Gadopentetate Dimeglumine Excretion into Human Breast Milk during Lactation

**PURPOSE:** To analyze the amount of gadopentetate dimeglumine excreted into human breast milk following intravenous injection of a clinical dose.

**MATERIALS AND METHODS:** Gadopentetate dimeglumine was injected intravenously in 20 lactating women (23–38 years of age). Breast-feeding was interrupted for at least 24 hours. Serial samples of expressed milk were collected and analyzed for gadolinium concentration by means of inductively coupled plasma atomic emission spectrometry at a wavelength of 342.247 nm.

**RESULTS:** The cumulative amount of gadolinium excreted in human breast milk during 24 hours was 0.57 μmol ± 0.71 (SD; range, 0.05–3.0 μmol). The excreted dose was thus less than 0.04% of the administered intravenous dose (range, 0.001%–0.04%; mean, 0.009% ± 0.010) for all cases.

**CONCLUSION:** Less than 0.04% of administered gadopentetate dimeglumine is excreted into human breast milk. The amount transferred to a nursing infant orally would be far more than 100 times less than the permitted intravenous dose (200 μmol per kilogram of body weight) for neonates. The recommendation of a 24-hour suspension of breast-feeding for lactating women should thus be reconsidered.

Unsurpassed soft-tissue contrast, multiplanar imaging capabilities, and an inherent sensitivity to flowing spins have led to an increased use of magnetic resonance (MR) imaging in the postpartum setting. Many of the new MR imaging applications, however, require the use of a paramagnetic contrast agent, such as gadopentetate dimeglumine (1–5). Thus, the likelihood of nursing women becoming potential recipients of a paramagnetic contrast agent has considerably increased in recent years.

Although the pharmacokinetics of extracellular gadolinium-based MR contrast agents are similar to those of iodinated contrast agents (6), they are characterized by a far superior safety profile: Anaphylactoid reactions are rare (7), and there is no associated nephrotoxicity (8). While the agent is generally cleared through renal filtration, little is known about excretion in human milk during lactation. Although several case reports have suggested minimal excretion (9,10), because of a lack of an appropriate database, manufacturers and regulatory agencies recommend a 24-hour administration of paramagnetic contrast agent prior to resuming regular breast-feeding. The physical and emotional hardship to both mother and child caused by this “precautionary” interruption of an established breast-feeding routine can be considerable. Hence, the threshold for performing an MR imaging examination is elevated, which thereby potentially delays an efficient MR imaging-based diagnostic work-up.

The purpose of this study was to determine whether the currently practiced precautionary measures are indeed warranted. Therefore, the amount of gadopentetate dimeglumine excreted into human breast milk following intravenous injection of a clinical dose was quantified in a large study population.

**MATERIALS AND METHODS**

Twenty lactating women (23–38 years of age) agreed to participate in the study on a voluntary basis. The study had been approved by the institutional review board of our institution, and written informed consent was obtained from all subjects.
Gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was injected intravenously. Following the gadopentetate dimeglumine injection, the women were asked to report all associated undesired sensations or side effects. Breast-feeding was discontinued in all participating women for at least 24 hours. Serial samples of expressed milk were collected at different, individually chosen time points that corresponded to the normal breast-feeding schedule of each woman. The women were, however, instructed to attempt to empty both breasts completely at each collection. For each collected sample, the time point after gadopentetate dimeglumine injection and the total volume were recorded, and about 5 mL of each sample was deep-frozen and was stored for subsequent analysis.

Among the 20 women participating in the study, an interruption of breast-feeding was indicated independently of this study in four women. In these patients, contrast agent had to be administered for diagnostic purposes (contrast-enhanced MR imaging, n = 2; excretory urography, n = 2). Two women with preterm deliveries participated because they produced more milk than needed to be stored to feed their neonates at the neonatal intensive care unit. Ten women were weaning their infants at the time of the study, either because of pain or other problems during breast feeding (n = 3), mastitis that required antibiotic treatment (n = 2), or voluntary termination of breast-feeding (n = 5). The remaining four women chose to interrupt breast-feeding for the study, since the infants accepted alternative nutrition. All four continued breast feeding at irregular intervals following the study.

