Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings, and Radiation Dosimetry*

Michael G. Stabin and Hazel B. Breitz

Departamento de Energia Nuclear, Universidade Federal de Pernambuco, Recife, Brazil; and Department of Nuclear Medicine, Virginia Mason Medical Center, Seattle, Washington

The excretion of radiopharmaceuticals in breast milk is studied to understand excretion mechanisms and to determine recommended breast feeding interruption times for many compounds based on the radiation absorbed dose estimated. A literature review is summarized, providing information on breast milk excretion of many radiopharmaceuticals, including the observed fractions of administered activity excreted and the disappearance half-times. Radiation doses to the infant and to the mother's breasts have been calculated using mathematical models of the activity clearance into milk, with interruption schedules for the nursing infant derived using a dose criteria of 1 mSv effective dose to the infant. In only 9 of the 25 radiopharmaceuticals considered here is interruption in breast feeding thought necessary. However, in the literature, breast milk concentrations of radiopharmaceuticals and half-times varied considerably between subjects, and individual measurements are encouraged to raise confidence in specific cases. The absorbed dose to the mother's breast approaches 10–20 mGy (1–2 rad) for a few nuclides, but most doses are quite low. Therapeutic administration of ^{131}I-NaI is a special case, for which the breast dose for a 5550 MBq (150 mCi) administration could approach 2 Gy (200 rad). In this article, these data are discussed, with the aim of assisting others in evaluating the significance of administration of radiopharmaceuticals to lactating women. An example of a sampling scheme and calculation to determine dose for a specific patient is also developed.

Key Words: dosimetry, breast, radiopharmaceuticals

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The issue of breast milk excretion of radiopharmaceuticals and ingestion of the associated radionuclides by the nursing infant has been of concern for many years, as has been reported in the literature for many years. Ingestion of the radioactive material by a nursing infant may result in a significant radiation dose to some of the organs of the infant, and several documents have been published suggesting guidance for the lactating patient (*1–4*). In addition, there may be a radiation dose to the infant from proximity to the mother before the radionuclides have cleared from her body (assuming that there are some photon decay components) (*5*). Transfer of ^{131}I-NaI from nursing mothers to infants, involving "significant" uptakes in the children's thyroids, has been documented (*6*). More commonly, the issue involves balancing the risk and benefits of interruption or cessation of breast feeding in a setting in which the mother receives a diagnostic administration of a radiopharmaceutical.

In this article, we (a) describe the female breast anatomy and the physiology of the production and excretion of breast milk; (b) summarize the known data on breast milk excretion of radiopharmaceuticals from data available in the literature; (c) estimate the possible infant radiation doses from ingestion of excreted radionuclides (computer models were used to simulate the excretion of breast milk and the uptake of milk by the infant and dose conversion factors were then applied for the infant); (d) discuss the impact on these doses provided by interruption of breast feeding cycles; and (e) evaluate the radiation dose to the mother's breast from radiopharmaceuticals in the breast milk.

The published literature dates back many years, and, although some radiopharmaceuticals are no longer widely used, the doses from these radiopharmaceuticals are evaluated here, to provide a better understanding of the range of results possible.

FEMALE BREAST ANATOMY

There is substantial variation of the normal anatomy of the breast among individuals and within an individual at different stages of life. Specific changes occur with puberty, the menstrual cycle, pregnancy, lactation, postlactation involution, and menopause.

The breasts, or mammary glands, consist of milk-producing cells (glandular epithelium) and a duct system embedded within connective tissue and fat (*7*). Each breast extends from approximately the second to the sixth rib below and from the side of the sternum to the anterior axillary line. The left breast is generally larger than the right, and the weight varies in different individuals and at different times. For example, a single breast in a nonpregnant woman

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For correspondence or reprints contact: Michael Stabin, PhD, CHP, Departamento de Energia Nuclear, UFPE, Av. Prof. Luiz Freire, 1000-Cidade Universitaria, CEP 50740–540, Recife PE, Brazil.

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may weigh 200 g. By the end of pregnancy it may weigh 400–600 g and during lactation may increase to 600–800 g.

The mammary glands lie within superficial fascia on the front and sides of the chest. The superficial layer of fascia forms an irregular boundary for the anterior surface and is separated from the skin by 0.5–2.5 cm of fat and areolar tissue. Strands of fibrous tissue extend from this fascia through the subcutaneous fat to the skin. At the nipple there is no separation between fascia and skin. The posterior surface of the breast is enclosed by the deep layer of fascia and is separated from the pectoralis muscle by a layer of fat.

In the adult mammary gland there are 15–20 irregular lobes converging on the nipple and separated by thin, poorly defined, fibrous septae. Each lobe is drained by its own lactiferous duct, which is 2–4.5 mm in diameter. Before the duct ends, there is a local dilatation, the lactiferous sinus beneath the areola. Each duct narrows as it passes toward the summit of the nipple, and each duct ends in its own opening of 0.4–0.7 mm. Alternately, several ducts may join and have a common opening. Thus there may be as few as 6–8 openings. Epithelial debris within the subareolar ducts is considered normal and may be associated with diffuse or localized thickening of the ducts. The number of the tubules and the size of these structures vary, being most numerous during lactation.

The essential parts of the breast are the functional elements and the supporting structures. The walls of the secretory portions, the alveolar ducts and alveoli, consist of a row of low columnar cells, with larger myoepithelial cells arranged near their bases. These myoepithelial cells can behave as functional tissue or supporting tissue. The ducts are surrounded by fibrous connective tissue. Intralobular connective tissue consists of many cells, few collagen fibers, and little fat. This loose connective tissue is a distensible medium for hypertrophy of the epithelial portion of the breast during pregnancy.

During pregnancy there is an increase in size and density of the breasts. Glandular tissue fills all of the central portion of the breast.

THE PHYSIOLOGY OF LACTATION

Lactation becomes fully established within the first week after the baby is born. In the first few days, colostrum is secreted (*8*). This is high in protein, which is derived from the mother's plasma protein. Initiation and maintenance of lactation is a complex neuroendocrine process. This involves the sensory nerves of the nipples and adjacent skin, the spinal cord, the hypothalamus, and the pituitary gland with its various hormones. Milk production occurs in 2 phases, synthesis and secretion into the alveolar lumen and the propulsion or ejection phase.

