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Duration of cisplatin excretion in breast milk

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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

cisplatin; breastfeeding; human milk; breast 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

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milk”^{5,6}, but does not specify if or when breastfeeding can be safely resumed. Cisplatin is one of these medications. Cisplatin, the parent compound, has a plasma half-life of 31 to 37 minutes following bolus injections or 4–15 minutes infusions of 40 or 100 mg/m².⁸ However, platinum from cisplatin becomes 90% protein bound and shows a more prolonged elimination half-life of five 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, 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/m²), a standard dose in the treatment of her type and stage of cancer,^{11–14} at six weeks postpartum. She received cisplatin 70 mg IV weekly for four cycles with one additional dose. Following University of Washington ethics committee approval and written 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 subject discontinued breastfeeding when she was started on cisplatin at 6 weeks postpartum. She pumped and dumped her breast milk for one week, then discontinued collecting breast milk before receiving her second dose of cisplatin. Although the subject was initially committed to breastfeeding, she abandoned breastfeeding secondary to treatment side effects and her concern about infant exposure. The subject 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 boy¹⁶] / [(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 (Figure). 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 breast-fed infant would ingest was $8.8 \pm 1.5 \mu\text{g}$ (range, 7.3–10.3 μg). The relative infant oral dose of platinum ranged between 0.29–0.40% of the mother's weight-adjusted dose.

Discussion

This is the first case where platinum in breast milk was followed until its disappearance. Previous cases have only determined 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 have shown a single measurement of 1.1 after 19.5 hours, and in another case with 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 adults¹⁹). The infant would orally ingest <0.2–0.3% of a therapeutic dose²⁰ if fed continuously for 57 hours post-dose. Adjusting for a ~40% bioavailability, systemic exposure would be between 0.08–0.12% 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.

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References

1. Lanowska M, Köhler C, Oppelt P, et al. Addressing concerns about cisplatin application during pregnancy. *J Perinat Med*. 2011 May; 39(3):279–285. 5 + [PubMed: 21391877]
2. de Vries EG, van der Zee AG, Uges DR, et al. Excretion of platinum into breast milk. *Lancet*. 1989 Mar 4; 1(8636):497–497. 1 + [PubMed: 2563865]
3. Ben-Baruch G, Menczer J, Goshen R, et al. Cisplatin excretion in human milk. *J Natl Cancer Inst*. 1992 Mar 18; 84(6):451–452. 2 + [PubMed: 1538424]
4. Egan PC, Constanza ME, Dodion P, et al. Doxorubicin and cisplatin excretion in human milk. *Cancer Treat Rep*. 1985; 69:1387–1389. 2 + [PubMed: 4075315]
5. American Academy of Pediatrics, Section on Breastfeeding. Breastfeeding and the use of Human Milk. *Pediatrics*. 2012; 129(3):827–841.
6. American Academy of Pediatrics, Section on Breastfeeding. Breastfeeding and the use of Human Milk. *Pediatrics*. 2005; 115(2):496–506. [PubMed: 15687461]

7. Ip S, Chung M, Raman G, et al. Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries. *Evid Rep Technol Assess.* 2007 Apr.(153):1–186. 5 +
8. Calan, P. Platinum Compounds: Pharmacokinetics and Pharmacodynamics. In: Grochow, LB.; Ames, MM., editors. *Clinician's Guide to Chemotherapy Pharmacokinetics and Pharmacodynamics.* Vol. chap 16. Baltimore, MD: Lippincott Williams & Wilkins; 1998.
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. [PubMed: 7197583]
10. Cuccurullo V, Mansi L. *Ajcc Cancer Staging Handbook: from the Ajcc Cancer Staging Manual.* European Journal of Nuclear Medicine and Molecular Imaging (7th Ed.). 2011; 38.2
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; 25:2804. 4 + [PubMed: 17502627]
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; 23:8289. 5 + [PubMed: 16230678]
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; 340:1144. 5 +
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; 340:1154. 5 +
15. McGahan MC, Tyczkowska K. The determination of platinum in biological materials by electrothermal atomic absorption spectroscopy. *Spectrochim Acta B.* 1987; 42B:665–668.
16. National Center for Health Statistics and the National Center for Chronic Disease Prevention and Health Promotion. [Accessed July 17, 2012] Birth to 36 months: boys, length-for-age and weight-for-age percentiles. 2000 May 30. <http://www.cdc.gov/growthcharts> Updated April 20, 2001
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 Oct; 16(9):1009–1016. 9 + [PubMed: 16162978]
18. Evans, WE.; Schentag, JJ.; Jusko, WJ. *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring.* Spokane, WA: 1986. *Applied Therapeutics*
19. Urien S, Brain E, Bugat R, et al. Pharmacokinetics of platinum after oral or intravenous cisplatin: a phase I study in 32 adult patients. *Cancer Chemother Pharmacol.* 2005; 55:55–60. 5 + [PubMed: 15258698]
20. Tao Y, Rezai K, Brain E, et al. A phase I trial combining oral cisplatin (CP Ethypharm) with radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. *Radiotherapy and Oncology.* 2011; 98(1):42–47. 9 + [PubMed: 21176985]
21. Hale, TW. *Medications and Mother's Milk.* 15th ed.. Amarillo, TX: Hale; 2012.

Figure. 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).