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Pattern of Uptake and Excretion of ^{18}F -FDG in the Lactating Breast

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Excretion of radiopharmaceuticals into breast milk poses a potential risk to infants and clear recommendations regarding interruption times are required. There are few data available regarding the impact of ^{18}F -FDG on this issue. With increasing use of PET for oncologic imaging and its potential advantages to nursing mothers because of its short physical half-life compared with other commonly used tumor imaging agents such as ^{67}Ga and ^{201}Tl , evaluation of the excretion pattern of this agent in breast milk is important. **Methods:** We have evaluated the uptake of FDG in the breasts in 7 women, 6 of whom were lactating and 1 of whom was in early postpartum but had not commenced breast-feeding. Milk samples were obtained from 4 of the lactating women, including serial samples from 1. **Results:** Significantly increased breast uptake was identified in all lactating breasts but not in 1 breast consistently refused by the nursing infant or in the woman who had not begun breast-feeding after delivery of her child. No qualitative change or semiquantitative estimate of radiotracer uptake in the breast was seen after expression of breast milk. Decay-corrected activity measurable in breast milk ranged from 5.54 to 19.3 Bq/mL/MBq injected. Using a standard model of breast-feeding, the calculated maximum cumulative dose to the infant, 0.085 mSv with no interruption of breast-feeding, is well below the recommended limit of 1 mSv. **Conclusion:** High uptake of FDG in the lactating breast appears to be related to suckling. There is, however, little secretion of activity into breast milk. Accordingly, a higher radiation dose is received by the infant from close contact with the breast than from ingestion of radioactive milk.

Key Words: dosimetry; breast; radiopharmaceuticals; ^{18}F -FDG; milk

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The lactating breast concentrates a range of radiopharmaceuticals more intensely than in nonlactating breasts and most normal tissues (1–3). High uptake of radiotracer in the breast represents a potential external radiation hazard to the nursing infant because of close physical contact with the breast. Furthermore, because of the potential for internal radiation hazard to the newborn infant from ingestion of radiopharmaceuticals excreted in the breast milk, cessation

of breast-feeding is generally recommended for several biologic half-lives of the radiotracer.

$^{99\text{m}}\text{Tc}$ -pertechnetate (2) and ^{131}I (3) are widely recognized to be avidly concentrated in the lactating breast. Increased uptake of ^{201}Tl (4) and ^{67}Ga in the breast and secretion into breast milk (5) have also been reported. Although high uptake of ^{18}F -FDG in the lactating breast has been reported (6,7), little information is available on excretion of this tracer into milk. Because of the increasing use of FDG PET scanning in oncology and the potential for studies to be performed in women who are currently breast-feeding, information regarding the uptake, retention, and secretion of FDG in the lactating human breast is important when discussing radiation protection of their infants with nursing mothers undergoing treatment.

We have reviewed our experience with FDG PET scanning of women in the early postpartum period who were referred for evaluation of known or suspected malignancy.

MATERIALS AND METHODS

Because of the short physical half-life of ^{18}F and the lower administered activity of ^{18}F -FDG used at our institution compared with other oncologic imaging agents including $^{99\text{m}}\text{Tc}$ -sestamibi (MIBI), ^{201}Tl , and ^{67}Ga (8), we have recommended use of PET scanning for oncologic evaluation of all women with young infants whenever practical. From the time our facility became operational in late 1996 we have studied 6 women who were breast-feeding around the time they received FDG PET scanning and who provided an opportunity to study the biodistribution of FDG in the lactating breast. Another woman was imaged early in the postpartum period but had not commenced breast-feeding. The clinical details and results of PET scanning for these patients are outlined in Table 1.

FDG was synthesized using a commercially available system (GE Minilab; GE Medical Systems, Milwaukee, WI). Radiochemical purity is >98% for all batches cleared for patient use at our facility.

After a period of fasting of ≥ 6 h, all patients were administered 50–160 MBq FDG and then imaged 1 h later on a dedicated PET scanner (PENN-PET 300H; UGM Medical Systems, Philadelphia, PA). This scanner operates in 3-dimensional mode and requires lower administered activities than conventional 2-dimensional PET scanners (9). The doses administered to patients described in this study were generally based on weight, but in 1 case the administered dose (50 MBq) was limited by availability because the patient was added to the scanning list as an urgent investigation

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TABLE 1
Clinical and Imaging Details

