PHYSICS AND RADIATION BIOLOGY

Absorbed Dose to Man from the Se-75 Labeled Conjugated Bile Salt SeHCAT: Concise Communication

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The absorbed radiation dose that would result from the oral or intravenous administration of SeHCAT (23-[^{75}Se]selena-25-homotaurocholate) has been calculated using the MIRD tables and formulas and data from measurements of whole-body distribution and from long-term whole-body counting in rats, mice, and man. When SeHCAT is administered to normal subjects, the gallbladder is the critical organ, receiving 12 mrad (oral dose) or 22 mrad (i.v.) per microcurie. The whole-body dose is 1 mrad/μCi, whatever the route of administration. In severe hepatic failure the liver might receive 200 mrad/μCi. The activity likely to be used in routine clinical practice is 10 μCi. Where a whole-body counter is used, an activity of 1 μCi has proved adequate. Even at an administered activity of 25 μCi, the absorbed dose is small compared with established techniques of investigating the gastrointestinal tract.

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A bile acid containing a gamma-emitting nuclide would be of considerable clinical importance, providing a simple and esthetically acceptable means of studying the enterohepatic circulation, including especially the functional integrity of the distal part of the ileum without the need to collect feces. Any risks inherent in using such a compound must be offset against the reduced need for more invasive tests such as panendoscopy or ileal biopsy, and the risks incurred by nursing and laboratory staff collecting and processing feces.

Studies in the experimental animal (*1*) and in man (*2*) indicate that SeHCAT has most, possibly all, of the properties of an ideal tracer for this purpose. We report here calculations of the absorbed dose that would result from its administration to man.

Four situations are considered, namely, oral administration to normal subjects, intravenous administration to normal subjects, oral administration to subjects without a functioning gallbladder, and to subjects with severe cholestatic jaundice. These examples have been chosen because each results in a different maximal absorbed dose to critical organs. In practice the symptoms most likely to give cause for investigation with SeHCAT—diarrhea with or without lower abdominal pain—are likely to be associated with bile-acid malabsorption, accelerated excretion, and a lower absorbed dose.

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DOSIMETRY MODELS

Oral administration to normal subjects. Following oral administration of SeHCAT in aqueous solution, the activity is assumed to spend one hour in the stomach and four in the small intestine, during which time physical decay is insignificant. At the end of the fifth hour, 4% of the activity is taken to be uniformly distributed throughout the body, from which it is eliminated with an effective half-time of 42 days. The chemical form of this fraction is at present unknown. No free selenium is present in the administered radiopharmaceutical, and no enzyme systems are known to be capable of cleaving

TABLE 1. DISTRIBUTION OF SeHCAT IN MICE, EXPRESSED AS PERCENTAGE OF THE ADMINISTERED ACTIVITY IN THE WHOLE ORGAN (MEAN OF 5 ANIMALS AND RANGE)

	4 hr	8 hr	24 hr	67 hr
Liver	2.5	3.3	1.6	0.012
	(1.5–3.3)	(1.3–5.0)	(1.4–1.8)	(0.007–0.019)
Kidneys	0.08	0.14	0.16	0.004
	(0.035–0.12)	(0.07–0.17)	(0.14–0.24)	(0.002–0.006)
Gallbladder	3.0	2.1	1.4	*
	(0.09–4.7)	(1.6–2.5)	(0.2–3.9)	
Ovaries	0.004	0.008	0.009	0.0003
	(0.002–0.007)	(0.001–0.02)	(0.004–0.014)	(0.0003–0.0006)
Small intestine	84.9	88.3	67.5	0.003
	(63.7–91.2)	(79.8–93.3)	(58.8–75.6)	(0.001–0.003)
Large intestine	4.4	5.5	5.5	0.002
	(1.1–7.0)	(3.6–8.4)	(2.9–7.6)	(0.001–0.002)
Blood	0.07	0.22	0.14	†
	(0.05–0.11)	(0.14–0.51)	(0.10–0.18)	

* Included with liver.

† None detectable (<0.00001).

the Se—C bond. We postulate the presence of a small pool of bile acids, turning over slowly.

The remaining 96% circulates in the enterohepatic circulation, being excreted with a half-time of 2.6 days (*2*). Excretion is exclusively into the colon. With the exception of the gallbladder, the organ distribution in man is assumed to be similar to that in the mouse (Table 1). Unfortunately, little is known about the percentage of bile-acid pool in the gallbladder in man. It is maximal after an overnight fast and minimal after a large meal. The figure of 3% in the gallbladder of the mouse may represent a minimal value if there was agonal autonomic stimulation causing that organ to contract. Some workers have suggested a peak gallbladder content of up to 50% of the bile-salt pool (*3*). Averaging over the 24 hr, a mean gallbladder content of 15% has been assumed in nonfasting man.

