Dosimetry of Iodine-131 Ethiodol in the Treatment of Hepatoma

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The in vivo distribution and kinetics of [^{131}I]Ethiodol injected through the hepatic artery have been measured on a group of four patients with hepatocellular carcinoma. The [^{131}I]Ethiodol was distributed predominantly in the liver (70–90%) and lungs (10–20%) and was selectively concentrated and retained in the patients with massive and multinodular hepatomas with ~10% of the administered activity localizing in tumor. The radioactivity in the blood 2 hr postinjection was <0.1% and was never higher than 0.9% of the administered activity. The radioactivity cleared from normal liver tissue with an effective half-life of ~4 days while the clearance time from the tumor was 20–25% longer. Activity in the lungs initially increased and then cleared with a 5-day effective half-life. Based on these measurements, the estimated dose per mCi of [^{131}I]Ethiodol administered is 31 rad to the liver, 22 rad to the lungs, 1.9 rad to the total body and 239 rad to a 4-cm diameter tumor. These results suggest that [^{131}I]Ethiodol has the potential to deliver curative radiation doses to hepatomas with acceptable radiation burdens to normal tissues.

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Iodinated esters of poppy seed oil have been used as contrast agents in lymphangiography and hysterosalpingography (*1*). Two commercially available compounds used in these applications are Ethiodol (Savage Laboratorie, Melville, NY 11747) and Lipiodol (Laboratoire Guerbet, France) which contain 37–38% iodine by weight. In 1979, Nakakuma et al. (*2*) reported that lipiodol was selectively retained in vascular hepatomas when injected directly into the hepatic artery. Since that time Ethiodol or Lipiodol has been utilized in the detection of hepatoma (*3–5*) and also in therapeutic protocols where it has been mixed with chemotherapeutic agents (*6–9*) or labeled with iodine-131 (^{131}I) (*10–12*). Although there have been several reports on the biodistribution of intraarterially administered Ethiodol in animals (*13,14*), little is reported about the initial distribution and kinetics of [^{131}I]Ethiodol in humans. Such information is obviously important in calculating the radiation doses to the tumor and normal tissue in therapeutic regimens. At our institution we have investigated the distribution and kinetics of [^{131}I]Ethiodol in a group of four patients. The information was obtained from scintigraphic images and x-ray computed tomographic (CT) scans acquired over the period in which significant radioactivity was found in the body.

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METHODS

The Ethiodol was labeled with ^{131}I using an exchange reaction. The labeling procedure begins by boiling ^{131}I in 0.1*M* NaOH to dryness in the presence of 0.5 mg of KI. The residue is refluxed in 25 ml of acetone for 20 min and then 1–2 ml of Ethiodol is added. The solution is refluxed for an additional 30 min. The acetone is then removed using a rotary evaporator with a water bath at 70°C. The product is cooled and drawn into a sterile vial and is autoclaved in a boiling butanol bath. The labeling efficiency is verified by chromatography and has been found to be >99%. The compound is very stable and no dehalogenation was observed over a one month period.

The distribution and kinetics of the [^{131}I]Ethiodol were studied in a group of four patients diagnosed with hepatocellular carcinoma (HCC). The patient group consisted of three males and one female ranging in age from 44 to 63 yr (Table 1). The hepatic tumors were classified as either massive, multinodular or infiltrative on the basis of CT and angiographic studies. Prior to the administration of the [^{131}I]Ethiodol, transmission images through the lungs and liver regions were acquired on the scintillation camera system and were stored on a computer. Approximately 1 mCi of ^{131}I in solution was mixed into a flood field phantom and scintigraphic images were acquired both with and without the patient interposed between the phantom and the scintillation camera. The trans-

TABLE 1
Summary of Patient Information

Patient	Sex	Age (yr)	Tumor type	Tumor mass (g)	Estimated liver mass (g)*
1	M	58	Infiltrative	†	1800
2	F	44	Massive	12	900
3	M	63	Multinodule	33	1800
		(second treatment)		33	1500
4	M	53	Infiltrative	†	1800

* The values are estimates of the mass of liver tissue in which the [^{131}I]Ethiodol is distributed.
† The infiltrative tumor masses were not determined.

mission factor over an area of interest was calculated from the ratio of counts in selected regions of the two images described above.