Synthesis and Secretion

Milk secretion is most active when the infant is suckling and occurs at lower levels at other times. Milk production occurs under the influence of many hormones, prolactin being the most important. Prolactin is produced in the posterior pituitary gland and combines with receptors in the breast tissue. The hormone receptor complex is internalized into the cell, and milk production stimulated. Each milk-producing cell proceeds through a secretory process that is preceded and followed by a resting phase. Prolactin increases the production of the milk protein casein and its products and also increases the rate of fatty acid synthesis in breast tissue. The secretory cells are cuboidal in their resting phase but become elongated as water content is increased just before secretion. As secretion begins, the apical membrane becomes thickened and clublike and the tips pinch off; thus the milk is secreted and the cell remains intact. There are 4 processes of excretion from the alveolar cells into the lumen.

1. Proteins, carbohydrate, calcium, phosphate, and citrate are packaged into secretory vesicles and secreted by exocytosis. The proteins are made predominantly in the breast from amino acids derived from the blood or synthesized in the breast tissue and include casein, α-lactalbumin, and β-lactalbumin. The plasma-derived proteins occur predominantly in the colostrum in the first few days of lactation. The predominant carbohydrate is lactose, which is synthesized in association with the Golgi apparatus in the cell, from circulating glucose. The concentration of lactose in milk is constant, and this appears to be the limiting factor in the volume of milk produced. Calcium, phosphate, and citrate are transported into the Golgi vesicles from the cytoplasm. Water is drawn into the Golgi by osmosis. Secretory vesicles then bud off from the Golgi complex and move toward the apical portion of the cell, where they fuse with the apical membrane and release their contents into the alveolar lumen. The mammary ducts are freely permeable to water, but milk remains iso-osmotic with plasma.
2. Lipids and triglyceride are formed within the cell and coalesce to form large droplets that gradually make their way to the top of the alveolar cell, where they are enveloped in apical plasma membrane. The milk fat globule then separates from the cell. Milk fat composition is altered by diet.
3. Monovalent ions and water penetrate the apical membrane freely. Water and sodium and potassium ions move across the membrane in response to the osmotic gradient set up by the lactose, and the electrolytes follow the water. Chloride and bicarbonate ions may have an active transport system at the apical membrane.
4. Immunoglobulin and, possibly, other proteins attach to the basolateral wall of the alveolar cell. They are endocytosed and then transported through the cell to the apical membrane, from which they are released.

Ejection

Ejection of the milk is stimulated by the baby suckling on the nipple. This triggers a discharge of the hormone oxytocin

from the posterior pituitary gland, which causes the myoepithelial cells around the alveoli to contract and eject the milk along the alveolar ducts to the baby.

PUBLISHED DATA ON BREAST MILK EXCRETION OF RADIOPHARMACEUTICALS

The content of breast milk varies considerably among different species; therefore we will focus exclusively on measurements from human breast milk when considering the excretion of radiopharmaceuticals. Measurement of breast milk concentrations of radiopharmaceuticals at different times after administration is a relatively easy task, if the patient cooperates in providing the samples. The samples are placed into a well counter or other suitable γ counting device and counted with a calibration standard of known activity. For this reason, data on radiopharmaceutical excretion in breast milk have been relatively plentiful.

Reports usually include concentrations at several different times after administration of the radiopharmaceutical. The concentration of radioactivity in the milk at the time of peak activity and the biologic half-times of clearance from the breast milk are summarized in Table 1 (*9–41*). Noteworthy in the table is the variation in concentrations reported by different authors for the same radiopharmaceutical. It is notable that concentrations of the administered radiopharmaceuticals in the breast milk may vary over orders of magnitude as reported in different studies involving the same radiopharmaceutical, even in studies in which the same pharmaceutical was administered to the same subject at different times (*6*). The reported clearance half-times do not seem to vary quite as widely.

MATERIALS AND METHODS

Dose to the Infant

As has been done previously (*1–3*), we evaluated the possible dose to an infant from ingestion of radiopharmaceuticals, using typical values of administered activity, and a best and worst case model from data reported in the literature. The methods were essentially the same as in those used in NUREG-1492 (*1*), except that a total ingestion of 850 mL/d (not 1000) was used, assumed to be ingested in feedings of 142 mL every 4 h (instead of 125 mL every 3 h) (*3*). For the worst case, we used the highest reported concentration and the longest reported retention half-time; for the best case we used the lowest concentration and shortest half-time. In either case, we combined these 2 worst and best case parameters (concentration and half-time), even if they were not necessarily observed in the same individual (i.e., 1 subject's half-time might be combined with another's concentration). To estimate the amount of the radiopharmaceutical that the infant might ingest, we assumed that the peak concentration was reached at 3 h after administration of the radiopharmaceutical and that the infant also breast fed starting at 3 h after administration and then at 4 h intervals thereafter, consuming 142 mL per feeding (for a total ingestion of 850 mL/day). The breast milk retention curve was thus sampled at 4 h intervals, and the total amount that might be ingested by the infant was determined by summing all of the contributions until the concentrations dropped (as a result of biologic removal or radioactive decay) to negligible values. The effect of interruption for a fixed amount of time was studied by allowing the computer program that sampled the breast milk retention curve to simply start at a later time when performing its summation.

Table 1 lists the observed values for excretion of radiopharmaceuticals in breast milk. For each compound, the table gives the peak fraction per milliliter of milk. The number in parenthesis is the time (h) at which this maximum was observed. "Lowest" is the peak value measured from the patient in the series with the lowest concentration, similarly for "highest." If data from only 1 patient are reported, they are given under the "Highest" column. The lowest and highest biologic half-times are also given for each study. In some cases, as noted above, the total amount of activity excreted in the milk, expressed as a fraction of that administered to the mother, was reported (instead of milk concentrations). These values are documented in the table and noted as such.