Patient no.	Clinical indication	History	Pattern of breast uptake	SUV
186	Melanoma restaging	Resected right thigh melanoma and inguinal metastasis. One-year-old infant, second breast-fed child. Both preferred to feed from left breast.	Unilateral	No attenuation correction
353	Suspected sarcoma staging and grading	Two weeks post partum. Recent LUCS due to impacted labor. Large pelvic mass.	Diffuse bilateral	No attenuation correction
761	Melanoma restaging	Resected melanoma of the cheek.	Diffuse bilateral	R pre 4.15 L pre 4.98 R post 4.65 L post 4.96
782	Suspected sarcoma staging and grading	Soft tissue mass above right patella suggestive of sarcoma.	Diffuse bilateral	R 5.24 L 5.09
1722	Sarcoma staging and grading	Presumed sarcoma of bone but diffuse bone marrow abnormality on PET suggested hematologic malignancy. Bone marrow biopsy confirmed NHL.	Diffuse bilateral	R 3.51 L 2.56
2579	SCC tongue		Diffuse bilateral	R 3.45 L 3.18
1420	NHL staging	Two days post partum. Newly diagnosed mediastinal mass shown to be NHL. Did not begin breast-feeding.	Not increased	Not calculated

pre = prior to expression of breast milk; post = after expression of breast milk; LUCS = lower uterine caesarean section; NHL = non-Hodgkin's lymphoma; SCC = squamous cell carcinoma; SUV = standardized uptake value.

before planned surgery the following day. All areas of known or suspected tumor were included in the imaging field. Emission scans were acquired for 5 min per bed position. Transmission images of the thorax were obtained using a ^{137}Cs single-photon source in 5 patients, and standardized uptake values (SUV) were calculated for the breast tissue in the 4 patients with higher breast uptake than normal soft tissues. The transmission scan was acquired for 2 min per bed position. Generous regions of interest were drawn for the breast and the maximum SUV within this region was recorded. Images were processed with iterative reconstruction using the ordered subset estimation maximization method (10). Breast-to-background ratios were calculated using a region of interest in the superior mediastinum.

Breast milk was obtained from 4 of the patients who were willing to express samples for measurement. These samples were measured in a well counter. The amount of activity and the volume of the sample were recorded. The activity per milliliter of breast milk was corrected for the activity administered to the patient and

corrected for decay to both the time of collection and to the time of FDG administration. One patient provided serial samples at 45, 70, 195, and 210 min after FDG administration.

RESULTS

Pattern of Breast Uptake

All but 1 of the 6 patients who were breast-feeding an infant in the days before PET scanning was performed had diffuse and symmetric uptake in the breasts (Fig. 1). One patient had unilateral uptake in the left breast (Fig. 2). The patient was subsequently questioned regarding her breast-feeding routine. She reported that for many months her infant had refused to feed from the right breast and consequently she effectively only fed from the left breast. One patient with newly diagnosed lymphoma had not begun breast-feeding after delivery of her child 2 d earlier. She had

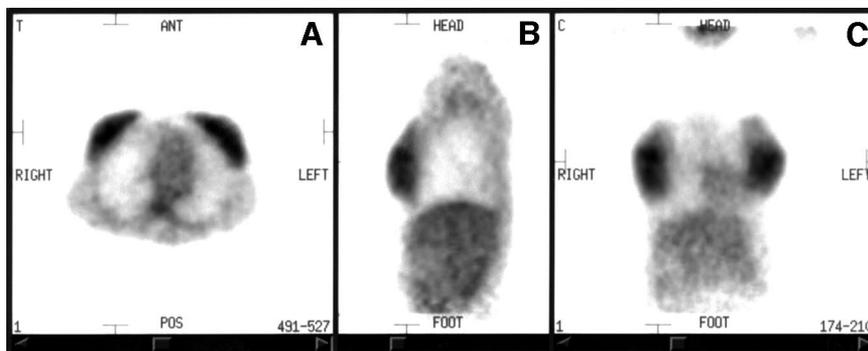
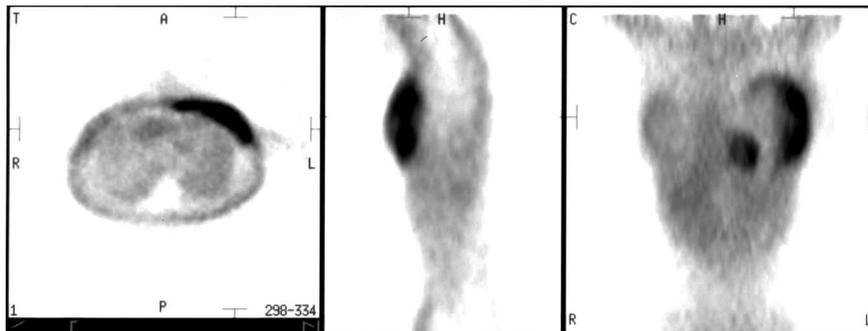


FIGURE 1. FDG PET scan of patient 2579 acquired 65 min after administration of 60 MBq radiotracer demonstrates diffusely increased activity in both breasts. Representative transaxial (A), sagittal (B), and coronal (C) planes through right breast are shown. The images were processed with measured attenuation correction.

