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Aztreonam in human serum and breast milk

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Serum and milk concentrations of aztreonam were studied in 12 lactating, healthy subjects over the 8 h period after the administration of a single intramuscular or intravenous 1 g dose. Milk concentrations of aztreonam were found to be much lower than serum concentrations at all time points after both routes of injection. Peak milk concentrations of aztreonam averaged less than 1% of peak serum concentrations. Times to peak concentrations averaged 6 and 10 times longer in milk than in serum after intramuscular and intravenous injections, respectively. The low milk levels, as well as the previously determined poor oral absorption of aztreonam, suggest a low risk of untoward effects in the nursing infant.

Keywords aztreonam milk serum pharmacokinetics

Introduction

Aztreonam is a new, monocyclic, β-lactam antibiotic useful specifically for the treatment of infections due to aerobic, gram-negative bacteria. It has minimal activity against anaerobes or aerobic gram-positive bacteria but is extremely active against a broad spectrum of aerobic gram-negative bacteria, with MIC_{50} values often below 0.5 μg/ml (Neu & Labthavikul, 1981).

The most likely use of aztreonam in lactating patients will be in the therapy of infections usually requiring only a single injection, e.g., uncomplicated cystitis and gonorrhoea. Accordingly, this study was designed to examine the passage of aztreonam into human milk after a single intramuscular or intravenous injection.

Methods

Twelve, healthy, lactating subjects, each of whom provided written informed consent, participated in this study. All subjects agreed to discontinue nursing their children for a 48 h period. The first six subjects enrolled in the study each received a single, 1 g intramuscular injection of aztreonam in a volume of 3 ml of sterile water. Six additional subjects received a single, 1 g intravenous injection of aztreonam over a 2 min period, in a volume of 10 ml of sterile water. The subjects averaged 31 years in age (range 23 to 35 years), 56 kg in weight (range 43 to 70 kg) and 159 cm in height (range 128 to 172 cm). Simultaneous serum and milk samples were obtained just before the administration of aztreonam and 15 and 30 min, 1, 1.5, 2, 3, 4, 6 and 8 h after completion of the aztreonam injection. Milk samples were obtained from alternate breasts at each collection period.

Aztreonam concentrations in serum and milk were determined by a previously reported (Swabb *et al.*, 1981) microbiological agar diffusion method using *Escherichia coli* strain SC 12155 as the test organism. Serum samples and standards (pooled human serum 'spiked' with aztreonam) were initially diluted 1:20 in 0.1 M phosphate buffer (pH 6). Subsequent dilutions to test level were made in a diluent of 5% serum

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and 95% buffer. The quantitation limit of this method was 0.45 μg/ml. Serum samples containing less than 0.45 μg/ml as well as pooled serum standards 'spiked' with aztreonam were extracted with methanol, centrifuged and supernatants diluted with 0.1 M phosphate buffer (pH 6), before being assayed microbiologically. The detection limit of the latter assays was 0.04 μg/ml.

All milk samples, except four, were negative (< 0.6 μg/ml), when the samples were initially diluted 1:20 in phosphate buffer, pH 6.0 and assayed directly. Therefore, milk samples and pooled milk standards 'spiked' with aztreonam were centrifuged to separate the fat and the aqueous sample portion was combined with equal volumes of acidified methanol. Following precipitation and centrifugation, the supernatant was filtered through a Millex 0.45 μm filter. The clear filtrate was combined with an equal volume of phosphate buffer, pH 6.0 and these final mixtures were assayed microbiologically. The detection limit of the latter assay was 0.09 μg/ml.

Results and discussion

Mean concentrations of aztreonam in serum and milk over the 8 h time period after each route of injection are shown in Table 1. Milk concentrations of aztreonam were much lower than serum concentrations at all time points after both routes. Measurable milk concentrations that were above the limit of detection of the assay (0.09 μg/ml) were not detectable until 2 h after intramuscular injection and 1.5 h after intravenous injection.

