Radiation-Dose Calculation for Five Tc-99m IDA Hepatobiliary Agents

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The radiation absorbed doses from five commercially available hepatobiliary agents—Tc-99m-tagged analogs of IDA (EIDA, PIPIDA, HIDA, PBIDA, DISIDA*) have been calculated from biokinetic data in 41 normal subjects. Serial gamma images, with blood and urine samples, were obtained to calculate cumulated radioactivity in the source organs: blood, kidney, bladder, liver, gallbladder, and intestines. The critical organ was the gallbladder, with an absorbed-dose range of 690 to 780 mrad/mCi. Absorbed doses for other target organs were: upper large intestine 320 to 370 mrad/mCi, lower large intestine 210 to 240, small intestine 170 to 200, liver 65 (DISIDA) to 130 (PBIDA), ovaries 63 to 72, and urinary bladder wall 23 (PBIDA) to 36 (EIDA). The radiation absorbed dose was largely independent of changes in chemical structure except in (a) the liver, where absorbed dose varied by a factor of two in proportion to the rate of excretion of the IDA agent from the liver, and (b) the urinary bladder, where absorbed dose varied by a factor of 1.6 because of differences in rate of excretion. When the stimulus for gallbladder emptying is changed from whole-meal ingestion to cholecystokinin injection, the absorbed dose to the gallbladder increases to ~1 rad/mCi; if no gallbladder emptying is assumed, its absorbed dose increases to ~1.9 rad/mCi. In the absence of contraindication, the gallbladder absorbed dose may thus be decreased by inducing gallbladder emptying at the end of the imaging study.

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Hepatobiliary imaging with Tc-99m-labeled derivatives of iminodiacetic acid (IDA) has become a clinically useful procedure since its introduction in 1976 (*1*,*2*). Calculations of absorbed dose for many of these agents are based either on data extrapolated from animals or on incomplete collection in humans. We have recently reported in this journal an absorbed-dose calculation for the first agent, Tc-99m HIDA (*3*), in both health and disease. The current work extends this method of calculation to four of the more recent Tc-99m-labeled analogs of iminodiacetic acid (EIDA, PIPIDA, PBIDA, DISIDA*) using pharmacokinetic data obtained from normal subjects. The recent public awareness, and publication of the effects of low levels of radiation (*4*) should remind the nuclear medicine community of the radiation risks accompanying radiopharmaceutical agents that show high concentration in target organs. The target organs that receive appreciable absorbed dose from IDA agents have been classified (*4*) according to a scheme of radiosensitivity for cancer induction (high, moderate, low, absent) as follows: liver and biliary tract (moderate), alimentary tract (moderate to low), kidney and bladder (low). It thus becomes important to be well informed of absorbed-dose levels and to monitor the administered radioactivity constantly to remain consistent with the policy of minimum radioactivity to obtain adequate diagnostic information.

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MATERIALS AND METHODS

The biokinetic data for the five compounds were collected in 41 healthy adult volunteers (n = 7 for EIDA,

10 for PIPIDA, 10 for HIDA, 7 for PBIDA, and 7 for DISIDA) after intravenous injection of 3–5 mCi (110–190 MBq) of Tc-99m IDA. All subjects fasted overnight before the study. Serial computerized gamma-camera images were obtained for 60 min, with periodic blood and urine sampling for 24 hr as described previously (*3*). The agents to be injected were prepared from the kits* according to the manufacturers' instructions in the packages. The absorbed doses were calculated by the MIRD method (*5*) with mathematical functions fitted to time-activity curves used to calculate the cumulated activity. Source organs included the kidney, bladder, liver, gallbladder, small intestine, and upper and lower large intestine as described previously (*3*).