Two women had had preeclampsia during pregnancy. Renal function at the time of the study, however, was within normal limits in all subjects.

In 19 women, a dose of 0.1 mmol per kilogram of body weight was administered. One woman undergoing MR angiography to exclude renal arterial stenosis received a dose of 0.2 mmol/kg body weight, which corresponded to a weight-adjusted volume of 30 mL.

In one of the subjects receiving 0.1 mmol/kg body weight, analysis of the samples was not possible because of technical difficulties, and the patient was therefore excluded from the study. For reasons of homogeneity, the data from the patient who received a double dose of the contrast agent were excluded from comparative data analysis. The statistical results are thus based on a study population consisting of 18 women. Their body weight varied from 48 to 74 kg (mean, 58.7 kg ± 7.0 [SD]).

A mean dose of 5.9 mmol ± 0.6 (range, 4.8–7.4 mmol) of gadopentetate dimeglumine (0.1 mmol/kg body weight) was administered in the 18 subjects, whereas the patient undergoing MR angiography (dose, 0.2 mmol/kg body weight) received a total dose of 15 mmol of gadolinium.

**Sample Analysis**

Aliquots (1 mL) of all samples were digested in a microwave oven under acidic conditions at high temperature and pressure. The clear solutions were then analyzed for gadolinium concentration by using inductively coupled plasma atomic emission spectrometry at a wavelength of 342.247 nm. The total amount and concentration of gadolinium excreted at each time point for each sample were determined. The lower limit of quantification was 0.6 mmol/L of milk. For the purpose of statistical analysis, a value of 0.6 mmol/L was used for those samples in which the amount of gadolinium was below the limit of detection.

**Statistical Analysis**

For each woman, the individual and cumulative amounts of gadolinium in the breast milk excreted during a period of 24 hours and the excreted dose as a percentage of the administered dose were calculated. Gadolinium-excretion values determined in women who were weaning their infants from breast-feeding at the time of the study were compared with those determined in women who were merely interrupting their regular breastfeeding schedule; a volume of expressed milk of 200 mL was chosen as a cutoff value between those two groups.

Data are presented as the mean ± SD. Correlations between person-related data were analyzed by using Spearman rank correlation. Differences between weaning and actively nursing women were analyzed by using the Mann-Whitney test. To provide deeper insight into factors influencing the relative and absolute gadolinium concentrations in the expressed milk, we analyzed individual samples by using simple linear and stepwise regression analyses. In these analyses, logarithmic transformations were used to achieve approximately normal distributions of gadolinium concentrations and milk volumes. All analyses were performed by using STATVIEW (version 4.51; Abacus Concepts, Berkeley, Calif). A P value less than .05 was considered to indicate a statistically significant difference.

**RESULTS**

No unpleasant sensations or side effects were associated with the administration of gadopentetate dimeglumine in any of the 20 women participating in the study.

The results in the 18 women who received a standard dose (0.1 mmol/kg body weight) were included in the statistical data analysis. A mean of 4.0 samples ± 1.5 (range, one to seven samples) were collected over 24 hours in these 18 subjects. The mean volume of milk expressed per sample varied between individual subjects from 2.5 to 161.7 mL (mean, 50.3 mL ± 52.9) (Fig 1). In one woman with mastitis, the administration of Liserdol (metergolinum; Wyeth, Zug, Switzerland; 4-mg dose) resulted in a sudden reduction of the produced breast milk volume. In this woman, only one sample of 2.5 mL could be collected. The mean total volume collected over 24 hours was 224.6 mL ± 273.7 (range, 2.5–970 mL).