The peak liver activity observed in the mouse was 3.3% at 8 hr. This would be expected to fluctuate. In order to obtain an upper value of absorbed dose, a mean liver concentration of 5% has been assumed in the calculations. This leaves 76% in the gut, all initially in the small intestine. On each cycle of the enterohepatic circulation, 95% of the bile acid reaching the ileum is reabsorbed (*4*). Because liver, gallbladder, and small-intestinal lumen are in equilibrium, the relative distribution remains constant as the total activity declines.

The time integral of activity in the small intestine is therefore 4 μCi-hr per ingested microcurie for the first 4 hr, when all the activity is in the small intestine. Subsequently the time integral $\tilde{A}_{(t>5)}$ is given by

$$\tilde{A}_{(t>5\text{ hr})} = 0.76/\lambda = 68\ \mu\text{Ci-hr}/\mu\text{Ci}.$$

The total time integral $\tilde{A}$ is therefore 72 μCi-hr/μCi. Time integrals for other organs are calculated similarly, and are given in Table 3.

Since all the activity is eliminated through the colon, and because the delay caused by the enterohepatic circulation is small compared with the physical half-life, the dosimetry of the gastrointestinal tract has been approached simply by allotting time integrals of activity of 13 and 24 μCi-hr to the upper and lower large intestines, respectively. These time integrals of activity correspond to mean residence times of 13 and 24 hr described by Eve (*5*) and accepted by I.C.R.P. Any error resulting from this simplification would cause the absorbed dose to be overestimated.

Oral administration to subjects without a functioning gallbladder. The rat does not have a gallbladder and is therefore a suitable model for humans with absent or nonfunctioning gallbladders. Organ distributions are given in Table 2. There is remarkably little difference between Tables 1 and 2. Clearly the lack of a gallbladder should increase the bile-acid load in the small intestine, and possibly also increase loss into the large intestine. Some bile acids decrease sodium (and thus water) reabsorption by the colon, and in excess can cause diarrhea. It is not clear whether this is responsible for the apparently lower gut-content activities at 24 hr in the rat.

For the purposes of calculating time integrals of activity, all the activity other than in the gallbladder is assumed to be in the small intestinal lumen.

$$\tilde{A}_{(t>5)} = 0.91/\lambda = 82$$

$$\tilde{A} = 82 + 4 = 86\ \mu\text{Ci-hr}/\mu\text{Ci}.$$

In some subjects without a functioning gallbladder, bile

TABLE 2A. DISTRIBUTION OF SeHCAT IN RATS, EXPRESSED AS PERCENTAGE OF THE ADMINISTERED ACTIVITY IN THE WHOLE ORGAN (MEAN OF 5 ANIMALS AND RANGE)

	24 hr	48 hr	7 days	41 days
Small intestine and contents	46.4 (39.7–50.3)	41.0 (25.7–58.5)	1.0 (0.3–1.4)	0.007 (0.004–0.011)
Large intestine and contents	16.4 (11.6–27.3)	14.9 (7.2–25.9)	1.0 (0.23–2.1)	0.005 (0.002–0.009)
Liver	4.1 (3.4–5.5)	3.6 (2.8–5.0)	2.3 (1.0–3.7)	0.025 (0.012–0.049)
Kidneys	0.19 (0.17–0.22)	0.16 (0.04–0.33)	0.20 (0.08–0.44)	0.007 (0.001–0.020)
Carcass	7.3 (3.2–11.1)	6.4 (2.9–10.3)	7.1 (2.6–13.3)	0.053 (0.03–0.12)

TABLE 2B. CUMULATIVE EXCRETION AFTER 10 DAYS (5 ANIMALS)

Urine	0.58%	(0.40–0.81)
Feces	97.2%	(97.2–97.5)

is stored in dilated bile ducts. The absorbed dose to the wall of such structures is considered to be equivalent to that absorbed by the wall of the gallbladder.

Oral administration to subjects with severe cholestatic jaundice. In the extreme case, assume all the activity is absorbed. We have no evidence how it would be distributed. As an example, the time integral is calculated assuming half the activity to be taken up by the liver and to remain there with an effective half-time equal to the physical half-life. The remaining 50% is assumed to be distributed throughout the body with a similar half-time. In practice such severe hepatic disease is incompatible with prolonged survival.

$$\tilde{A}_{liver} = \tilde{A}_{tb} = 0.5/\lambda = 2080\ \mu Ci\text{-hr}/\mu Ci.$$

Intravenous administration to normal subjects. Following intravenous injection into healthy human subjects, SeHCAT is cleared from the blood with a half-time of 5.1 min (*2*). It is taken up exclusively by the liver and is excreted in bile. Assume it takes one hour to move through the liver, and in a fasting subject all remains in the gallbladder for 12 hr. When the gallbladder contracts, the contents are expelled into the duodenum. They then spend 4 hr in the small intestine. Their subsequent fate is identical to that of activity administered orally.