RESULTS

Cumulated activity. The cumulated activity for the urinary bladder (Table 1) was obtained from the urine data (Table 2) by utilizing a model that included repeated bladder filling and emptying (*3*). Kidney cumulated activity was calculated by assuming instantaneous uptake of activity in the kidney equal to the cumulative 24-hr urinary excretion, with a biological half-time in the kidney of 5 min as reported for Tc-99m DTPA in humans (*6*) and for Tc-99m diethyl-IDA in rabbits (*7*). The cumulated activity for the blood (Table 1) was calculated from the data shown in Table 3, which were fitted by a tri-exponential model (*3*) with parameters shown in Table 4. Hepatic cumulated activity was calculated by measuring the liver uptake and excretion half-time for each agent, based on biexponential fits of time-activity curves for liver minus a blood background (Table 5) (*3*). The liver was considered to be the first compartment in a catenary model of the digestive tract, (*8*,*9*) with the percent activity at t = 0 in the liver determined as 100 minus the percent of activity excreted in the urine in 24 hr (*3*). The short uptake half-time in the liver was ignored. The cumulated activity in the gallbladder (GB) was calculated using light-pen regions of interest at the 59- through 60-min frame of the study, which show that the liver activity divides into two portions, with 56 ± 8% (mean ± s.e.) being diverted into the GB and 44 ± 8% excreted directly into the small intestine (SI). This division of liver activity between GB and SI

TABLE 1. CUMULATED ACTIVITY (μCi-hr) IN SOURCE ORGANS PER mCi OF ADMINISTERED ACTIVITY FOR FIVE Tc-99m IDA DERIVATIVES WHEN WHOLE MEAL IS USED FOR GALLBLADDER STIMULATION

	Agent*				
Source Organ	EIDA	PIPIDA	HIDA	PBIDA	DISIDA
Blood	165	275	167	226	218
Gallbladder	1315	1289	1325	1274	1481
Kidney	20	16	18	6.6	13
Liver	677	1053	770	1883	382
Small intestine	1639	1604	1325	1585	1844
Upper large intestine	2128	2083	1650	2059	2394
Lower large intestine	1040	1019	2143	1007	1170
Urinary bladder	119	100	102	41	71

* See footnote p. 1030.

TABLE 2. URINARY EXCRETION (AS PERCENT OF ADMINISTERED RADIOACTIVITY) FOR FIVE Tc-99m IDA DERIVATIVES (MEAN ± s.e.)

	Hours			
Agent*	0–1	1–3	3–24	Sum 0–24
EIDA	6.9 ± 0.8	4.3 ± 2.9	5.9 ± 1.3	17.1 ± 3.2
HIDA	7.6 ± 1.0	4.1 ± 2.4	3.8 ± 0.8	15.5 ± 2.7
PIPIDA	5.8 ± 0.7	3.3 ± 0.3	5.2 ± 0.7	14.3 ± 1.0
DISIDA	6.1 ± 1.1	1.9 ± 0.6	3.1 ± 0.8	11.1 ± 1.5
PBIDA	2.0 ± 0.4	0.8 ± 0.3	2.8 ± 1.0	5.6 ± 1.1

* See footnote p. 1030.

TABLE 3. BLOOD CLEARANCE (AS PERCENT OF ADMINISTERED ACTIVITY) FOR FIVE Tc-99m IDA DERIVATIVES (MEAN ± s.e.)

Agent*	2 min	4 min	6 min	8 min	10 min	15 min	30 min	60 min	3 hr	24 hr
EIDA	24.1 ± 2.2	18.0 ± 2.0	14.2 ± 1.7	11.8 ± 1.3	9.8 ± 1.3	7.4 ± 1.1	4.2 ± 0.8	3.0 ± 0.6	1.5 ± 0.5	0.6 ± 0.1
PIPIDA	39.2 ± 4.5	34.1 ± 1.7	26.7 ± 1.7	23.3 ± 1.7	18.4 ± 1.4	13.7 ± 1.0	8.5 ± 0.6	4.9 ± 0.3	2.4 ± 0.2	1.2 ± 0.1
HIDA	27.1 ± 4.0	20.0 ± 1.8	18.3 ± 2.0	14.3 ± 2.2	12.7 ± 1.9	10.7 ± 1.1	6.1 ± 0.7	3.0 ± 0.5	1.2 ± 0.2	0.6 ± 0.1
PBIDA	41.4 ± 11.0	39.7 ± 7.7	26.6 ± 7.2	23.3 ± 4.2	20.1 ± 4.0	18.5 ± 5.3	9.9 ± 2.8	2.6 ± 3.9	2.0 ± 0.5	0.7 ± 0.2
DISIDA	33.1 ± 3.7	21.5 ± 2.6	16.3 ± 2.1	13.2 ± 2.1	11.3 ± 1.9	8.5 ± 1.7	5.3 ± 1.4	3.4 ± 1.1	2.0 ± 0.6	0.9 ± 0.2

