, a platinum-based chemotherapy agent, is commonly used in treating cancers that may affect women of childbearing age, including cervical cancer, triple-negative breast cancer, and pediatric tumors in adolescents. The authors found that platinum was undetectable in breast milk at 66 hours and beyond following a 70-mg dose of intravenous cisplatin. Relative infant dose of platinum was calculated to be between 0.29% and 0.40% of the maternal dose corrected for body weight. This case demonstrates minimal exposure to platinum via breast milk, following a single 70-mg intravenous dose of cisplatin.

Keywords

breastfeeding, breast milk, cisplatin, human milk

Background

Cisplatin is commonly used in treating cancers that may affect women of childbearing age, including cervical cancer, triple-negative breast cancer, and pediatric tumors in adolescents. Postpartum administration of cisplatin is uncommon and pharmacokinetic data are limited to a few cases.[1-4] The safety of breastfeeding during or after cisplatin therapy is unclear. It is universally recommended that infants be exclusively breastfed for at least the first 6 months of life, which benefits the short- and long-term health of both mother and infant.[5,7]

Breastfeeding, however, can be challenging for lactating women after receiving a contraindicated medication. The American Academy of Pediatrics states that breastfeeding is not recommended during therapy with chemotherapeutic agents "until they clear the milk"[5,6] but does not specify if or when breastfeeding can be safely resumed. Cisplatin is 1 of these medications. Cisplatin, the parent compound, has a plasma half-life of 31 to 37 minutes following bolus injections or 4- to 15-minute infusions of 40 or 100 mg/m^2.[8] However, platinum from cisplatin becomes 90% protein bound and shows a more prolonged elimination half-life of 5 days or more.[1,9] This brings into question how long women who require cisplatin chemotherapy should stop breastfeeding. Several investigators have examined the excretion of cisplatin into human breast milk,[1-4] but the full duration of cisplatin excretion has yet to be described. The objective of this report is to present a case in which the presence of platinum in breast milk was followed until its disappearance.

Case Report

A 29-year-old white female (weight 65.4 kg) during her first pregnancy underwent a planned cesarean and radical hysterectomy at 37 weeks gestation for treatment of a stage IB1 adenocarcinoma of the uterine cervix discovered at 20 weeks gestation during an otherwise healthy pregnancy. Adenocarcinoma at this stage is defined as invasive cancer that is confined to the cervix, is no larger than 4 cm (about 1 3/5 inches), and has not spread to nearby lymph nodes or distant sites.[10] Her tumor biology suggested an increased risk of recurrence. She therefore started radiation with concurrent weekly cisplatin (40 mg/m^2), a standard dose in the treatment of her type and stage of cancer,[11-14] at 6 weeks postpartum. She received cisplatin 70 mg IV weekly for 4 cycles with 1 additional dose. Following University of Washington ethics committee approval and written

Date submitted: October 7, 2012; Date accepted: January 29, 2013.

[1]Department of Pharmacy, University of Washington, Seattle, WA, USA
[2]Department of Nursing, University of Washington, Seattle, WA, USA
[3]Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA
[4]Mary Babb Randolph Cancer Center, West Virginia University Health Sciences, Morgantown, WV, USA

Corresponding Author:
Mary F. Hebert, PharmD, FCCP, University of Washington, Department of Pharmacy, 1959 NE Pacific Street, H-375 Health Sciences Center, Box 357630, Seattle, WA 98195-7630, USA
Email: mhebert@uw.edu

informed consent, both breasts were completely emptied of milk at 4.25, 9.25, 13, 16.83, 21, 25, 28.67, 33.33, 40.75, 45.17, 48.58, 51.17, 57, 65.83, and 69.58 hours after the first dose of cisplatin and saved for cisplatin analysis. Sample collection times were primarily determined by patient convenience, however, they reflect a reasonable frequency and range to adequately address our pharmacokinetic objective. The participant discontinued breastfeeding when she was started on cisplatin at 6 weeks postpartum. She pumped and dumped her breast milk for 1 week, then discontinued collecting breast milk before receiving her second dose of cisplatin. Although the participant was initially committed to breastfeeding, she abandoned breastfeeding secondary to treatment side effects and her concern about infant exposure. The participant responded well to the therapeutic approach for her malignancy, and the infant is alive and well.