The time integral of activity in the liver is therefore

$$\tilde{A}_{liver} = 1 + 0.05/\lambda = 1 + 4.5 = 5.5\ \mu Ci\text{-hr}/\mu Ci,$$

and in the gallbladder

$$\tilde{A}_{gb} = 12 + 0.15/\lambda = 12 + 13.5 = 25.5\ \mu Ci\text{-hr}/\mu Ci.$$

Time integrals for other organs are identical to those based on oral administration.

DOSIMETRY CALCULATIONS

The mean absorbed dose to a target organ k is given by D_k (*6*) where

TABLE 3. CUMULATIVE ACTIVITY $\tilde{A}$ (μCi-hr PER ADMIN. μCi)

	Oral administration to subjects with			Intravenous administration to
	Normal health	No gallbladder	Severe jaundice	normal subjects
Liver	4.5	4.5	2080	5.5
Gallbladder	13.5	—	—	25.5
Small intestine	72	86	—	72
Upper large intestine	13	13	—	13
Lower large intestine	24	24	—	24
Total body	58	58	2080	58

TABLE 4. ABSORBED DOSE FROM Se-75 PER UNIT CUMULATIVE ACTIVITY IN VARIOUS ORGANS. S (RADS PER μ-Ci-hr)

To target organs	From source organs: Liver	Gall-bladder	Small intestine	Upper large intestine	Lower large intestine	Total body
Liver	9.3×10^{-5}	1.4×10^{-5}	5.2×10^{-6}	7.2×10^{-6}	8.1×10^{-7}	5.2×10^{-6}
Gallbladder	1.4×10^{-5}	8.4×10^{-4}	3.8×10^{-6}	2.6×10^{-6}	1.2×10^{-6}	6.0×10^{-6}
Small intestine	4.6×10^{-6}	2.4×10^{-6}	1.3×10^{-4}	4.7×10^{-5}	2.6×10^{-5}	6.1×10^{-6}
Upper large intestine	7.0×10^{-6}	2.7×10^{-6}	7.0×10^{-5}	1.9×10^{-4}	1.2×10^{-5}	5.8×10^{-6}
Lower large intestine	7.2×10^{-7}	7.1×10^{-7}	2.0×10^{-5}	8.6×10^{-6}	2.6×10^{-4}	5.5×10^{-6}
Ovaries	1.2×10^{-6}	1.7×10^{-6}	2.9×10^{-5}	3.3×10^{-5}	5.2×10^{-5}	5.7×10^{-6}
Total body	5.3×10^{-6}	5.3×10^{-6}	6.1×10^{-6}	5.8×10^{-6}	5.8×10^{-6}	4.6×10^{-6}

$$D_k = \sum_h \tilde{A}_h \times S_{(k \leftarrow h)} \quad \text{rad.}$$

$\tilde{A}_h$ is the time integral of activity in source organ h per microcurie administered activity, expressed in microcurie-hours. Values of $\tilde{A}$ have been derived from the dosimetry models of the previous section, and are listed in Table 3. $S_{(k \leftarrow h)}$ is the absorbed radiation dose in target organ k per unit cumulative activity in source organ h, expressed in rads per microcurie-hour. Where they exist, values of S have been taken directly from MIRD Pamphlet No. 11 (*6*). To deduce the appropriate values of S for the gallbladder, the following procedures have been adopted:

(a) Where the gallbladder is either source or target organ (but not both), we consider it sufficiently accurate for the purpose of these calculations to use the S value for the adrenals listed in MIRD Pamphlet No. 11 (*6*), on the basis that the differences in size, shape, and position within the human body have a negligible effect on the result calculated.

(b) For the particular situation where the gallbladder is both source and target organ, the S value was deduced by applying appropriate absorbed fractions to each element of the decay scheme, i.e., by evaluating the equation

$$S = \sum \Delta_i \phi_i / m.$$

ϕ_i is the fraction of i-type energy, emitted by the source organ, that is absorbed in the target organ. The adult gallbladder, when full, is taken to have a volume of 65 ml (*7*). Assuming unit density for tissue and contents, the weight of the full gallbladder plus contents is therefore 65 g. Most of this weight is due to the contents, because the empty gallbladder of "reference man" (*7*) weighs only 10 g.

Values of ϕ for photon emission were obtained by linear extrapolation from Table 7 of MIRD Pamphlet No. 8 (*8*), considering the gallbladder and its contents to be a unit-density ellipsoid of 65 g mass with axes 1:2:4. This approach gives the average absorbed dose in the source/target organ, and will be somewhat higher than that actually required, i.e., the dose to the gallbladder wall. The overestimate is allowed to stand because there is no simple way of making an accurate adjustment, and the uncertainty in the data would not justify an elaborate calculation.