* See footnote p. 1030.

was considered independent of structural variation in the IDA agent. The GB emptying fraction has been measured by Fisher and Malmud in normal subjects as 87% following a whole meal (*10*). A meal schedule at 4, 10, and 16 hr after injection was assumed; this led to the same cumulated activity as that for a 3.4-hr biological half-time for excretion from the GB as the second compartment in the catenary model. We have measured the GB emptying fraction in normal subjects following injection of 10 ng/kg of octapeptide of cholecystokinin (CCK-8) as 50 ± 8%, representing a 6.8-hr biological half-time for discharge from the GB (*11*). The radiation dose was calculated for two types of gallbladder emptying stimulation: whole meal and CCK-8, and also for none, as would apply in a fasting patient. For simplicity, Table 1 is only for whole-meal stimulation, in which case the GB cumulated activity was lower by a factor of 1.5 than for CCK-8 stimulation, and lower by a factor of 2.8 than for a fasting patient. Cumulated activities in the SI and upper and lower large intestine (ULI & LLI) were calculated via the catenary model with biological excretion half-times of 2.8, 9, and 17 hr, respectively, as previously published (*3,8,9*). The SI cumulated activity for whole-meal stimulation was higher by a factor of 1.1 than for CCK stimulation, and higher by a factor of 1.8 than in a fasting patient.

Absorbed dose. The calculation of absorbed dose in Tables 6, 7, and 8 was straightforward by the MIRD method using the cumulated activities in Table 1 and the S-factors (*12*) for source and target organs, with the exception of the GB since the GB S-factors are not listed in the MIRD data (*12*). For the gallbladder wall as the target it was possible to use recently published S-factors (*13*). For the gallbladder contents (GBC) as a source, a simplifying calculation was performed using S (target ← liver) (*12*) instead of the unavailable S (target ← GBC), so long as the target is not the liver. This approximation for S(target ← GBC) is equivalent to simple addition of the cumulated activities of GBC and liver, and ignoring the GB as a separate source organ as discussed previously (*14*). The only remaining case, liver as target with GBC as source, was handled with the MIRD absorbed-fraction formalism (*5,16*) by assuming that only penetrating radiation from the GBC reaches the liver (LIV), with the unknown specific absorbed fraction Φ_p(LIV ← GBC) replaced with the known Φ_p(LIV ← LIV) (*17*) as first suggested for absorbed-dose calculations with rose bengal (*14*). This yields:

$$S(\text{LIV} \leftarrow \text{GBC}) \simeq \sum_p \Delta_p \Phi_p(\text{LIV} \leftarrow \text{LIV})$$

$$= 0.25 \times 10^{-4} \text{ rad}/\mu\text{Ci-hr}$$

DISCUSSION

For all five Tc-99m IDA agents, with whole-meal gallbladder stimulation (which is typical for a normal

TABLE 4. BLOOD CLEARANCE OF FIVE Tc-99m IDA DERIVATIVES (A = PERCENT ACTIVITY AT t = 0, AND $t_{1/2}$ = BIOLOGICAL HALF-TIME, FOR THE THREE COMPONENTS OF THE EXPONENTIAL FIT)

	Slow		Medium		Fast	
Agent*	A (%)	$t_{1/2}$ (min)	A (%)	$t_{1/2}$ (min)	A (%)	$t_{1/2}$ (min)
EIDA	1.86	855	7.77	19.6	23.2	3.12
PIPIDA	2.15	1720	8.81	39.1	38.5	5.10
HIDA	1.41	1140	16.2	17.4	20.1	2.16
PBIDA	1.44	1600	25.2	17.8	28.8	3.09
DISIDA	2.59	896	13.2	13.5	40.7	1.77

* See footnote p. 1030.

