Case Report

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Transfer of Doxazosin into Breast Milk

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Abstract

To the best of our knowledge, there have been no published studies of doxazosin transfer into human milk. In rats, milk concentrations twentyfold higher than in plasma have been reported. Based on these animal data, some references advise to avoid breastfeeding during doxazosin therapy. However, the physicochemical properties of doxazosin suggest low transfer into human milk. A 37-year-old breastfeeding woman who was administered doxazosin 4 mg daily for 2 doses was studied. Doxazosin concentrations in milk and plasma were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The milk/plasma area under the concentration–time curve ($AUC_{0\text{-}18\ hours}$) ratio was 0.1. This finding is consistent with what could be predicted based on the physicochemical properties of doxazosin. The average and maximum milk concentrations were 2.9 and 4.2 µg/L. These values correspond to estimated relative infant doses of 0.06% and 0.09%, respectively, assuming standard infant milk intake. These values are well below the generally accepted cutoff of 10% for predicting safety during breastfeeding. A low relative infant dose of < 0.1% suggests that maternal doxazosin therapy may be compatible with breastfeeding after careful individual risk–benefit analysis.

Keywords

breastfeeding, doxazosin, liquid chromatography-tandem mass spectrometry, milk, plasma

Background

Little is known about the transfer of the α-blocker doxazosin into human milk. A search of published literature, including a search of Medline (Ovid 1946–2012) and Embase (Ovid1947–2012) with the relevant MESH headings for each database ("breastfeeding," "breast milk," "lactation," "drug milk level," and "milk, human") and cross-referenced with doxazosin, found no reports investigating transfer into human milk. The manufacturer's product information states that "studies in lactating rats indicate that doxazosin accumulates in rat milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when doxazosin is administered to a nursing mother and in general, nursing should be interrupted."[1] Rats given 1 mg/kg of oral doxazosin had concentrations in milk around 20 times higher than those in their plasma.[2] The data are also limited for the other α-blockers in the class, prazosin and terazosin (literature searched, including Medline and Embase, as described above). Prazosin has been shown to be transferred into human milk in small amounts (weight-adjusted maternal dose [WAMD] < 3%),[3] whereas there are no data for terazosin. Thus, there is little information available to guide the decision of whether to continue feeding in a case in which the mother needs treatment with doxazosin.

Doxazosin (1-[4-amino-6,7-dimethoxy-2-quinazolinyl]-4-[{2,3-dihydro-1,4-benzodioxin-2-yl} carbonyl] piperazine) is an α_1-adrenergic blocker. It reduces peripheral vascular resistance and blood pressure as a result of its vasodilating effects. It is used in treatment of hypertension and benign prostatic hyperplasia.[4] It is also effective in facilitating the passage of urinary stones[5-7] in doses of 2-4 mg/day,[6,7] although this is not a licensed indication.[1] It has a molecular weight of 451.5 g/mol, a pKa of 6.93 (rendering it partly positively charged at physiological pH) and a logP of 2.09.[4,8] Doxazosin is highly protein bound (98%). It is well absorbed after oral administration; peak concentrations are reached within 2-4 hours, and the oral bioavailability is approximately 65%. The volume of distribution is 1-2 L/kg, and the

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mean plasma half-life is 11 hours. Doxazosin is extensively metabolized, mainly by O-demethylation and hydroxylation, and less than 0.5% is excreted unchanged in the urine.[4] The 6′-hydroxymetabolite (which accounts for 5% of a dose) is an α_1-adrenergic blocker, however, studies suggest that the overall contribution from active metabolites is minor.[4,9]

The present single case report provides the first quantitative data on the transfer of doxazosin into human milk.