Table 1 indicates that, in some cases, the reported effective half-time was longer than the radionuclide physical half-time, thus suggesting some mechanism of continued concentration of activity into the milk over time. In these cases, the effective half-time used in the model was that reported in the literature. For ^{131}I-NaI, 2 authors (*13,30*) reported a 2-component clearance model (with cases involving thyrotoxicosis and carcinoma), whereas others reported only 1. These 2 authors took samples over a much longer period of time (up to 30 and 40 d instead of only to 2–7 d). Only 1 of these authors (*13*), however, gave the associated fractions of administered activity associated with the 2 half-times. Thus, instead of the standard best and worst case model, we used only the Dydek and Blue model (*13*) for both ^{131}I and ^{123}I-NaI.

For the cases in which authors did not report milk concentrations but only the total fraction of the administered radiopharmaceutical that was excreted over time in the milk and the observed half-times, we approached the calculation differently. We used a separate computer program to back-calculate the peak concentration at 3 h after administration that would have produced these total excretion fractions, with the scheme used in our analysis (sampling of 142 mL every 4 h). If appropriate, such concentrations may have been used as either best case or worst case concentrations, with the reported half-times.

For some radiopharmaceuticals, the use of regular periodic sampling of the worst-case retention curve could actually cause the total amount ingested by the infant to exceed 100% of the amount given to the mother. Because of the competition from other pathways to excretion, it was thought reasonable to put a "cap" on the amount ingested by the infant at 50% of the activity given to the mother. This is conservative and is consistent with measurements of excre-

TABLE 1
Biokinetic Parameters for Radiopharmaceuticals Excreted in Breast Milk

Radiopharmaceutical	Excretion fractions* Lowest	Excretion fractions* Highest	Biologic half-time (h)	Reference
^{67}Ga-citrate		9.5E–5 (72)	216	37
	2.7E–5 (38)	3.7E–5 (58)	82–385	32
		5.6E–5 (96)		20
		1.0E–4 (88)		14
		4.3E–5 (48)		40
	3.2E–2†	9.9E–2†	20–390	4
^{99m}Tc-DTPA		6.0E–7 (2.8)	15	24
	5.0E–4†	2.4E–3†	6.5–30	4
		~6.0E–7 (~3)	9.6	9
^{99m}Tc-MAA		1.4E–4 (2.2)	20	22
	~7.1E–5 (5)	~3.1E–4 (7)	9–20	21
		3.6E–5 (4)	5.3	10
		1.4E–4 (3.5)	12‡	12
		7.0E–6 (6)	72	15
	~2.7E–5	~2E–4	4.6–54	31
	~1.5E–5	~2.8E–4	7.3–18	9
^{99m}Tc-pertechnetate		~6.7E–6 (8.5)	~15	35
	2.6E–5 (10)	6.4E–5 (2)	9–66	41
		1.4E–4 (22)	20	38
		~1.8E–5 (3)		29
	7.19E–3 (2.4)	1.7E–2 (2)	7–12	28§
		~5.0E–4 (~5)	6.9	9
		1.7E–4 (8.2)	6	25
		~1.4E–4 (~3)	5.2	16
^{131}I-NaI	2.2E–5 (24)	4.0E–4 (6)	~9.9	6
		6.7E–4 (~6)		39
		6.6E–4	12	13 (2 compartment model)
		+1.6E–5	526	
		2.8E–2 (18)	~9.4	33
		~5.0E–4	14	30
			11	30 (2 compartment model)
			235	
		2.3E–1†	12	4
	2.5E–1†	4.6E–1†	7.6–12	3
^{51}Cr-EDTA	1.5E–4†	6.5E–4†	5.0–7.0	9
^{99m}Tc-DISIDA	1.0E–3†	2.8E–3†	10–(9.1)‖	4
^{99m}Tc-glucoheptonate		1.4E–3†	9.0	4
		2.6E–6	12	25
^{99m}Tc-HAM	8.8E–3†	1.1E–2†	6.0–(7.0)‖	4
^{99m}Tc-MIBI		1.4E–6 (3.3)	23	34
	1.0E–4†	3.0E–4†	18–(6.7)‖	4
^{99m}Tc-MDP/HDP		~2E–6 (~4)	8.4–34	9
^{99m}Tc-PYP	1.5E–3†	4.4E–3†	8.4–(6.8)‖	4
^{99m}Tc-RBC in vivo	~4.8E–6 (~4)	~4.5E–5 (~8)	(6.8–9.5) ‖	31
		~1.5E–7 (~4)	(7)‖	9
^{99m}Tc-RBC in vitro	2.0E–4†	3.0E–4†	(7.8–9.0) ‖	4
^{99m}Tc-sulfur colloid	1.6E–3†	1.5E–2†	35–(8.3)‖	4
^{111}In-WBC		3.3E–7 (13)	(85.3)‖	23
		7.3E–7 (16)	(140)‖	17
		2.4E–7 (20)		11
^{123}I-NaI		2.6E–2†	10.4	16
^{123}I-OIH		6.0E–5	4.8	26
	~3E–5 (~3)	~1.5E–4 (~4)	8.1–10.2	31
^{123}I-MIBG¶		7.2E–6 (8)	85	19
^{125}I-OIH		2.4E–2†	4.8	9
^{131}I-OIH	1.8E–2†	4.9E–2†	2.2–6.0	9

TABLE 1 (*Continued*)

Radiopharmaceutical	Excretion fractions* Lowest	Highest	Biologic half-time (h)	Reference
^{99m}Tc-DTPA aerosol	Fraction of administered aerosol assumed to reach bloodstream (0.406) treated as ^{99m}Tc-DTPA.			
^{99m}Tc-MAG3	Treated as ^{99m}Tc-DTPA (renal agent for which data exist).			
^{99m}Tc-WBC	Treated as ^{99m}Tc-pertechnetate, as fraction of free ^{99m}Tc is highly variable			
^{201}Tl-chloride		2.2E–6	43	27 (2-compartment model)
		+1.9E–7	(362)‖	
		5.9E–7	13	18 (2-compartment model)
		+1.1E–6	(164)‖	

*Peak fraction per milliliter of milk. All values corrected to time of activity administration. Number in parenthesis is time (h) at which this maximum was observed. "Lowest" is lowest concentration observed at peak, and "Highest" is highest concentration observed at peak, in an individual patient. If data from only 1 patient are reported, they are given under "Highest" column.

†Total fraction excreted. Milk concentrations not given.

‡Pooled data from 4 patients.