TABLE 5. HEPATIC UPTAKE AND EXCRETION (BIOLOGICAL) HALF-TIME FOR FIVE Tc-99m IDA DERIVATIVES (MEAN ± s.e.)

Agent*	Uptake $t_{1/2}$ (min)	Excretion $t_{1/2}$ (min)
DISIDA	4.82 ± 0.71	18.8 ± 2.5
EIDA	3.70 ± 0.16	37.3 ± 11.8
HIDA	5.90 ± 0.41	42.3 ± 5.4
PIPIDA	4.70 ± 0.26	59.3 ± 5.0
PBIDA	5.20 ± 0.50	107.6 ± 14.1

* See footnote p. 1030.

subject), the critical organ was the GB, with absorbed dose of 690–780 mrad/mCi (Table 6). Absorbed doses in mrad/mCi for other target organs were: ULI (320–370), LLI (210–240), SI (170–200), and liver (65–130). For the DISIDA, GB and intestinal absorbed doses were 10–15% higher than with the other agents, and the absorbed dose to the liver was lower because of the more rapid clearance of DISIDA from the liver (Table 5). The highest absorbed dose to the liver resulted from PBIDA, which had the longest excretion half-time. For urinary bladder and kidneys, PBIDA showed the lowest absorbed dose and EIDA the highest, in accordance with their 24-hr cumulative urine excretions (Table 2).

A recent paper on HIDA absorbed-dose calculation, based partly on animal data, reported absorbed doses that were similar to those calculated here except that the dose for the gallbladder wall was lower by a factor of six (*15*). The lower gallbladder wall absorbed dose found in that report resulted from several factors including:

1. It assumed that only 10% of the injected activity localizes in the gallbladder [a historical assumption obtained from visual interpretation of film intensities with rose bengal (*14*)], contrasting with our measured mean value of 56% of the 83–94% of the administered activity that localized in the liver.

TABLE 6. RADIATION ABSORBED DOSE (mrad/mCi) FROM FIVE Tc-99m IDA DERIVATIVES WHEN WHOLE MEAL IS USED FOR GALLBLADDER STIMULATION

	Radiopharmaceutical*				
Target Organ	EIDA	PIPIDA	HIDA	PBIDA	DISIDA
Liver	73	90	78	130	65
Gallbladder wall	690	690	700	690	780
Small intestine	180	170	180	170	200
Upper large intestine	330	320	330	320	370
Lower large intestine	220	210	220	210	240
Kidney	24	25	24	26	24
Urinary bladder wall	36	33	33	23	30
Ovaries	65	63	65	63	72
Testes	4	4	4	4	4
Spleen	9	9	9	10	9
Bone	9	9	9	10	10
Total body	16	17	16	18	17

* See footnote p. 1030.

TABLE 7. RADIATION ABSORBED DOSE (mrad/mCi) FROM FIVE Tc-99m IDA DERIVATIVES WHEN 10 ng/kg OCTAPEPTIDE OF CHOLECYSTOKININ IS USED FOR GALLBLADDER STIMULATION

Target Organ	Radiopharmaceutical*				
	EIDA	PIPIDA	HIDA	PBIDA	DISIDA
Liver	90	100	92	140	81
Gallbladder wall	1010	990	1010	990	1030
Small intestine	160	160	160	150	180
Upper large intestine	290	280	290	280	320
Lower large intestine	190	190	190	190	220
Kidney	25	26	25	27	25
Urinary bladder wall	34	31	31	21	28
Ovaries	57	57	58	56	64
Testes	4	4	4	3	4
Spleen	9	9	9	9	9
Bone	9	9	9	10	10
Total body	16	17	16	18	17

* See footnote p. 1030.