FIGURE 2. FDG PET scanning on patient 186 was performed 50 min after intravenous administration of 100 MBq radiotracer. Representative images of the thorax without attenuation correction show diffuse and intense uptake of activity in left breast comparable to cardiac uptake but little uptake in right breast. The patient reported that her infant had refused to feed from right breast.



not received any medication to suppress lactation and described tender breast engorgement at the time of PET scanning. Radiotracer uptake was not significantly increased in her breasts (Fig. 3).

Excretion of FDG into Breast Milk

The collection of milk samples was constrained by the circumstances under which these studies were performed in a busy clinical PET facility. However, breast milk samples were provided by 4 patients. One patient provided serial samples between 45 min and 3.5 h after administration of FDG. Correcting for decay from the time of FDG administration and for the activity administered to the patient, the maximum specific activity in breast milk was 19 Bq/mL/MBq administered. This was recorded for the sample obtained at 3 h. The single samples from the other 3 patients had lower decay-corrected specific activity than this (17 Bq/mL/MBq administered on a sample obtained at 2 h and 5 Bq/mL/MBq administered obtained at 1.5 h after administration, respectively) but were comparable with the decay-corrected results obtained at similar time points in the patient with serial samples. Because of the short physical half-life of ^{18}F , the absolute specific activity in the late milk samples was substantially less than these decay-corrected values. The highest measured value at the time of the sample was expressed was 9.8 Bq/mL/MBq administered. This was recorded for a sample obtained at 1 h. Only 1 sample was obtained at 3 h. The measured specific activity at this time was 5.6 Bq/mL/MBq administered.

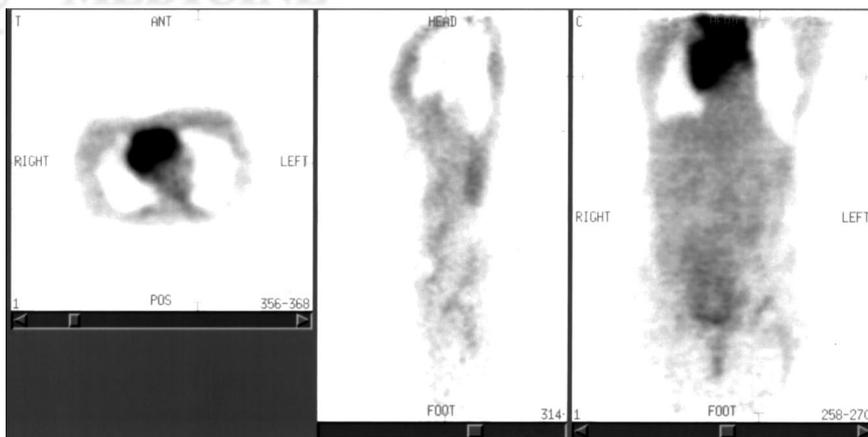
Imaging was performed before and after expression of milk from 1 breast in 2 patients. Qualitatively, and based on breast-to-background activity ratios, no change in breast activity was demonstrable after expression of breast milk. A 200-mL sample of breast milk placed in the PET field view with the breasts could not be visualized. In 1 case SUV calculations were performed for each breast before and after expression of breast milk. There was no significant change in SUV in either breast on this evaluation (Table 1).

In 1 patient use of a personal dosimeter (Berthold UMO-LB1236 dose rate probe) applied to the skin over each breast yielded average dose rates of 59 and 62 $\mu\text{Sv/h}$ at the 2.5 h after intravenous administration of 160 MBq FDG compared with 70 $\mu\text{Sv/h}$ recorded over the lower abdomen.

DISCUSSION

Lactation is under the control of pituitary and adrenal hormones, particularly prolactin. The “let-down” phenomenon is a bilateral sensorineural reflex stimulated by suckling and mediated by oxytocin. Although bilateral breast uptake would be generally expected in breast-feeding women, 1 of our cases shows that protracted use of only 1 breast for nursing can lead to loss or reduction of metabolic uptake of FDG in the unused breast. The lack of breast uptake in the woman who had not begun breast-feeding and who had not received medication to reduce prolactin secretion also suggests that suckling rather than prolactin is an important stimulus for FDG uptake in the breast.

FIGURE 3. FDG PET scan of patient 1420, 2 d after delivery of her child but before breast-feeding commenced. No medications had been given to suppress lactation. No increase in uptake is noted in breasts but intense uptake in mediastinal lymphoma is shown on these images acquired 70 min after 110 MBq radiotracer and processed with measured attenuation correction.