§Patient admitted for study of enlarged thyroid.

‖Effective half-time > T_P indicates continued activity accumulation.

¶Speciation tests indicated that activity excreted was most likely in form of NaI, not MIBG.

DTPA = diethylenetriamine pentaacetic acid; MAA = macroaggregated albumin; EDTA = ethylenediaminetetraacetic acid; DISIDA = disofenin (iminodiacetic acid derivative); HAM = human albumin microspheres; MIBI = methoxyisobutyl isonitrile; MDP = methylene diphosphonate; HDP = hydroxymethylene diphosphonate; PYP = pyrophosphate; RBC = red blood cells; WBC = white blood cells; OIH = orthoiodohippurate; MIGB = metaiodobenzylguanidine; MAG3 = mercaptoacetyltriglycine.

tion of up to 25% of administered ^{131}I-NaI in milk reported by Robinson et al. (*30*) and Weaver et al. (*39*).

The activity ingested by the infant was assumed to be instantaneously and completely absorbed by the gastrointestinal tract and then to behave as it would in an adult (i.e., the adult biokinetic model for intravenous administration of the radiopharmaceutical was applied to the infant). In this study, the effective dose (ED), as defined by the International Commission on Radiological Protection (ICRP) (*42*) to both the newborn and 1-y-old phantom of Cristy and Eckerman (*43*), was calculated from the individual organ dose estimates obtained. [In the NUREG (*1*), the effective dose equivalent (*44*) was used.] Values used are given in Table 2. One exception was ^{131}I-NaI, because of the possibility of therapeutic amounts of this compound being administered and the possibility that the infant might consume a significant portion. The dose to the infant's thyroid was thought to be the more appropriate quantity to calculate. Because breast feeding might extend past the first year of life, both phantoms need to be considered, although for studying the worst-case dose estimate, one can study only the dose to the newborn.

The presence of possible radioactive contaminants in some of the pharmaceutical products was also considered. The cases considered were: (a) ^{114m}In/^{114}In contaminant in ^{111}In products, (b) ^{125}I contaminant in ^{123}I products, and (c) ^{200}Tl and ^{202}Tl contaminants in ^{201}Tl-chloride. Finding published information about possible levels of these contaminants was difficult. The most common sources of these data are the radiopharmaceutical package inserts. Discussion with some industry experts, however, indicated that the levels listed in most of these inserts may considerably overestimate actual levels encountered in current practice. Therefore, the levels adopted for this analysis were those gathered as a consensus of some experts in measuring these quantities and some values reported in actual case studies. The values used were: (a) ^{114m}In/^{114}In, 0.25%; (b) ^{125}I, 2.5%; and (c) ^{200}Tl, 0.3% and ^{202}Tl, 1.2%. Although industry experts suggested that the level for ^{125}I should be around 0.01%, in 1 case study, this higher value of 2.5% had been reported, and so was used for this analysis.

Estimation of the dose to the infant from scattered photon radiation from the mother is a more difficult task. Mountford and Coakley (*5*) measured the radiation dose for a limited number of radiopharmaceuticals. Extension to other compounds cannot be reasonably made from this short list. In some cases, the dose received by the infant from the mother may be comparable with that received by ingestion of the radiopharmaceutical. In these cases, however, the doses are necessarily low to begin with. It was deemed outside the scope of this investigation to further evaluate this component of the dosimetry. A study to look at this problem more completely would be interesting.

Dose to the Mother's Breasts

The number of disintegrations that will occur during radiopharmaceutical secretion in the milk was estimated from a model that assumed linear filling of the breasts to 142 mL every 4 h and then instantaneous emptying. The radiation dose was calculated using S values for breast-to-breast from the adult female model of Stabin et al. (*45*). The effect of interruption of breast feeding was not studied,

TABLE 2
Values of ED Used in This Analysis

Radiopharmaceutical	ED* Newborn mSv/MBq (rem/mCi)	ED* 1-y-old mSv/MBq (rem/mCi)
^{67}Ga-citrate	1.2 (4.4)	0.490 (1.81)
^{99m}Tc-DTPA	0.030 (0.111)	0.014 (0.052)
^{99m}Tc-MAA	0.17 (0.63)	0.068 (0.252)
^{99m}Tc-pertechnetate	0.14 (0.52)	0.062 (0.229)
^{131}I-NaI†	5,400 (20,000)	3,900 (14,400)
^{51}Cr-EDTA	0.028 (0.104)	0.012 (0.044)
^{99m}Tc-DISIDA	0.22 (0.81)	0.095 (0.35)
^{99m}Tc-glucoheptonate	0.080 (0.30)	0.036 (0.13)
^{99m}Tc-HAM	0.20 (0.74)	0.083 (0.31)
^{99m}Tc-MIBI	0.14 (0.52)	0.065 (0.24)
^{99m}Tc-MDP	0.063 (0.23)	0.026 (0.096)
^{99m}Tc-PYP	0.066 (0.24)	0.028 (0.10)
^{99m}Tc-RBC in vivo labeling	0.070 (0.26)	0.031 (0.12)
^{99m}Tc-RBC in vitro labeling	0.071 (0.26)	0.031 (0.12)
^{99m}Tc-sulfur colloid	0.092 (0.34)	0.042 (0.16)
^{111}In-white blood cells	5.5 (20)	2.2 (8.1)
^{123}I-NaI	2.7 (10)	1.9 (7.0)
^{123}I-OIH	0.051 (0.19)	0.022 (0.081)
^{123}I-MIBG	2.7 (10)	1.9 (7.0)
^{125}I-OIH	0.20 (0.74)	0.082 (0.30)
^{131}I-OIH	0.23 (0.85)	0.093 (0.34)
^{99m}Tc-DTPA aerosol	0.052 (0.19)	0.022 (0.081)
^{99m}Tc-MAG3	0.027 (0.10)	0.012 (0.044)
^{99m}Tc-white blood cells	0.20 (0.74)	0.074 (0.27)
^{201}Tl-chloride	3.6 (13)	2.1 (7.8)

*ED equivalent to infant per unit activity administered intravenously to infant.

†Dose to infant's thyroid per unit activity administered intravenously (or orally) to infant.