TABLE 8. RADIATION ABSORBED DOSE (mrad/mCi) FROM FIVE Tc-99m IDA DERIVATIVES IN FASTING SUBJECTS (NO GALLBLADDER STIMULATION)

Target Organ	Radiopharmaceutical*				
	EIDA	PIPIDA	HIDA	PBIDA	DISIDA
Liver	130	140	130	180	130
Gallbladder wall	1860	1830	1880	1810	2090
Small intestine	100	100	100	100	120
Upper large intestine	190	190	190	190	210
Lower large intestine	120	120	120	120	140
Kidney	28	28	28	29	28
Urinary bladder wall	29	26	26	17	23
Ovaries	38	37	38	37	42
Testes	3	3	3	3	3
Spleen	8	9	8	9	9
Bone	9	9	9	10	9
Total body	16	17	16	18	17

* See footnote p. 1030.

2. It used a derived S-factor for S(GBW ← GBC) that is 25% smaller than the value used here (*13*).

3. It used shorter excretion half-times for the ULI and LLI than those used here (*8,9*). Other researchers have reported values as high as 71% for IDA localization in the GB after an overnight fast (*18*). Another recent absorbed-dose calculation for PIPIDA gallbladder absorbed dose, using the same S-factor as that used here, was based solely on mouse data and showed a GB dose 25% less than that reported here (*13*).

The more interesting observation from our study is that there were only small differences, generally less than 10%, in the absorbed doses for the five agents with the exception of those for liver and urinary bladder. A factor of two in the liver-dose range for the five agents was caused by the varying hepatic excretion half-time, and a factor of 1.6 in the range for the urinary bladder dose was caused by variation in urinary excretion. The absorbed-dose values for the other organs show less variation among the agents because the residence time in the intestines and the degree of GB emptying are independent of changes in the chemical structure of the radiopharmaceutical. Predictions of relative independence of absorbed dose from structural changes in IDA derivatives have been made on the basis of a theoretical model (*15*). As shown in our previous paper dealing with absorbed-dose calculations for HIDA, the change from normal to abnormal liver function has a far greater influence on absorbed dose, since for patients with high bilirubin the critical organ becomes the urinary bladder,

with a 9-fold drop in GB dose caused by severe hepatocellular disease (*3*).

The absorbed dose to the GB is strongly dependent on the type of stimulation used to induce gallbladder emptying. A reduction of GB ejection fraction from 87% (whole meal) to 50% (CCK-8) will increase the GB dose by about 45% (Tables 6 & 7), with smaller increases in liver dose and decreases in intestinal dose. A reduction of GB ejection fraction from 87% (whole meal) to 0% for a fasting patient will increase GB absorbed dose by about 170% (Tables 6 & 8), with increases in liver dose by 40–94%, and decrease in intestinal dose by about 40%.

The data provided here will raise some important questions concerning safe procedures and administered radioactivity limits for Tc-99m IDA agents. What level of administered radioactivity is appropriate for a patient with normal liver function? We have restricted our doses to less than 3 mCi (111 MBq) of Tc-99m IDA in patients with normal bilirubin levels, and have obtained consistently good-quality hepatobiliary imaging studies. By how much may the administered activity be increased to obtain clinically useful images in the presence of jaundice? The dose adjustment for a jaundiced patient is more difficult and requires knowledge of total bilirubin and protein. In jaundiced patients we have increased the dose level up to 8 mCi (300 MBq). After the GB is visualized and the study is complete, it is appropriate to try to reduce the absorbed dose to the gallbladder by either cholecystokinin or meal stimulation? The relative contraindications of inducing gallbladder contractions in a patient with suspected upper abdominal disease require careful study and must be evaluated on an individual basis. In the absence of contraindication, it appears appropriate to give milk to reduce absorbed dose to the gallbladder.

FOOTNOTES

* EIDA or diethyl-IDA, Amersham Corp., Arlington Heights, IL.

PIPIDA or paraisopropyl-IDA, Diagnostic Isotopes Inc., Bloomfield, NJ.

HIDA, Medi-Physics Co., Emeryville, CA.

PBIDA or parabutyl-IDA, Syncor Int., Sylmar, CA.

DISIDA or di-isopropyl-IDA, New England Nuclear, North Billerica, MA.