TABLE 5. ABSORBED DOSE FROM SeHCAT (mrad/μCi)

	Oral administration subjects with: Normal health	No gallbladder	Severe jaundice	Intravenous administration to normal subjects
Liver	1.4	1.3	204	1.7
Gallbladder	12		42	22
Small intestine	11	13	22	11
Upper large intestine	8.2	9.2	27	8.3
Lower large intestine	8.1	8.4	13	8.1
Ovaries	4.1	4.5	14	4.2
Total body	1.0	1.0	21	1.1

Values of ϕ for charged particles, and photons of energy <10 keV were taken to be 0.5 following the method of paragraph 3.2 of MIRD Pamphlet No. 11 (*6*). This corresponds to the assumption that the dose at the surface of the wall from charged particles is one-half the dose to the contents far from the wall.

Δ_i is the mean energy emitted per unit cumulated activity (in gram-rads per microcurie-hour) and relates to the energy emitted per disintegration in the form of i-type radiation. Values of Δ_i for selenium-75 were taken from MIRD Pamphlet No. 10 (*9*). The value obtained by the above procedure for the estimation of S (gallbladder contents → gallbladder wall) was 8.0×10^{-4} rad/μCi-hr. Table 4 lists the various values of S for the source-target configurations used in the calculations.

CONCLUSIONS

The absorbed radiation doses that would result from the oral or intravenous administration of SeHCAT to normal subjects, subjects without functioning gallbladders, or subjects with severe (lethal) hepatic failure, are summarized in Table 5. The absorbed radiation dose to the lower G.I. tract from the clinical use of SeHCAT has been calculated on the basis that 100% of the administered activity leaves the body through the colon and that negligible physical decay takes place during transit. For materials with a shorter physical half-life, this assumption would not necessarily be valid and would result in a significant overestimate of dose.

The uptake in the liver and gallbladder was assumed to be substantially higher than the figure actually observed in the mouse, and may therefore overestimate the absorbed dose actually received by these organs. Similarly, the case of severe cholestatic jaundice effectively requires the patient to be suffering from fatal hepatic failure. In practice the dose could not possibly reach such a high level in a patient with any hope of survival. Moreover in clinical practice the indication for the use of SeHCAT, namely, suspected bile-acid malabsorption, is likely to be associated with a much faster rate of excretion and therefore a lower absorbed dose. The calculated figures thus represent an upper limit of the dose likely to be received, and are probably substantially higher than the doses that actually would be received in clinical practice.

Depending upon the sensitivity of the available detecting equipment, an administered activity of 10 μCi (370 kBq) is adequate for most clinical purposes (*2*). If a whole-body counter is available, 1 μCi is adequate. Even in lethal jaundice the maximum critical organ dose following the administration of 25 μCi (925 kBq) of SeHCAT (*3*) is much less than skin doses received routinely during gastrointestinal fluoroscopy. In normal subjects the absorbed dose would be less than the natural annual background in many areas of the world, and in patients with bile-acid malabsorption the dose would be negligible.

Thus, despite the long physical half-life of the Se-75 label, the absorbed dose resulting from its administration in the form of SeHCAT to humans is small and within acceptable limits.

REFERENCES

1. BOYD GS, MERRICK MV, MONKS R, et al: Se-75 labeled bile acid analogs. New radiopharmaceuticals for investigating the enterohepatic circulation. *J Nucl Med* 22:720-725, 1981
2. MERRICK MV, EASTWOOD MA, ANDERSON JR, et al: SeHCAT—a gamma emitting bile acid. Absorption and excretion in man. *J Nucl Med* 23:126-130, 1982
3. MELLER ST, KUPFER RM, PAYNE JH, et al: Dynamic imaging of the enterohepatic circulation with SeHCAT. *Br J Radiol* 54:702-703, 1981
4. HEATON KW: Clinical aspects of bile acid metabolism. *Rec Adv Gastroenterol* 3:199-230, 1976
5. 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
6. SNYDER WS, FORD MR, WARNER CG, et al: "S," absorbed dose per unit cumulated activity for selected radionuclides and organs. MIRD Pamphlet No. 11, 1975
7. SNYDER WS, COOK MJ, NASSET ES, et al: Report of the Task Group on Reference Man. I.C.R.P. Report No. 23, 1975
8. ELLETT WH, HUMES RM: Absorbed fractions for small volumes containing photon-emitting radioactivity. MIRD Pamphlet No. 8, Suppl No. 5:25-32, 1971
9. DILLMAN LT, VON DER LAGE FC: Radionuclide decay schemes and nuclear parameters for use in radiation dose estimation. MIRD Pamphlet No. 10, 1975