Asymmetric uptake of ^{131}I appears to be common in lactating women; it was present in 60% of women in one recent study in which women had ceased nursing not long before receiving radioactive iodine therapy for thyroid carcinoma (3). In 3 of 20 patients (15%), unilateral breast uptake was noted that was unrelated to prior mastectomy. However, 1 of the patients had had an episode of mastitis on the side with low uptake. Earlier studies (11) also reported asymmetric radioactive iodine uptake, which the authors ascribed to infant preference of selective breast-feeding from 1 side as described by 1 of our patients.

Four patterns of breast uptake of ^{131}I have been described for the recently lactating breast: full, focal, crescent, and irregular (3). The "full" pattern, similar to that observed in our patients, appears to be the most common and was observed in 20 of 38 breasts (53%). The "crescent" pattern has been suggested to reflect, possibly, recent emptying of milk. The lack of change in the absolute activity or the distribution of radiotracer after expression of milk would independently suggest low excretion of FDG, which is supported by the low activity measured in expressed milk. This was documented in all 4 cases where the patient was able to express a milk sample. Given the metabolically inert nature of phosphorylated FDG which leads to intracellular trapping of this agent, low excretion into milk is not unexpected. It is possible that the measured activity in the milk is related to the cellular elements of breast milk, particularly lymphocytes. Further characterization of the chemical form and partition component of the activity in milk requires additional study.

Experimental studies in rats have revealed that there is increased expression of the insulin-independent glucose transporter, GLUT-1, and absence of the insulin-dependent transporter, GLUT-4, in the lactating breast. GLUT-1 expression decreases rapidly after cessation of suckling (12,13). This is also the likely explanation for high uptake of FDG in the lactating breast and further supports the importance of suckling as the primary stimulus for the phenomenon. Because GLUT-1 is also the major glucose transport protein in malignant tissues, detection of breast malignancy in the lactating breast is likely to be compromised.

Allowing for decay, the concentration of FDG in the breast milk appeared to peak at 3 h after administration. However, the highest actual activity in expressed breast milk at any time point was found at 1 h. This value was 9.8 Bq/mL/MBq administered. The standardized model of breast-feeding (14) assumes no interruption, with a first feed at 3 h after administration and then every 4 h thereafter, with the baby consuming 142 mL per feeding and a dose factor for the infant of 0.23 mGy/MBq ingested for ^{18}F . Only 1 sample was obtained at 3 h, but, allowing for decay, this sample appeared to be representative of activity appearing in milk at other time points; therefore, decrease of activity in the milk was assumed to occur only by radioactive decay. Using the activity in this sample (5.6 Bq/mL/MBq admin-

istered) the estimated cumulative dose to the infant was calculated to be approximately 0.085 mSv, well below the 1 mSv recommended for cessation of breast-feeding (1). The administered activity routinely used with dedicated, 3-dimensional sodium-iodide detector PET scanners is around 120–150 MBq. This usage is substantially less than that generally used for conventional bismuth germanate PET scanners operating in 2-dimensional mode, for which administered activities are generally 300–500 MBq. Despite these differences, there is still a significant safety margin in these calculations allowing the recommendations to be applied irrespective of the imaging device used.

Based on the scan appearances we suspect that the high uptake and retention of FDG in the breast even after expression of breast milk suggests intracellular trapping of the radiotracer in active glandular tissue. Consequently, the breast itself is likely to pose a direct and significant source of radiation exposure to the nursing infant. Confirmation of this potential hazard would require detailed assessment of radiation doses using thermoluminescent dosimeters on the mother's chest and abdomen. This approach was not feasible in these cases but, in 1 case, use of a personal dosimeter applied to the skin suggested that the dose received over the breasts was similar to that recorded over the lower abdomen at 2.5 h after FDG administration, presumably primarily from urinary activity within the bladder, the major route of physiologic excretion of FDG.

The pattern of uptake and low excretion of FDG into breast milk mirrors that of MIBI. In a study of 11 different $^{99\text{m}}\text{Tc}$ -labeled radiopharmaceuticals (2), MIBI had the lowest effective dose from the breast milk (0.08 mSv) but the highest close-contact dose (1.40 mSv) of the agents evaluated. The authors concluded that cessation of breast-feeding is unnecessary after MIBI studies but close contact should be avoided. We believe that similar recommendations are pertinent to FDG studies.

CONCLUSION

These findings indicate the influence of breast-feeding on glandular uptake of FDG in the breast, which has implications for the diagnosis of breast cancer in the postpartum woman undergoing PET scanning. Furthermore, they suggest that the main source of potential radiation hazard to a breast-feeding infant is likely to be in close proximity to the breast (external) rather than ingestion of milk (internal). In patients reluctant to discontinue breast-feeding, expression of breast milk and bottle-feeding by a third party could help to minimize radiation exposure to the infant. The short physical half-life of ^{18}F and the low excretion of FDG into breast milk support the use of PET as the preferred oncologic imaging procedure in nursing mothers if imaging cannot otherwise be avoided.

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