REFERENCES

1. WEISSMANN HS, BADIA J, SUGARMAN LA, et al: Spectrum of ^{99m}Tc-IDA cholescintigraphic patterns in acute cholecystitis. *Radiology* 138:167–175, 1981
2. LOBERG MD, COOPER M, HARVEY E, et al: Development of new radiopharmaceuticals based on n-substitution of iminodiacetic acid. *J Nucl Med* 17:633–638, 1976
3. BROWN PH, KRISHNAMURTHY GT, BOBBA VVR, et al: Radiation dose calculation for Tc-99m HIDA in health and disease. *J Nucl Med* 22:177–183, 1981
4. Committee on the biological effects of ionizing radiation: *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980.* Washington, DC, National Academy Press, 1980, Table A-1, p 266
5. LOEVINGER R, BERMAN M: A revised schema for calculating the absorbed dose from biologically distributed radionuclides. In *MIRD Pamphlet #1, Revised*, New York, The Society of Nuclear Medicine, 1976
6. O'REILLY PH, SHIELDS RA, TESTA HJ: *Nuclear Medicine in Urology and Nephrology*, London/Boston, Butterworth & Co., Ltd., 1979, p 187
7. DIRKSEN JW, QUAIFE MA, MCINTIRE RH, et al: Initial kinetics and cumulative biodistribution of Tc-99m-Diethyl IDA in a mammalian animal model. In *Third International Radiopharmaceutical Dosimetry Symposium*, FDA #81-8166, US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Bureau of Radiological Health, 1981, Rockville, MD. pp 413–420
8. EVE IS: A review of the physiology of the gastrointestinal tract in relation to radiation doses from radioactive materials. *Health Phys* 12:131–161, 1966
9. BERNARD SR, HAYES RL: Dose to various segments of the gastrointestinal tract. In *Medical Radionuclides: Radiation Dose and Effects.*, CONF-691212, US National Technical Information Service, Springfield, VA, 1970, pp 295–314
10. FISHER RS, MALMUD LS: Functional scintigraphy: Diagnostic applications in gastroenterology. In *Development in Digestive Diseases*, Philadelphia, Lea & Febiger, 1980, p 146
11. KRISHNAMURTHY GT, BOBBA VR, KINGSTON E: Optimum OP-CCK dose for gallbladder (GB) emptying. *Clin Nuc Med* 6:451, 1981 (abst)
12. SNYDER WS, FORD MR, WARNER GG, et al: "S" absorbed dose per unit cumulated activity for selected radionuclides and organs, *MIRD Pamphlet #11*, New York, The Society of Nuclear Medicine, 1975
13. BERNARD SR, CHEN SM: Dose to the gallbladder from a ^{99m}Tc labeled gallbladder scanning agent. In *Third International Radiopharmaceutical Dosimetry Symposium*, FDA #81-8166, US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Bureau of Radiological Health, 1981, Rockville, MD, pp 546–553
14. MIRD dose estimate report no. 7: Summary of current radiation dose estimates to humans from 123-I, 124-I, 126-I, 130-I and 131-I as sodium rose bengal. *J Nucl Med* 16: 1214–1216, 1975
15. LOBERG MD, BUDDEMEYER EV: Application of pharmacokinetic modeling to the radiation dosimetry of hepatobiliary agents. In *Third International Radiopharmaceutical Dosimetry Symposium*, FDA #81-8166, US Department of Health and Human Services, Public Health Service, Food and Drug Administration, Bureau of Radiological Health, 1981, Rockville, MD, pp 318–332
16. DILLMAN LT, VON DERLAGE FC: Radionuclide decay schemes and nuclear parameters for use in radiation dose estimation. In *MIRD Pamphlet No. 10*, New York, The Society of Nuclear Medicine, 1975
17. SNYDER WS, FORD MR, WARNER GG: Estimates of specific absorbed fractions for photon sources uniformly distributed in various organs of a heterogeneous phantom. In *MIRD Pamphlet No. 5, Revised*, New York, The Society of Nuclear Medicine, 1978
18. SHAFFER EA, MCORMOND P, DUGGAN H: Quantitative cholescintigraphy: Assessment of gallbladder filling and emptying and duodenogastric reflux. *Gastroenterology* 79: 899–906, 1980