The first milk sample was collected 1–13 hours (mean, 2.4 hours ± 2.8) following the injection of gadopentetate dimeglumine. In 15 subjects, the peak value of the gadolinium concentration was detected 1–8 hours following contrast agent administration. In one woman, the peak value was observed in the first sample obtained 13 hours following contrast agent injection (1.91 μmol of gadolinium per liter), while in two women the maximal gadolinium
concentration was identified in the fourth milk sample, which was collected after 9 hours (2.37 μmol/L) in one woman and after 11 hours (13.05 μmol/L) in the other woman (Fig 2).

The gadolinium concentration and the absolute amount of gadolinium in the samples for each subject at the selected time points are depicted in Figure 2a and 2b. The maximum gadolinium concentration excreted over 24 hours varied between 1.64 and 86.3 μmol/L (mean, 9.8 μmol/L ± 19.8) for the individual subjects. The highest concentration of 86.3 μmol/L was measured in the single 2.5-mL milk sample provided by the woman with mastitis in whom the administration of metergolinum had resulted in a sudden reduction in breast milk production. The absolute amount of excreted gadolinium (0.22 μmol) in this case was, however, well within the range in the other cases.

The cumulative amount of gadolinium excreted in human breast milk during 24 hours was 0.57 μmol ± 0.71 (range, 0.052–3.0 μmol). This resulted in an excreted dose of less than 0.04% of the intravenously administered dose (range of the maximum excreted percentage of the cumulative dose, 0.001%–0.04%; mean, 0.009% ± 0.010%) for all cases.

The cumulative amount of gadolinium was significantly correlated with the injected contrast agent volume (P = .01) and thus to the body weight of the nursing mother (P = .03) in the 18 subjects receiving 0.1 mmol/kg body weight. In the patient receiving a double dose (who was excluded from statistical analysis), a similar amount of excreted gadolinium was measured (Fig 2).

There was a significant correlation between the cumulative amount of gadolinium and the volume excreted over 24 hours (P = .002). Gadolinium excretion values in women who were weaning their infants from breast-feeding (n = 13; milk production, 75 mL ± 49; range, 2.5–170 mL; cumulative excretion, 0.25 mmol ± 0.22) were significantly less than those in women who produced more than 200 mL of milk over 24 hours (n = 5; milk production, 613 mL ± 222; range, 357–970 mL; cumulative excretion, 1.39 mmol ± 0.90) (P = .002).

When analyzing 72 individual milk samples by means of linear simple regression analysis, there was no significant correlation between the logarithm of the absolute amount of gadolinium within a sample and the time that passed after injection (P = .12). Results of stepwise regression analysis show, however, that the amount of gadolinium in the samples significantly decreased with time (P < .001) and increased with volume excreted (P < .001) and injected dose (P < .001).

### DISCUSSION

The findings of this study suggest that the recommended 24-hour suspension of breast-feeding following the intravenous administration of gadopentetate dimeglumine should be reconsidered.

The maximal cumulative amount of gadolinium excreted in breast milk over 24 hours was 0.003 mmol. Thus, for any neonate weighing more than 1,000 g, the maximal orally ingested dose would under no circumstance have been higher than 1% of the permitted intravenous dose of 0.2 mmol/kg. In relative terms, the amount of excreted gadolinium in human breast milk over the critical 24-hour period never exceeded 0.04% of the intravenously administered dose. Therefore, even for a heavy mother weighing 100 kg and receiving a maximal dose of 0.3 mmol/kg body weight (administered volume of 0.5-mol/L gadopentetate dimeglumine = 60 mL), a 1,000-g neonate would ingest less than 10% of the maximal dose permissible for intravenous injection.

