TITLE: DAPTOMYCIN EXCRETION IN HUMAN MILK

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1 table

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

Guidelines on classification and treatment of SSTI were recently update due to increased incidence of methicillin-resistant Staphylococcus aureus (MRSA) [1]

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

Challenges arise in the pharmacologic treatment of the breastfeeding mothers: prescribing medications for a breast-feeding mother requires weighing the benefits and risks for both the woman and neonate.

To our knowledge, a unique case report was published on daptomycin concentration in human milk after parentally administration to the nursing mother[3] .

We report a daptomycin exposure during breastfeeding and we analyzed the exposure of the breastfed neonate.

A 34 years old pregnant woman at 39 weeks of gestation first presented with a spreading erythema of the second finger extending to the hand and to the entire left arm, associated with swelling, tenderness, and warmth and accompanied by lymphangitis and inflammation of the regional lymph nodes and fever with chills. She had one previous pregnancy with spontaneous delivery of a healthy neonate. This pregnancy was uncomplicated until the admission to the hospital. She denied diabetes mellitus, alcoholism, and tobacco use and the BMI was 24 kg/m^2.

Two weeks ago, she reported a little injury to the second finger self caused by a scissor. From that time she complained pain and extending edema.

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

Due to clinical status, labour was induced and a 3270 gr healthy male newborn was delivered. No complications occurred to both mother and neonate during delivery.

The culture result showed a MRSA-related SSTIs and daptomycin 500 mg intravenously once a day (at 6.30 p.m) was prescribed for 14 days. The maternal post partum weight was 68 kg.

She was counseled about the lack of data about drug excretion in breast milk and about possible risks to the infant. Thus informed, the patient wished to continue breastfeeding and gave her informed consensus for this study. Several samples of breast milk and maternal plasma were collected during and at the end of the treatment to carry out the milk-plasma concentration ratio (table 1).

For the analysis breast milk or plasma (400 μL) were added with 100 □L of erythromycin solution (internal standard, 10 μg/mL in acetonitrile) and 300 □L of acetonitrile. The mixture was vortexed for 1 min, sonicated for 15 min and centrifuged for 15 min (60 rpm). The supernatant was withdrawn, centrifuged for 10 min (60 rpm) and filtered on a 0.45 □m filter.

The sample (10 □L) was injected in a Acquity UPLC Class System (Waters, Manchester, UK) equipped with two chromatographic pumps and an autosampler. The chromatographic system is coupled with a TQD tandem mass spectrometer, an ESI Z-Spray Ion Source, a Acquity TQ Waters analyzer and a Acquity TQD Waters detector. The instrument is managed by a Mass LinkxTM Software. The instrument was operated in MRM conditions.

Daptomycin is excreted in human milk in very low concentration (maximum dosage 0.32 □g/mL) and the maximum M/P ratio was 0,05, probably due to daptomycin high protein binding and to its high molecular weight [8] .

The theoretic Absolute Infant Dose (AID) was 36.5 □g/Kg/day, calculated as the product of

median milk concentration and an assumed milk intake of 0,15 L/kg/day.

The Relative Infant Dose (RID), estimated as AID expressed as percentage of the maternal dose g/Kg/day, was 0.50%, well below the most common accepted cut-off of 10% of the weight-adjusted maternal dose. [11] .

The therapy was effective for the mother and no adverse events on the breastfed newborns were noted during therapy and during the subsequent seven days.

References

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Table 1. Milk vs plasma concentrations of Daptomycin (μg/mL)

Time of withdrawal	Milk Sample	Daptomycin in milk (μg/mL)	Plasma Sample	Daptomycin in plasma (μg/mL)	M/P ratio
Day 11; 6.30 pm	M1	0.2291	nc	/	/
Day 12; 0.30 am	M2	0.2701	nc	/	/
Day 12; 6.30 am	M3	0.2698	nc	/	/
Day 13; 12.30 pm	M4	0.2094	nc	/	/
Day 14; 6.30 pm	M5	0.1862	P1	44.4	**0.004**
Day 0; 0.30 am	M6	0.3286	P2	199.07	**0.002**
Day 0; 6.30 am	M7	0.3298	P3	65.85	**0.005**
Day 0; 6.30 pm	M8	0.2431	P4	64.21	**0.004**
Day 1; 06.30 pm	M9	0.1214	P5	19.89	**0.006**

Legend
Day 0: day free of therapy; nc : not collected