Case Report

A 37-year-old woman (58 kg) presented with urinary stones. She was breastfeeding a 6-month-old infant (5.6 kg), who was healthy and born at term (3.6 kg). Her doctors wished to prescribe doxazosin 4 mg daily (69 µg/kg/d) until the urinary stones were cleared. Because of the lack of data on the transfer of doxazosin into human milk and the unfavorable animal data, a predicted milk/plasma (M/P) ratio was calculated from the physicochemical characteristics of doxazosin,[10] and absolute and relative infant doses were determined as described in Begg et al.[11] These calculations (described below) predicted doxazosin's transfer into milk to be low, with an estimated relative infant dose of < 0.1%, which is well below the generally accepted cutoff for safety of 10%. Based on this information, the woman agreed to commence doxazosin therapy, which presented an opportunity to sample milk and plasma to study the transfer of doxazosin into human milk. The woman gave written informed consent (protocol approved by the Upper South A Regional Ethics Committee New Zealand, Ethics no. URA/09/06/037). She was not taking any other regular medications, but she had taken some paracetamol intermittently in the days prior to the study.

The woman was administered 2 oral doses of doxazosin 4 mg approximately 24 hours apart. The planned blood sample times were modified to fit in with staff availability, and the planned milk collection times were adjusted by the patient, to accommodate pain and other factors. It was feasible to obtain venous blood samples (5 mL) 18:15 and 21:05 hours after the first dose and 01:00, 13:42, and 18:10 hours after the second dose. The blood was collected in BD Vacutainer K_2 EDTA tubes and centrifuged at 4°C at 4000 × *g* for 10 minutes, and the plasma was stored at -80°C until analysis. Approximately 10 mL of mixed milk (predominantly foremilk) was expressed via a breast pump 17:15 and 21:25 hours after the first dose and 00:55, 10:45, 13:35, and 17:45 hours after the second dose and stored at -80°C until analysis. During the study, the mother also expressed milk for comfort and to prevent mastitis.

The patient's urinary stones were passed prior to administration of a third dose of doxazosin. The patient was discharged without prescription for further doxazosin and declined further participation in the study as an outpatient.

Doxazosin in milk and plasma was quantified by LC-MS/MS (liquid chromatography–tandem mass spectrometry) using the iMethod "Drug Screening–Positive Ions–CES" method from AB Sciex (Foster City, CA). A mixture of 50 µL sample (plasma or milk) and 50 µL internal standard solution (100 µg/L prazosin in acetonitrile) was briefly vortexed, and 100 µL acetonitrile was added to precipitate proteins. Following vortexing and centrifugation for 10 minutes at 14,000 × *g*, an aliquot of 100 µL of the supernatant was added to 150 µL of mobile phase A (2 mM ammonium formate and 0.2% formic acid in water) and 20 µL was injected onto the LC-MS/MS system (Agilent 1200 HPLC, AB Sciex 3200 MS). A PFP propyl column (Restek, Bellefonte, PA), 5 µm, 60Å, 50 × 2.1 mm was used with a 10 × 2.1 mm precolumn of the same material. Mobile phase A consisted of 2 mM ammonium formate and 0.2% formic acid in water, and mobile phase B consisted of 2 mM ammonium formate and 0.2% formic acid in acetonitrile. A gradient was run from 10% B to 90% A over 8 minutes with a 4-minute equilibration time. The analytes were detected by mass spectrometry using positive electrospray and monitoring the 452/344 transition for doxazosin and 384/247 for prazosin.

Standard curves over the range of 1-50 µg/L in both plasma and milk were determined by linear regression weighted 1/x ($r^2 \geq 0.999$). Repeatability (% CV) and bias of triplicate quality control (QC) samples at concentrations of 1 (limit of quantification), 2.5, 10, and 50 µg/L were within 12% for both plasma and milk. Recovery of doxazosin and prazosin from plasma and milk was determined in triplicate at 10 µg/L and was found to be within 95%-104%. There was no evidence of matrix effects, as doxazosin and prazosin spiked in triplicate at 10 µg/L in mobile phase resulted in 103%-104% of the signal obtained in plasma or milk. As the plasma and milk samples were stored for 18 months at -80°C before analysis, QC samples (n = 3 at 10 and 50 µg/L) stored under the same conditions were compared with freshly prepared QC samples and found to be stable (results deviated less than 9%). Each maternal plasma and milk sample was analyzed in triplicate (% CV ≤ 7.3% in all cases), and the mean value was used for pharmacokinetic calculations.

