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LETTER TO THE EDITOR

Daptomycin excretion into human milk

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Skin and soft tissue infections (SSTIs) are among the most common infectious disease diagnoses in both inpatient and outpatient settings.

Guidelines on the classification and treatment of SSTIs have been recently updated owing to the increased incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections [1].

Daptomycin is indicated for complicated skin and skin structure infections caused by susceptible isolates of the gram-positive microorganism [2].

Challenges arise in the pharmacological treatment of breastfeeding mothers; to prescribe medications for a breastfeeding mother, the benefits and risks must be weighed up for both the woman and the neonate. Food and Drug Administration and European Medicines Agency labelling sheets report limited experience on daptomycin excretion into human milk, suggesting that caution should be exercised during breastfeeding until more experience is gained [3, 4].

To our knowledge, there has been only one case report published on daptomycin concentration in human milk after parenteral administration to the nursing mother [5].

We report on a case of daptomycin exposure during breastfeeding, and on the results of the analyses performed in the breastfed neonate.

A 34-year-old pregnant woman at 39 weeks' gestation first presented with spreading erythema of the second finger extending to the hand and to the entire left arm, associated with swelling, tenderness and warmth, accompanied by lymphangitis and inflammation of the regional lymph nodes, and fever with chills. She had had one previous pregnancy, with spontaneous delivery of a healthy neonate. The current pregnancy was uncomplicated until she was admitted to the hospital. She denied having diabetes mellitus, alcoholism and tobacco use, and her body mass index was 24 kg m^{-2}.

She reported a self-provoked small injury to the second finger caused by a pair of scissors 2 weeks before the evaluation, and had experienced pain and extending oedema ever since.

The infectious disease specialist was consulted and a purulent acute soft skin infection was diagnosed, and cultures of purulent drainage were obtained.

Owing to her clinical status, labour was induced at 39 weeks' gestation, and a 3270 g healthy male neonate was delivered. There were no complications to either mother or neonate during delivery.

The culture results showed an MRSA-related SSTI, and daptomycin 500 mg intravenously once a day (at 18:30 h) was prescribed for 14 days. The maternal postpartum weight was 68 kg.

The patient was counselled about the lack of data about drug excretion into breast milk, and about possible risks to the infant. Thus informed, the patient wished to continue breastfeeding, and gave her oral informed consent for the current study. Nine samples of breast milk (hindmilk, collected by electric breast pump expression) and five maternal plasma samples were collected during and at the end of the treatment, to determine the milk/plasma concentration ratio of the drug (Table 1).

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Table 1

Milk *vs*. plasma concentrations of daptomycin during the last 4 days of therapy and up to 1 day after the end of treatment

Collection time (Day/time)	Milk sample	Daptomycin in milk (μg ml^{-1})	Plasma sample	Daptomycin in plasma (μg ml^{-1})	Milk/plasma concentration ratio
−4 / 18:30	M1	0.2291	NC	–	–
−3 / 00:30	M2	0.2701	NC	–	–
−3 / 06:30	M3	0.2698	NC	–	–
−2 / 18:30	M4	0.2094	NC	–	
−1 / 18:30	M5	0.1862	P1	44.4	0.004
0 / 00:30	M6	0.3286	P2	199.07	0.002
0 / 06:30	M7	0.3298	P3	65.85	0.005
0 / 18:30	M8	0.2431	P4	64.21	0.004
+1 / 18:30	M9	0.1214	P5	19.89	0.006

Days 0 and +1 were free of therapy
NC, not collected

Daptomycin was quantified by high-performance liquid chromatography, both in the milk and the plasma. Briefly, 400 μl of drug was added with 100 μl of erythromycin solution (internal standard, 10 μg ml^{-1} in acetonitrile) and 300 μl of acetonitrile. The mixture was vortexed for 1 min, sonicated for 15 min and centrifuged for 15 min (0.805 × *g*). The supernatant was withdrawn, centrifuged for 10 min (0.805 × *g*) and filtered on a 0.45 μm filter.

The sample (10 μl) was injected into an Acquity ultra performance liquid chromatography (UPLC) Class System (Waters Corporation, Manchester, UK) equipped with two chromatographic pumps and an autosampler. The chromatographic system is coupled with a triple quadrupole detector (TQD) tandem mass spectrometer, an electro spray ionization (ESI) Z-spray ion source, an Acquity TQ analyser (Waters Corporation) and an Acquity TQD detector (Waters Corporation). The instrument is managed by Mass LinkxTM Software. The instrument was operated in multiple reaction monitoring (MRM) conditions.

The theoretical absolute infant dose (AID) was 36.5 μg kg^{-1} day^{-1}, calculated as the product of median milk concentration and an assumed milk intake of 0.15 l kg^{-1} day^{-1}.

The relative infant dose, estimated as AID expressed as a percentage of the maternal dose in μg kg^{-1} day^{-1}, was 0.50%, well below the most common accepted cut-off of 10% of the weight-adjusted maternal dose [6].

Daptomycin is excreted into human milk at a very low concentration (maximum dosage 0.32 μg ml^{-1}) and the maximum milk/plasma concentration ratio was 0.05, probably due to daptomycin's high protein binding and its high molecular weight [7].

No adverse effects on the breastfed neonate were noted during therapy or during the subsequent 7 days.

Competing Interests

There are no competing interests to declare.

References

1 Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, *et al*. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014; 59: e10–52.

2 Aston JL, Dortch MJ, Dossett LA, Creech CB, May AK. Risk factors for treatment failure in patients receiving vancomycin for hospital-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. Surg Infect (Larchmt) 2010; 11: 21–8.

3 Food and Drug Administration. Highlights of prescribing information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021572s055lbl.pdf (Last accessed 9 November 2017).

4 European Medicines Agency. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000637/human_med_000730.jsp&mid=WC0b01ac058001d124 (Last accessed 9 November 2017).

5 Buitrago MI, Crompton JA, Bertolami S, North DS, Nathan RA. Pharmacotherapy 2009; 29: 347–51.

6 Neville MC, Walsh CT. Effects of drugs on milk secretion and composition. In: Drugs and Human Lactation, ed Bennett PN. Amsterdam: Elsevier, 1996; 15–46.

7 Mitrano JA, Spooner LM, Belliveau P. Excretion of antimicrobials used to treat methicillin-resistant *Staphylococcus aureus* infections during lactation: safety in breastfeeding infants. Pharmacotherapy 2009; 29: 1103–9.