DTPA = diethylenetriamine pentaacetic acid; MAA = macroaggregated albumin; EDTA = ethylenediaminetetraacetic acid; DISIDA = disofenin (iminodiacetic acid derivative); HAM = human albumin microspheres; MIBI = methoxyisobutyl isonitrile; MDP = methylene diphosphonate; PYP = pyrophosphate; RBC = red blood cells; WBC = white blood cells; OIH = orthoiodohippurate; MIGB = metaiodobenzylguanidine; MAG3 = mercaptoacetyltriglycine.

because it was assumed that if breast feeding was interrupted the mother would continue to express milk from her breasts periodically and the net effect would be similar to that under normal breast feeding conditions. We also took into account the considerable changes in breast mass that typically accompany pregnancy and lactation, which could involve increases in breast mass by factors of 2–5. These changes are quite variable among individuals and are difficult to model with certainty. However, the effect would be to decrease the dose because the energy will be deposited in a larger mass. The use of the standard breast mass (400 g, both breasts) will thus produce a conservative upper estimate of dose for many women, and a reasonable estimate for lactating individuals with smaller breasts. We also calculated the dose for a breast mass of 800 g, which might be a more appropriate mass for the average lactating individual.

RESULTS AND DISCUSSION

Breast Milk Excretion of Radiopharmaceuticals: Observed Values and Possible Mechanisms

The exact mechanisms for radiopharmaceutical uptake into breast milk are unclear, because detailed kinetic studies have not been performed and because there are no reports on the metabolism of foreign compounds by breast tissue (*46*). Physical properties of a drug, the pKa, water and fat solubility, and protein binding will affect drug distribution. Increasing lipid solubility increases the penetration across membranes and ability to concentrate in milk fat, as does ability to bind to protein. Blood flow to breast is 400- to 500-fold greater than the volume of milk produced, thus there is a selective blood–milk barrier for the ducts. These and other effects are not completely understood, thus our ability to explain all of the extant data is limited.

In general, the concentration of activity in milk samples is of the order of 10^{-4}–10^{-6}/mL. Cranage and Palmer (*12*) reported on the considerable variation in reported concentrations for one compound, ^{99m}Tc-macroaggregated albumin (MAA). However, also apparent from their data is that the reported half-times for reduction of the ^{99m}Tc concentrations are, in general, similar. Some authors report markedly different half-times for the same pharmaceutical, but the reason for the differences in these few cases is not apparent. This is evident for several radiopharmaceuticals in Table 1. Uptake into the breasts and excretion into the breast milk is fairly rapid, with most radiopharmaceuticals showing the highest concentration at the first collection time, usually within 4 h after administration. When the isotope is stably bound to the carrier, (e.g., blood cells) peak uptake is later, and the clearance half-time is slower.

With few exceptions, less than 10% of the administered dose is excreted in the breast milk, and typical estimates range from 0.3% to 5% injected dose, as with MAA and ^{123}I-hippuran (*31*). In one case, 10% of the injected dose of pertechnetate was reported to be excreted in breast milk (*9*). Several authors noted that the concentration and cumulative excretion was higher in patients with greater milk production, i.e., patients who expressed higher volumes. Only in patients receiving ^{131}I-NaI and ^{67}Ga-citrate have cumulative excretions >10% been reported (*30,36*).

For ^{99m}Tc agents, it seems unlikely that the radioactivity in the breast milk is in the same form as the radiopharmaceutical administered. Similarly, it is unlikely that labeled blood cells are being excreted in milk but more likely that the label is being taken up into the breast in some other form (e.g., ^{99m}Tc as pertechnetate). In only a few cases have the authors actually identified the species excreted in the milk. Pertechnetate and iodide have been identified in breast milk, pertechnetate to a lesser extent than iodide; the concentration in the milk being dependent on the labeling efficiency and the stability of the label. Based on the 4 mechanisms of secretion of the milk components suggested previously in this article, pertechnetate and iodide are likely to be secreted, as are other ions. Mountford et al. (22) identified

small fractions of ^{99m}Tc bound to breast milk protein (10%–20% in 1 patient after administration of ^{99m}Tc-diethylenetriamine pentaacetic acid [DTPA] aerosol and MAA). Hedrick et al. (*16*) reported that 7% of the breast milk pertechnetate was protein bound in a patient with thyroiditis.

^{99m}Tc products contain pertechnetate as an impurity, usually less <10%. Pertechnetate found in the urine and feces is from both breakdown products and excretion of injected impurity. Thus the ^{99m}Tc found in the breast milk is most likely entirely or almost entirely free pertechnetate. The variability of concentration of radioactivity in breast milk is thus likely related to the amount of impurity injected as well as the rate of breakdown of the radiopharmaceutical. For example, the method in which ^{99m}Tc-MAA is produced will influence the susceptibility of the MAA particles to breakdown and thus may influence the rate of accumulation in breast milk. The time until sequestration of MAA has occurred reduces the accumulation of radioactivity in the breast because of physical decay. Incomplete emptying, especially when breast milk is artificially expressed, may also contribute to the slow effective clearance from the breast (*31*). Also, there may be a relationship between the time postpartum and the concentration of radioactivity.

A separate investigation was made into the possible consequences of ^{99m}Tc-labeled pharmaceuticals being excreted in the milk in the form of pertechnetate. For all of the ^{99m}Tc-labeled compounds, the dose conversion factors were changed to that of ^{99m}Tc-pertechnetate, whereas the kinetic parameters were left the same. Interestingly, although the doses changed in accordance with the change in dose conversion factor, only for ^{99m}Tc-labeled red blood cells (in vivo) did the counseling recommendation change from no interruption to interruption for 12 h. Thus the consequence of this effect, at least for ^{99m}Tc-labeled compounds, is small. For iodine-labeled compounds, however, the consequence may be much larger, because of the possible concentration of iodine in the infant thyroid and subsequently high radiation doses.

Concentration of iodide in breast milk is several-fold (up to 30 times) higher than the free component in the plasma, because it is actively secreted into the breast (*31,47*). The patient's thyroid function will affect the breast milk concentration. Patients with thyrotoxicosis have a greater thyroidal uptake and less excreted in the breast milk than those patients who are euthyroid or hypothyroid (*16*). Mountford et al. (*48*) identified 5% iodide from ^{123}I-hippuran bound to protein in a study of goat's milk. Differences in chemical purity of iodinated hippuran products from different suppliers are well known and would also account for differences in the excretion measured.