Various pharmacokinetic parameters derived from the individual time curves of aztreonam concentrations in serum and milk are summarized in Table 2. The area under the concentration *vs* time curve (calculated by the trapezoidal rule) and the peak concentrations of aztreonam in milk were less than 1% of those in serum after both intramuscular and intravenous injections. Times to peak concentrations occurred much later (6–10 times later) in milk than in serum. Peak milk concentrations were slightly higher after intramuscular injection (0.3 μg/ml) than after intravenous injection (0.2 μg/ml). The milk/serum ratio for peak concentrations was more than three times higher after intramuscular injection than after intravenous injection but was quite low in both cases (less than 1%).

Acidic drugs and those with low lipid solubility tend to attain lower levels in milk than in blood. For these reasons, the low levels of aztreonam detected in human milk in this study are not surprising, since aztreonam is an acidic drug, having three ionizable groups with estimated pKa values of −0.89, 3.6 and 5.4. Aztreonam also has very low lipid solubility.

Assuming a large milk production of 1 l per day and taking the peak concentration of aztreonam in milk (0.3 μg/ml after intramuscular injection) as a mean concentration, the amount of aztreonam in the daily maternal milk would be about 300 μg or 0.3 mg. The latter is a miniscule proportion (0.03%) of the 1000 mg dose used in this study. On a weight basis, a 5 kg infant would consume a maximum of 60 μg/kg of aztreonam in a 24 h period (300 μg divided by 5 kg equals 60 μg/kg).

The low levels of aztreonam found in milk in this study, along with the very poor oral absorption of aztreonam (Swabb *et al.*, 1983)

Table 1 Mean (± s.e. mean) serum and milk concentrations (μg/ml) of aztreonam after administration of single 1 g intramuscular or intravenous doses

Time after injection (h)	*Intramuscular injection*		*Intravenous injection*	
	Serum	*Milk*	*Serum*	*Milk*
0.25	20.9 ± 5.6	0.00[a]	126.3 ± 17.1	0.00
0.5	33.9 ± 6.1	0.00	75.9 ± 6.5	0.00
1.0	38.3 ± 3.9	0.00	52.8 ± 4.4	0.07[a,b] ± 0.04
1.5	40.0 ± 1.8	0.02[a,b] ± 0.02	37.6 ± 2.8	0.11 ± 0.05
2.0	36.8 ± 1.8	0.14[a] ± 0.04	29.4 ± 2.9	0.18 ± 0.06
3.0	28.8 ± 1.3	0.41 ± 0.19	19.1 ± 1.9	0.18 ± 0.06
4.0	20.3 ± 1.1	0.33 ± 0.08	14.0 ± 1.8	0.22 ± 0.06
6.0	11.6 ± 1.0	0.34 ± 0.08	6.2 ± 1.0	0.14 ± 0.05
8.0	6.0 ± 0.7	0.30 ± 0.07	2.5 ± 0.5	0.12 ± 0.04

[a] Mean based on five subjects where indicated, otherwise based on six subjects.
[b] Measurable concentrations but below limits of accurate quantitation.

Table 2 Mean pharmacokinetic parameters for aztreonam determined from serum and milk concentration data

Parameter	*Units*	*Intramuscular injection*		*Ratio[a] milk/ serum*	*Intravenous injection*		*Ratio[a] milk/ serum*
		Serum	*Milk*		*Serum*	*Milk*	
AUC_{0-8h}	($\mu g\ ml^{-1}\ h$)	173.0	1.5	0.009	182.6	1.0	0.005
C_{max}	($\mu g/ml$)	42.6	0.3	0.007	126.2	0.2	0.002
t_{max}	(h)	1.3	6.0	6.0	0.25*	2.4	9.6

[a] Values based on mean of individual ratios.
* Initial blood sample was collected 15 min after aztreonam injection.

suggest that systemic ill effects would be unlikely to occur in a breast-feeding infant whose mother received a therapeutic dose of aztreonam.

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