Method

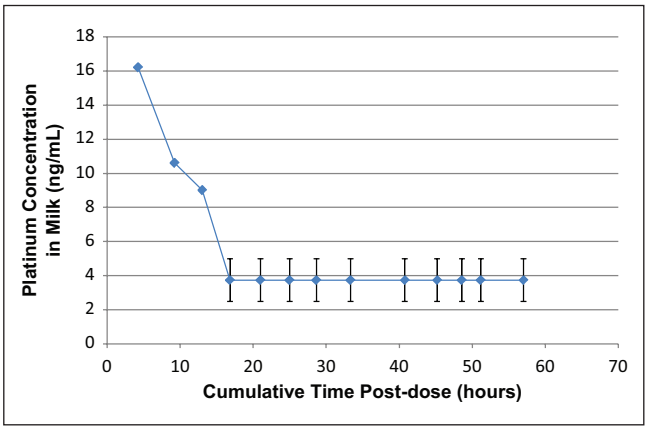
All samples were stored at -80°C until analysis. Breast milk samples were homogenized and wet ashed for evaluation of total platinum concentrations.[15] Quantification was determined by graphite-furnace atomic absorption spectrometry. The lower limit of detection (LLD) of platinum in breast milk was 2.5 ng/mL. The lower limit of quantification (LLQ) was 5 ng/mL.

The initial elimination rate constant (k_{el}) and half-life were determined by log-linear regression analysis. The infant dose of platinum excreted in milk was summed over the total collected interval (breast milk volume × concentration). Because platinum concentrations between 17 and 57 hours were detectable but not quantifiable, we performed 2 calculations to determine infant exposure. The first assumed the concentrations from 17 hours to 57 hours were 5 ng/mL (LLQ). The second assumed these concentrations were 2.5 ng/mL (LLD). Relative infant dose (RID) was calculated by [(infant dose of platinum in milk)/body weight of an age-matched 50th percentile infant boy[16]] / [(maternal dose/actual mother's body weight)] × 100.

Results

The platinum concentration-time curve exhibited biphasic elimination, quantifiable for the initial 13 hours post-dose and above detection limits up to 57 hours post-dose (see Figure 1). Platinum concentration was undetectable at 66 and 70 hours post-dose and not measured after that. The error bar represents concentration above the lower limit of detection (2.5 ng/mL) but less than the lower limit of quantitation (5 ng/mL). The estimated k_{el} was 0.068 $hours^{-1}$ and the calculated half-life was 10.2 hours. The platinum exposure that an exclusively breastfed infant would ingest was 8.8 ± 1.5 µg (range, 7.3-10.3 µg). The relative infant oral dose of platinum ranged between 0.29% and 0.40% of the mother's weight-adjusted dose.

Figure 1. Platinum Concentration in Breast Milk



Platinum concentration-time profile in breast milk following first dose of cisplatin 70 mg IV. The error bar represents concentration above the lower limit of detection (2.5 ng/mL) but less than the lower limit of quantitation (5 ng/mL).

Discussion

This is the first case where platinum in breast milk was followed until its disappearance. Previous cases have determined only the presence of platinum in breast milk and recommended against breastfeeding.[1-3] We found that platinum was undetectable in milk beyond 66 hours following a single infusion of cisplatin 70 mg.

We were unable to calculate the milk-to-plasma (M/P) ratio because maternal plasma was not collected. The M/P ratio documented in previous studies has shown a single measurement of 1.1 after 19.5 hours, and in another case, an average of 0.1 over an 18-hour interval.[2,3]

When cisplatin is given as a bolus injection or an infusion, platinum compounds from cisplatin are extensively and irreversibly protein bound. All pharmacological or toxicological activity from administration of cisplatin is thought to be due to the metabolism of the parent to reactive platinum compounds. These reactive platinum species include both protein-bound high molecular weight species and low molecular weight, non-protein-bound ultrafilterable compounds. Those that irreversibly bind to plasma proteins do not penetrate cells and thus are not able to exert cytotoxic effects. Unbound platinum compounds that are converted into metabolites and the intact drug enter the cell and cause cytotoxicity. Although the plasma half-life of the parent compound is approximately 31 to 37 minutes, platinum accumulates in tissues and is slowly eliminated over several days. In tissues, platinum was present for as long as 180 days and in red blood cells it showed biphasic elimination with a terminal half-life of 36 to 47 days.[8] Such

prolonged presence of platinum in the body has been the concern for exposing the infant to the drug. However, the potential for accumulation is based on daily dosing, not intermittent dosing. Also, it is the free (unbound) form that is therapeutically active. Our assay measured total platinum in breast milk, which is the sum of protein-bound and non-protein-bound platinum from parent and metabolites. Our analysis demonstrated that the amount of platinum present in breast milk was below the detection limit of the assay beyond 66 hours following dosing.