In the studies in which breast milk was counted for several weeks, the breast-milk concentration indicated a 2-compartment model. Initially, there is high uptake, with maximal uptake and excretion within 12 h. The very early excretion is most likely from free iodide in the preparations. The mechanism of this active concentration is most likely similar to that of gastric and urinary excretion. With iodinated protein, e.g., ^{125}I-fibrinogen, the second component of excretion is probably from injected, denatured protein from the breakdown of the injected intact preparation (*21*). Finally, the later slower clearance phase most likely represents turnover of thyroid hormone and breakdown, releasing iodide, which is then slowly taken up by the breast tissue and excreted at a slower rate. In mothers whose infants are nursing more actively, the amount of iodide in the breast milk is higher, probably because of more active milk production (*38*). Binding to breast milk proteins accounts for a small fraction of the activity, >90% is free iodide (*16*).

^{67}Ga has a high binding affinity to lactoferrin and is found in all tissues that contain lactoferrin; thus it is excreted in breast milk bound to lactoferrin (*49*). About 90% of the ^{67}Ga was associated with lactoferrin, which accounts for 15% of the protein in breast milk. The remainder is divided equally between casein and immunoglobulin, and there is a lesser degree of binding to other breast milk proteins.

In published data, several factors confound the assignment of radiation dose to the infant per unit activity ingested. First, the form of radiopharmaceutical excreted in the milk may be different from that given to the mother, but we have assumed that the doses are those from the administered pharmaceutical, except in 1 case. With ^{123}I-metaiodobenzylguanidine, 1 study identified the species in the milk as NaI; thus for this case we applied dose factors for NaI. As noted previously, the consequences are small for ^{99m}Tc-labeled compounds, but may be more significant for iodine-labeled compounds. Second, we assumed rapid and complete absorption of the radiopharmaceutical from the infant's gastrointestinal tract. Pharmaceuticals also may undergo degradation in the stomach and intestines before absorption into the blood and may not be completely absorbed into the blood. In 1 case involving breast-milk excretion of ^{67}Ga (*32*), imaging performed on the child seemed to indicate that the ^{67}Ga was not absorbed from the gastrointestinal tract. In such cases, the organ dose estimates used to obtain the infant ED values have underestimated dose to the gastrointestinal tract and overestimated doses to other organs, with an uncertain effect on the ED. Third, it is not clear that the radiopharmaceutical, even if absorbed into the infant's system as assumed, will have the same biokinetics as in an adult, an assumption that is almost universally made in the absence of specific biokinetic data for children of different ages. Research into all 3 of these areas is required to more credibly establish the dose estimates reported here. However, in many cases, the radiation doses and suggested breast feeding interruption times are small, and these uncertainties may not be terribly significant. In the most important case, that of ^{131}I-NaI, these assumptions are probably more reasonable than in other cases, except that in the very first few days after birth the infant thyroid uptake may be significantly higher than 25% [even approaching 100% (*50*)]. This fact was not taken into consideration in the calculation, because the dose to the

newborn may be used at any time in the first few months postpartum. For infants breast fed during the first few weeks, the doses reported here may be multiplied by a factor of up to 4 to include this consideration if desired.

For ^{131}I-NaI, in both the Dydek and Blue (*13*) and the Robinson et al. (*30*) 2-component models, the half-times of the 2 components are so similar to those for sodium iodide in the body (*51*) that it seems likely that this molecule is passing freely between the blood and the breast milk, probably under the third mechanism (monovalent ions and water) described in the synthesis and secretion section above. Hoffer et al. (*49*) reported that ^{67}Ga has a strong affinity for lactoferrin and proposed a mechanism for uptake. In other cases, it is possible to envision uptake through one of these pathways, e.g., ^{99m}Tc-pyrophosphate by the first excretion mechanism (proteins, carbohydrates, etc.), lipid soluble substances by the second mechanism (lipids and triglycerides), etc. Without identification of the species actually excreted in the milk in each case, however, such suggestions are speculative. The long effective time for ^{201}Tl-chloride suggests the presence of another effect for which an explanation is not readily apparent.

Radiation Dosimetry

In only 9 of the 25 radiopharmaceuticals considered in this article was any interruption in breast feeding thought necessary, given a dose criterion of 1 mSv (100 mrem) ED to the infant (Table 3). In addition, in several cases handled privately by 1 author but never published, involving excretion of ^{133}Xe in breast milk, the concentrations and resultant doses are trivially small, and, again, no interruption of breast feeding is deemed necessary for this pharmaceutical in any case. For 3 of these 9 radiopharmaceuticals, ^{67}Ga-citrate,^{123}I, and ^{131}I-NaI, complete cessation is suggested, because the interruption times needed are prohibitively long or the doses to the infant may be quite large in some cases. For ^{123}I-NaI, a major contributing factor to this recommendation is the reportedly high concentration of ^{125}I (2.5%). With no ^{125}I present at all, only a 24-h interruption is required to reduce the infant ED to 1 mSv, so the level of contaminant assumed is important to this analysis. For several of the ^{99m}Tc-labeled compounds, a short (12–48 h) interruption would be required in the worst case situation to reduce the infant ED to 1 mSv, because 60% of the excreted dose is excreted in the first 4 h.