In preparation for the administration of the [^{131}I]Ethiodol, an arterial catheter was inserted into the femoral artery and was advanced under fluoroscopic guidance to the hepatic artery. The patient was then transported to the nuclear medicine department and was positioned under a scintillation camera. A collimator designed for ^{131}I was used and a 20% window was centered on the 364-keV photopeak. The patients received from 0.2–24 mCi of [^{131}I]Ethiodol in a volume of 3–5 ml which was injected at a rate of 10–15 ml/hr via an automatic injection syringe. The amount of activity administered depended on the following. The first patient was part of an investigation to study the in vivo distribution of the [^{131}I] Ethiodol and therefore only received 0.2 mCi. The intent with the other patients was to deliver at least 7,000 rad to the tumor on the assumption that ~10% of the administered activity localizes in the tumor, with the additional constraint that the total activity would not exceed 25 mCi. However, technical problems limited the activity available for Patient 2 and for the first treatment of Patient 3. During the injection, a dynamic study was acquired on the computer at 1 frame/15 sec for 20 min. The radioactivity in the syringe and catheter was assayed in a dose calibrator both before and after the administration so that the administered amount was accurately known.

When the injection was completed, the catheter was removed and anterior images of the lungs, liver, and spleen regions were acquired and stored on a computer. A blood sample was also drawn and the patient was returned to his room. For the following 2–3 days, anterior and posterior scintigraphic views of the liver, lungs, and pelvic region were obtained along with images of an iodine standard. Blood samples were also taken and the urine was collected. The patients had a CT scan of the liver prior to release from the hospital. Additional scintigraphic images, blood samples and CT scans were acquired periodically over the following 2 mo. During this time Lugol's solution was prescribed for the patients to block the thyroid from circulating ^{131}I resulting from the metabolic breakdown of the Ethiodol in the liver and lungs.

The amount of activity localized in the tumor, lungs, and liver was determined by the conjugate view method described by Thomas et al. (*15*). The ^{131}I body transmission factor was determined from the transmission images described above. Regions of interest (ROIs) were carefully drawn about the organs in both the anterior and posterior views. For the counts in the tumor ROI, corrections were made for activity in surrounding tissues using bilinear interpolation (*16*). The

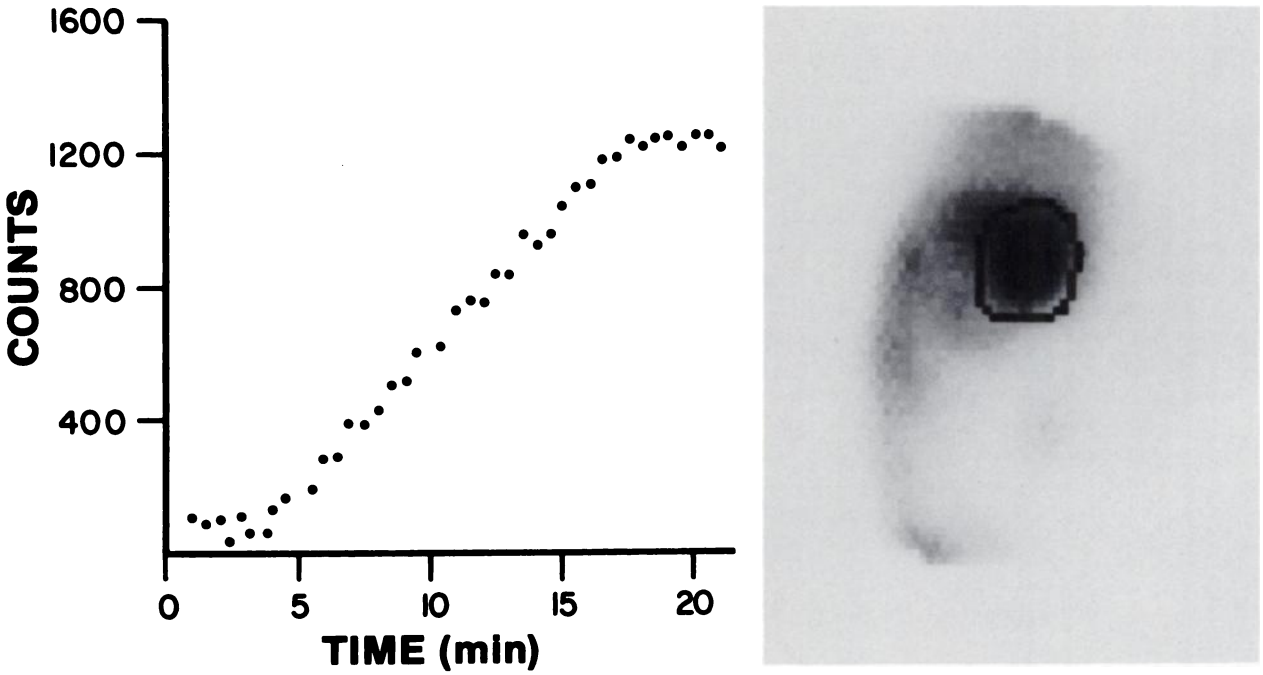

FIGURE 1
Counts as a function of time from an ROI over the tumor during the intraarterial injection of [^{131}I]Ethiodol. The counts in the region increase in proportion to the amount of activity injected.