Areas under the milk and plasma concentration time curves (AUCs) were calculated using the trapezoidal rule, and the milk/plasma $AUC_{0\text{-}18hours}$ (M/P) ratio was determined. Average concentrations (C_{av}) in milk and plasma were calculated as AUC/time. Absolute and relative infant doses were determined as described in Begg et al[11] with the following formulas:

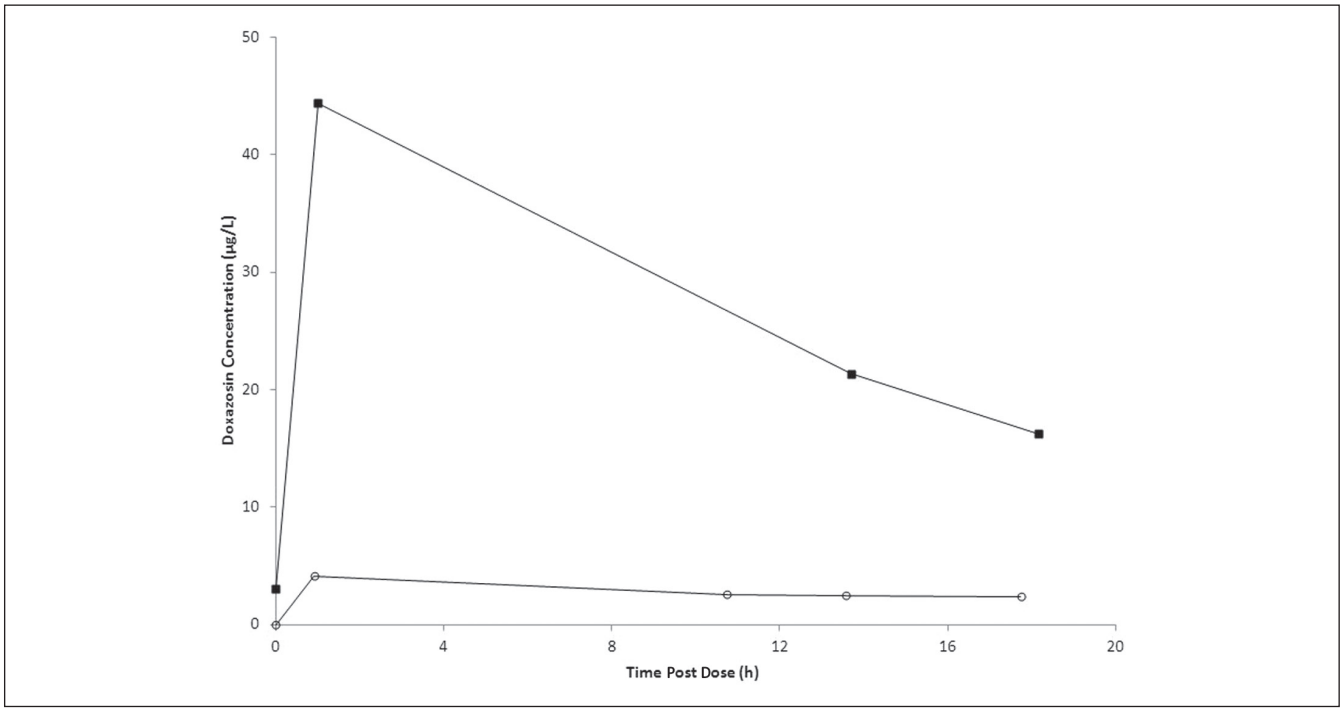
Absolute infant dose = $C_{milk} \times V_{milk}$

- where concentration in milk (C_{milk}) = M/P ratio × maternal plasma concentration
- where volume of milk ingested (V_{milk}) = 150 mL/kg/d