The reader is cautioned, however, that, as noted previously, individual concentrations vary tremendously (Table 1). In 1 case involving ^{131}I-NaI (*6*), the reported concentrations differ by a factor of perhaps 7–30, even though they were measured in the same subject, only 2 mo apart, while nursing the same infant. It is likely that the concentration was much lower the second time, because the baby was near weaning, when there was less milk production and less iodide being extracted from the blood into the breasts. The salient point here, however, is that the worst case observed so far in the literature may not necessarily be worse than any individual case that might be encountered. It is always advisable to take breast milk samples from subjects and determine on an individual basis the best recommendation, and to continue breast feeding when it is estimated that the infant would receive less than 0.1 mSv. Breast milk samples should be obtained: (a) at about 3 h after administration (this is when the peak concentrations have most often been observed); (b) then, as many more samples as the patient is willing and able to give, over 2–3 effective half-times of the radiopharmaceutical in the body. If there is uncertainty about the biologic half-time, the radionuclide physical half-life

TABLE 3
Summary of Recommendations for Radiopharmaceuticals Excreted in Breast Milk

Radiopharmaceutical	Administered activity in MBq (mCi)	Counseling*	Advised
^{67}Ga-citrate	185 (5.0)	Yes	Cessation
^{99m}Tc-DTPA	740 (20)	No	
^{99m}Tc-MAA	148 (4)	Yes	12 h
^{99m}Tc-pertechnetate	185 (5)	Yes	4 h
^{131}I-NaI	5550 (150)	Yes	Cessation
^{51}Cr-EDTA	1.85 (0.05)	No	
^{99m}Tc-DISIDA	300 (8)	No	
^{99m}Tc-glucoheptonate	740 (20)	No	
^{99m}Tc-HAM	300 (8)	No	
^{99m}Tc-MIBI	1110 (30)	No	
^{99m}Tc-MDP	740 (20)	No	
^{99m}Tc-PYP	740 (20)	No	
^{99m}Tc-RBCs in vivo	740 (20)	Yes	12 h
^{99m}Tc-RBCs in vitro	740 (20)	No	
^{99m}Tc-sulfur colloid	444 (12)	No	
^{111}Tc-WBCs	18.5 (0.5)	No	
^{123}I-NaI	14.8 (0.4)	Yes	Cessation†
^{123}I-OIH	74 (2)	No	
^{123}I-MIBG	370 (10)	Yes	48 h
^{125}I-OIH	0.37 (0.01)	No	
^{131}I-OIH	11.1 (0.3)	No	
^{99m}Tc-DTPA aerosol	37 (1)	No	
^{99m}Tc-MAG3	370 (10)	No	
^{99m}Tc-WBCs	185 (5)	Yes	48 h
^{201}Tl	111 (3)	Yes	96 h

*"No" means that interruption of breast feeding need not be suggested, given criterion of a limit of 1 mSv ED to infant and these amounts of administered activity. "Yes" means that some interruption is required, as noted in the next column.

DTPA = diethylenetriamine pentaacetic acid; MAA = macroaggregated albumin; EDTA = ethylenediaminetetraacetic acid; DISIDA = disofenin (iminodiacetic acid derivative); HAM = human albumin microspheres; MIBI = methoxyisobutyl isonitrile; MDP = methylene diphosphonate; PYP = pyrophosphate; RBC = red blood cells; WBC = white blood cells; OIH = orthoiodohippurate; MIGB = metaiodobenzylguanidine; MAG3 = mercaptoacetyltriglycine.

may be used to estimate this overall time period. A minimum of 2 more samples (after the first sample at 3 h) should be obtained to calculate a good estimate of the retention half-time in the milk.

Once the peak concentration and rate of decrease of the activity are determined, some approximate calculations can be performed by any physician or physicist to estimate the amount of activity that the infant will ingest starting at different points in time. A computer program, such as was used in this analysis to calculate the accumulation of activity in the milk over longer times, is probably not needed in most cases. One can set up a calculation in a simple spreadsheet that sums, for whatever sampling schedule the mother suggests that the infant is likely to follow, the amounts of activity likely to be ingested, using the observed concentrations and rate of elimination. Then, the dose conversion factors in Table 2 can be used to calculate the infant dose.

As an example, assume that for an administration of ^{99m}Tc-pertechnetate the breast-milk concentration reported at 3 h after administration to the mother is 2×10^{-2} MBq/mL. Three more samples, taken over the next 8 h, show a clearance biologic half-time of 20 h. The effective half-time is:

$$\frac{6\text{ h} \times 20\text{ h}}{6\text{ h} + 20\text{ h}} = 4.6\text{ h}.$$

The mother wants to feed the baby (a newborn) approximately every 4 h. Thus for the following times, starting at 12 h after administration (we are already at 11 h after administration), the baby's intakes for the next 7 feedings would be:

T (h)	A(t) (MBq)
12	0.735
16	0.403
20	0.221
24	0.121
28	0.067
32	0.036
36	0.020
40	0.011

Each value of A(t) is given by the expression:

$$A(t) = (142\text{ mL} \times 0.02\text{ MBq/mL}) \times \exp(-0.693 \times (T - 3)/4.6).$$

A(t) (MBq) is the activity ingested by the infant at the feeding at time T (h). We are assuming that the peak concentration (0.02 MBq/mL) occurred at 3 h and then decreased with the effective half-time (4.6 h) thereafter. We took the calculations out to 40 h, when the concentration seemed to have diminished to the point that further contributions would be negligible. The sum of the activity values listed previously is 1.62 MBq. In Table 2, we find a dose value of 0.14 mSv/MBq for a newborn. The cumulative dose, assuming that feeding started at 12 h, would be simply:

$$1.62\text{ MBq} \times 0.14\text{ mSv/MBq} = 0.23\text{ mSv}.$$

This dose is within the guidelines used here, and one would conclude that breast feeding could resume safely at 12 h after administration. If the dose had turned out to be too high, the calculation could be repeated easily, simply excluding some of the values in the table from the sum, starting at 16 h, then at 20 h, and so on, until an acceptable dose value was obtained. The time at which this value was obtained would represent the time at which breast feeding could be resumed. All of these calculations, including evaluation of the half-time by regression analysis, are manageable with available computer spreadsheet programs. Thus, with the aid of the data given in this article and measured data from individual patients, dose calculations can be calculated without the assistance of a radiation dose expert. If individual data are not taken, the values observed so far in the literature may be used as guidance; however, again, the reader is advised that individual variations from literature values may be substantial.