The data from this study encompassing 20 women are in good agreement with the results of two earlier case studies (9,10). A woman who received the standard 0.1-mmol dose of gadopentetate dimeglumine was reported by Rofsky et al (9) to have excreted a total of 1.6 μmol of gadolinium over 24 hours, which represents 0.023% of the administered dose. Schmiedl et al (10) calculated the measured cumulative amount of excreted gadolinium over 33 hours in another lactating woman as 0.011% of the total intravenously administered dose. These data are well within the range of values determined in this study, with cumulative amounts of gadolinium excreted over 24 hours varying from 0.05 to 3.0 μmol (mean, 0.57 μmol ± 0.71). Although a wide interindividual variability was observed, the excreted dose was less than 0.04% of the intravenously administered dose of gadolinium (range of the maximum excreted percentage of the cumulative dose, 0.001% to 0.04%; mean, 0.009% ± 0.010%) for all subjects in our study.

The results in lactating humans are about a factor of 10 lower than the 0.2% cumulative mammary excretion reported in lactating rats who received a dose of 0.5 mmol/kg body weight (Magnesist product information, Berlex Laboratories, Wayne, NJ, 1989). Schmiedl et al (10) attributed the lower gadolinium ex-
cretion in a patient to the fact that the woman was weaning the infant at the time of gadopentetate dimeglumine administration. By assuming a linear relationship between gadolinium excretion and milk production, a reduced amount of breast milk will result in less gadolinium excretion (10). Our data confirm a significant correlation not only between injected gadolinium volume and gadolinium excretion, but also between gadolinium excretion and milk production. Weaning women excreting a smaller volume of milk (milk volume less than 200 mL) did in fact excrete significantly less gadolinium than those who were merely interrupting their breast-feeding schedule ($P = .002$).

Our results also demonstrate, however, that a reduced milk volume cannot be the sole reason for the noted difference between human and animal data: The cumulative excreted gadolinium dose in women producing more than 200 mL of milk was still much lower than that reported in the animal study. Rofsky et al (9) speculated that the difference between human and rat data could be dose or species related. Our study findings fail to demonstrate a dose-related effect. The patient undergoing MR angiography and thus receiving a 0.2–mmol/kg body weight dose of gadopentetate dimeglumine did not excrete more gadolinium. Rather, the excreted amount was well within the range of the excreted amounts of the subjects who had received the 0.1–mmol/kg body weight dose (Fig 2). Our data thus indicate that the differences in the excretion of gadolinium in rats and in human beings might in fact be species related. A safety discussion should thus be based on the available human data.

Even under the most unfavorable human conditions, the cumulative gadolinium excretion over 24 hours, amounting to less than 0.04% of the administered intravenous dose, does not seem to justify the precautionary 24-hour breast-feeding interruption suggested by the manufacturer of gadopentetate dimeglumine. The gadopentetate dimeglumine volume ingested by the neonate is very small and is far less than the permissible gadopentetate dimeglumine dose for intravenous use in neonates. Of course, one has also to take into account that the allowable risks for a normal breast-feeding newborn compared with those for an infant undergoing contrast-enhanced MR imaging for the evaluation of potential disease might be different.

Gadopentetate dimeglumine has been used for some time as an oral gastrointestinal agent (11). The agent has been shown to be safe, and to our knowledge only mild gastrointestinal side effects have been observed. The majority of those have been attributed to the mannitol included in the oral solution (11,12). Concerns regarding the stability of the gadopentetate dimeglumine compound are considerably less relevant in neonates, since their gastric environment is only slightly acidic (13). Fecal excretion studies have shown 99.2% of the orally administered dose to be recovered in stools within 5 days; thus, only 0.8% of the already minimal orally administered dose is the maximum amount of gadopentetate dimeglumine that is absorbed by the body of an infant (10). This means that the absorbed dose under most unfavorable conditions would be less than 0.0004% of the intravenously administered maternal dose.

We conclude that the very small amount of gadopentetate dimeglumine transferred to a nursing infant does not warrant a potentially traumatic 24-hour suspension of breast feeding for lactating women.

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References