The effects of oral administration of an intravenous preparation of cisplatin have not been studied in infants. Reported adverse events in adults from oral cisplatin studies have been gastrointestinal side effects such as diarrhea, nausea, dysphasia, and constipation.[17] Although more data are clearly needed, it is likely that infants would exhibit similar adverse events if exposed to the drug in therapeutic doses. In neonates, oral bioavailability is likely to be higher than in adults due to elevated gastric pH, slower gastric emptying times, and sporadic peristalsis.[18] Nevertheless, the bioavailability of oral cisplatin is fairly low (30-40% in adults[19]). The infant would orally ingest < 0.2% to 0.3% of a therapeutic dose[20] if fed continuously for 57 hours post-dose. Adjusting for a ~40% bioavailability, systemic exposure would be between 0.08% and 0.12% of a therapeutic dose. Although adverse events could potentially occur at this dose, it is unlikely.

Conclusion

Drugs with a RID < 10% are generally considered compatible with breastfeeding.[21] However, cisplatin is cytotoxic and the prolonged terminal half-life is associated with accumulation following repeated daily dosing. Platinum might be excreted in breast milk for longer periods with repeated doses of cisplatin. Duration and extent of infant exposure to cisplatin via breast milk following serial dosing requires further study. After the first dose, however, resumption of breastfeeding after discarding milk for 72 hours should result in negligible infant exposure.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The project described was supported by grant number U10HD047892 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1RR025014 and the Mylan Chair of Pharmacology at WVU. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health.

References

1. Lanowska M, Köhler C, Oppelt P, et al. Addressing concerns about cisplatin application during pregnancy. *J Perinat Med*. 2011;39(3):279-285.
2. de Vries EG, van der Zee AG, Uges DR, et al. Excretion of platinum into breast milk. *Lancet*. 1989;1(8636):497.
3. Ben-Baruch G, Menczer J, Goshen R, et al. Cisplatin excretion in human milk. *J Natl Cancer Inst*. 1992;84(6):451-452.
4. Egan PC, Constanza ME, Dodion P, et al. Doxorubicin and cisplatin excretion in human milk. *Cancer Treat Rep*. 1985;69(12):1387-1389.
5. American Academy of Pediatrics. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3):827-841.
6. American Academy of Pediatrics. Breastfeeding and the use of human milk. *Pediatrics*. 2005;115(2):496-506.
7. Ip S, Chung M, Raman G, et al. *Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries.* Rockville, MD: Agency for Healthcare Research Quality; 2007. Evidence Report/Technology Assessment 153.
8. Calan P. Platinum compounds: pharmacokinetics and pharmacodynamics. In: Grochow LB, Ames MM, eds. *Clinician's Guide to Chemotherapy Pharmacokinetics and Pharmacodynamics*. Baltimore, MD: Lippincott Williams & Wilkins; 1998:350-351.
9. Pratt CB, Hayes A, Green AA. Pharmacokinetic evaluation of cisplatin in children with malignant solid tumors: a phase II study. *Cancer Treat Rep*. 1981;65(11-12):1021-1026.
10. Edge SB. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 5th ed. New York: Springer; 1997;190.
11. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25(19):2804-2810.
12. Lanciano R, Calkins A, Bundy BN, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2005;23(33):8289-8295.
13. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Eng J Med*. 1999;340(15):1144-1153.
14. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Eng J Med*. 1999;340(15):1154-1161.
15. McGahan MC, Tyczkowska K. The determination of platinum in biological materials by electrothermal atomic absorption spectroscopy. *Spectrochim Acta B*. 1987;42B(5):665-668.

16. National Center for Health Statistics and the National Center for Chronic Disease Prevention and Health Promotion. *Birth to 36 Months: Boys, Length-for-Age and Weight-for-Age Percentiles*. http://www.cdc.gov/growthcharts. Accessed July 17, 2012.
17. Royer B, Guardiola E, Polycarpe E, et al. Serum and intraperitoneal pharmacokinetics of cisplatin within intraoperative intraperitoneal chemotherapy: influence of protein binding. *Anticancer Drugs*. 2005;16(9):1009-1016.
18. Evans WE, Schentag JJ, Jusko WJ. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. Spokane, WA: Applied Therapeutics; 1986:295-299.
19. Urien S, Brain E, Bugat R, et al. Pharmacokinetics of platinum after oral or intravenous cisplatin: a phase 1 study in 32 adult patients. *Cancer Chemother Pharmacol*. 2005;55(1):55-60.
20. Tao Y, Rezai K, Brain E, et al. A phase 1 trial combining oral cisplatin (CP Ethypharm) with radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Radiother Oncol*. 2011;98(1):42-47.
21. Hale TW. *Medications and Mother's Milk*. 10th ed. Amarillo, TX: Hale; 2002:9.