Another problem that can be encountered in clinical situations occurs when women who are lactating receive a radiopharmaceutical for which no excretion data have yet been reported. There is no way to predict what such concentrations might be or to develop specific recommendations for these compounds. The best strategy in these cases is to obtain breast milk samples and perform specific dose calculations (dose conversion factors for other pharmaceuticals, such as those in Table 2 are widely available). This will provide the best safety for the patient and nursing child and also will result in acquisition of new data on breast milk excretion of radiopharmaceuticals that can be published. Failing this, if the pharmaceutical is labeled with ^{99m}Tc, as noted above, although the specific behavior is not predictable, a recommendation for interruption of breast feeding may be derived from the results shown here for other ^{99m}Tc pharmaceuticals. In addition, if the radionuclide is short-lived, one can always simply delay resumption of breast feeding for perhaps 10 physical half-lives and hope that this is sufficient to reduce the infant dose to acceptable levels. If the physical half-life is long or other uncertainties exist, the conservative approach would be to recommend cessation of breast feeding. It is always desirable, if possible, to simply delay the nuclear medicine study until the subject has voluntarily weaned the child.

The dose to the mother's breasts is given in Table 4. The worst case doses for a few nuclides (e.g., ^{67}Ga-citrate and ^{99m}Tc-white blood cells) approaches 10–20 mGy (1–2 rad), but most other doses are quite low. Of course, the most significant case involves therapeutic administration of ^{131}I-NaI, for which the dose reported here for a 5550 MBq (150 mCi) administration approaches 2 Gy (200 rad). Robinson et al. (*30*) estimated 1.6 Gy to the breasts for a woman who received 4000 MBq (~100 mCi), using certain simplifying assumptions. Even though much of the energy may be deposited in the milk itself, the dose will be fairly uniformly distributed over the tissue, so this is a reasonable estimate of the dose received by the radiosensitive cells. These doses are

TABLE 4
Breast Dose from Radiopharmaceuticals Excreted in Breast Milk

Radiopharmaceutical	Administered activity in MBq (mCi)	Breast dose (Gy)	
		Best case	Worst case
^{67}Ga-citrate	185 (5.0)	2.18E–04	1.10E–02
^{99m}Tc-DTPA	740 (20)	6.09E–06	1.20E–04
^{99m}Tc-MAA	148 (4)	1.55E–05	1.21E–03
^{99m}Tc-pertechnetate	1110 (30)	1.86E–05	2.52E–03
^{131}I-NaI	5550 (150)		1.96E+00
^{51}Cr-EDTA	1.85 (0.05)	4.21E–09	2.52E–08
^{99m}Tc-DISIDA	300 (8)	1.94E–05	5.98E–05
^{99m}Tc-glucoheptonate	740 (20)	3.58E–05	7.40E–05
^{99m}Tc-HAM	300 (8)	8.48E–05	2.33E–04
^{99m}Tc-MIBI	1110 (30)	5.54E–06	5.09E–05
^{99m}Tc-MDP	740 (20)	2.69E–05	3.76E–05
^{99m}Tc-PYP	740 (20)	4.16E–05	2.26E–04
^{99m}Tc-RBC in vivo	740 (20)	2.46E–06	1.14E–03
^{99m}Tc-RBC in vitro	740 (20)	9.25E–06	1.61E–05
^{99m}Tc-sulfur colloid	444 (12)	3.17E–05	4.64E–04
^{111}In-WBCs	18.5 (0.5)	5.03E–06	2.52E–05
^{123}I-NaI	14.8 (0.4)		4.74E–04
^{123}I-OIH	74 (2)	7.50E–05	5.84E–04
^{123}I-MIBG	370 (10)		2.71E–04
^{125}I-OIH	0.37 (0.01)		8.46E–07
^{131}I-OIH	11.1 (0.3)	4.97E–05	3.22E–04
^{99m}Tc-DTPA aerosol	37 (1)	1.22E–07	2.49E–06
^{99m}Tc-MAG3	185 (5)	3.04E–06	6.01E–05
^{99m}Tc-WBCs	370 (10)	1.11E–04	1.51E–02
^{201}Tl-chloride	111 (3)	2.35E–05	4.14E–05

Best and worst case as observed from the literature. See text and Table 1.

DTPA = diethylenetriamine pentaacetic acid; MAA = macroaggregated albumin; EDTA = ethylenediaminetetraacetic acid; DISIDA = disofenin (iminodiacetic acid derivative); HAM = human albumin microspheres; MIBI = methoxyisobutyl isonitrile; MDP = methylene diphosphonate; PYP = pyrophosphate; RBC = red blood cells; WBC = white blood cells; OIH = orthoiodohippurate; MIGB = metaiodobenzylguanidine; MAG3 = mercaptoacetyltriglycine.

calculated for the normal breast size of 400 g. If we now assume that the mass changes from 400 to 800 g, the calculated doses will decrease (Robinson et al. used 1200 g). For a given radionuclide, the electron component of the dose will decrease by exactly a factor of 2, and the photon component will decrease by a factor of $(0.5)^{2/3} = 0.63$. But this is so close to a factor of 2 that, given the other uncertainties in the model, we can assume that breast dose will be approximately a factor of 2 lower. Thus, the worst case doses would be approximately 5–10 mGy (0.5–1 rad), and the dose for ^{131}I-NaI is approximately 1 Gy (100 rad).

CONCLUSION

In this article, we have re-evaluated the radiation doses potentially arising from the administration of radiopharmaceuticals to lactating women with subsequent ingestion by the infant. We have updated previous evaluations by: (a) considering the effective dose rather than the older values of ED equivalent used by others; (b) investigating the possible mechanisms of breast milk uptake and excretion of radiopharmaceuticals; (c) evaluating the radiation dose to the mother's breasts during the excretion of the pharmaceuticals; and (d) investigating the effect of the pharmaceuticals being excreted in a form other than that administered to the mother, specifically of the effect of ^{99m}Tc pharmaceuticals being excreted as pertechnetate rather than as a labeled compound. In most cases (16 of 25 radiopharmaceuticals considered), interruption of breast feeding is not warranted to maintain the worst case dose to the infant below 1 mSv, based on data reported so far in the literature. If we assume that all ^{99m}Tc-labeled pharmaceuticals are excreted as pertechnetate, there is little effect on the interruption times. If we assume all iodine compounds are excreted as iodide, the effect may be larger. The dose to the mother's breasts is very high for therapeutic administrations of ^{131}I as NaI (perhaps 1–2 Gy) and approaches 1 mGy for a few cases with diagnostic compounds, but in most cases is quite low. The information and example program in this article should be useful in the further interpretation of situations involving the administration of radiopharmaceuticals to lactating women.

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