Relative infant dose = infant dose (mg/kg/d) × 100/maternal dose (mg/kg/d)

Calculation of predicted M/P ratio, using the values pKa = 6.93, logP = 2.01, and protein binding = 98%, was performed as described in Atkinson et al[9] with the following formulas:

Figure. Milk (○) and Plasma (■) Concentration–Time Curves for Doxazosin in a Lactating Woman following Administration of Doxazosin 4 mg.



$$\ln (M/P) = -0.09 + 2.54 \ln (Mu/Pu) + 0.8 \ln (fu, p) + 0.46 \ln K$$

$$Mu/Pu = \frac{1+10^{(pKa-7.2)}}{1+10^{(pKa-7.4)}}$$

(7.2 and 7.4 represent the mean pH of milk and plasma, respectively).

$$fu,m = \frac{fu,p^{0.45}}{\left(6.94 \text{ x } 10^{-4}\right)^{0.45} + fu,p^{0.45}}$$

(where fu, p = 1–protein binding)

$$K = \left(\frac{0.955}{fu,m}\right) + \left(0.045 \text{ milk lipid P}\right)$$

(where log milk lipid P = 1.29 log P − 0.88)

The concentration–time profiles for doxazosin in milk and plasma following the second dose of doxazosin are shown in the Figure. As no true predose (0 h) sample was collected, the values obtained for the milk and plasma samples taken 21 hours after the first dose were used. The resulting $AUC_{0\text{-}18 \text{ hours}}$ were 52.0 µg/L·h and 525 µg/L·h in milk and plasma, respectively, giving a M/P_{AUC} ratio of 0.099. This result is almost identical to the predicted value of 0.096, calculated from the physicochemical characteristics of doxazosin. The concentration–time profile of doxazosin in milk was relatively flat and varied less than twofold across the study period. The highest ilk and plasma concentrations were observed at 1 hour post-dose (4.15 and 44.4 µg/L, respectively). The average concentration in milk over the study period was 2.93 µg/L. Using C_{av} = 2.93 µg/L, M/P_{AUC} = 0.099 and an average infant milk intake of 0.15 L/kg/d,[8] an absolute infant dose of 0.044 µg/kg/d was calculated. This result corresponds to a relative infant dose (or WAMD) of 0.06%. For a more conservative approach, C_{max} = 4.15 µg/L could be used instead of C_{av}, giving an absolute infant dose of 0.062 µg/kg/d, corresponding to a relative infant dose of 0.09%.

During the mother's doxazosin treatment, including the study days, infant formula was given and the infant was not breastfed. The infant was not followed clinically by the group following the mother's hospital discharge.

Discussion

The M/P_{AUC} ratio observed in this case study corresponds well with that predicted based on the physicochemical properties of doxazosin. However, this finding contrasts with the 20-fold greater concentrations of doxazosin in milk compared with plasma that has been reported in lactating rats.[2] The ideal

method for quantifying transfer of a drug into human milk involves obtaining M/P_{AUC} ratios from full AUCs for milk and plasma from several subjects.[8] Further, samples of both fore- and hindmilk should ideally be collected (as the differing composition may influence milk concentrations), and any active metabolites of doxazosin should be measured (which was not done here, since the contribution from active metabolites is likely to be minor[9]). However, in reality, studies of transfer of drugs into human milk are often observational and opportunistic, with inherent limitations, as was the case in this study. For the purpose of making a clinical decision about the safety of prescribing a drug during lactation, human data—even if limited—are generally more valuable than extrapolations from animal data, especially when supported by predicted values of drug distribution into human milk from physicochemical characteristics, as was the case here.

Conclusion

In conclusion, a low relative infant dose of < 0.1% was calculated in this case report. As this result is 2 orders of magnitude less than the accepted cutoff for safety (10%), this report provides some reassurance for breastfeeding women who may benefit from doxazosin in the future. However, as this is a single case study, it does not provide definitive conclusions, and studies of more lactating women taking doxazosin would be beneficial.

Declaration of Conflicting Interests

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

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