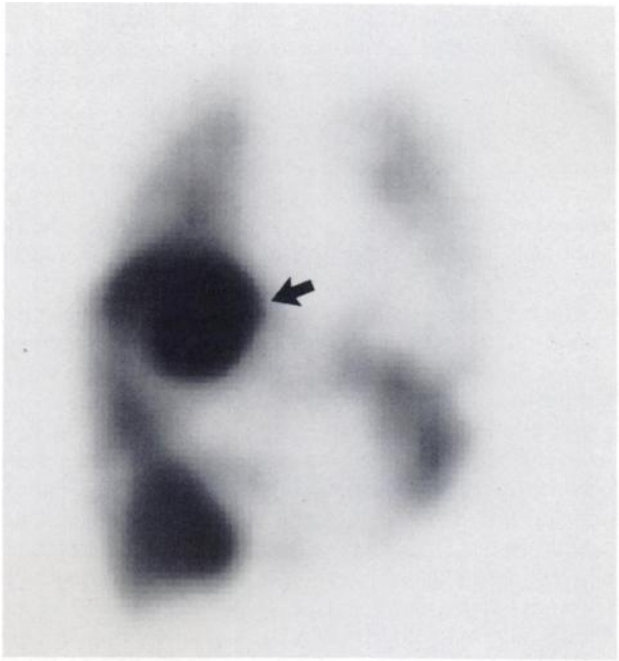

FIGURE 2
Anterior scintigraphic image of the thorax and abdomen on Day 2 after [^{131}I]Ethiodol administration. The image was acquired using a pinhole collimator and illustrates the distribution of [^{131}I]Ethiodol in the tumor, liver, and lungs. The activity seen below the left lung is located in the left lobe of the liver. The location of the tumor is indicated by the arrow.

activity in these ROIs was found from

$$\text{Activity}(\mu\text{Ci}) = \frac{(\text{Ca Cp TF})^{1/2}}{\text{CF}}, \quad (1)$$

where Ca and Cp are the anterior and posterior count rates in the ROI, TF is the ^{131}I transmission factor and CF is the system sensitivity (cpm/μCi). The activity in the blood and urine was determined by counting aliquots in a calibrated sodium iodide well counter.

The clearance of the [^{131}I]Ethiodol from selected organs was determined from the count rate in an ROI overlaid on the scintigraphic images. The ROIs were carefully drawn about the organ in the image on Day 1 or 2 and corrections for the surrounding activity around the tumor were made as described above. The images on all subsequent days were translated to compensate for differences in patient positioning. Time activity curves were generated and the effective clearance times were estimated by fitting the data to an exponential function.

The dose to the body organs was determined using the MIRD Method (*17*):

$$\text{Dose(rad)} = \tilde{A}\ S, \quad (2)$$

where $\tilde{A}$ is the cumulated activity in μCi hr and S is the absorbed dose per cumulated activity. The cumulated activities for the tumor, liver, lungs, and blood were estimated by integrating the observed time activity curves. The S value for the lungs was obtained directly from the MIRD tables (*17*). The liver value was estimated from the S table based on the distribution of the Ethiodol. For example, if [^{131}I]Ethiodol is injected into the right branch of the hepatic artery the distribution is essentially limited to the right lobe of the liver. The S value for the entire liver is clearly not appropriate in this case. However, since most of the dose results from the beta emission, one can expect that the S value scales inversely with the distribution mass. That is, $S \rightarrow S \times 1{,}800/\text{estimated mass}$. The liver distribution masses were estimated from the CT scans and scintigraphic images and are listed in Table 1. The total-body dose was calculated from the cumulated activities of the tumor, liver, lung, and blood. The S values for the lung and liver-to-total body were obtained from the MIRD tables. The S value for the tumor-to-total body was assumed to be the same as that of the liver-to-total body and the S value for the radioactivity in the blood was taken to be the total body-to-total body value.

The dose to the tumor was estimated using the equations below (*18*):

$$\text{Dose(rad)} = 73.8 \times E \times Te \times Ao/M + 0.0346 \times \Gamma \times Te \times g \times Ao/M, \quad (3)$$

where E is the average beta energy (MeV), Te is the effective half-life (days), Γ is the specific gamma ray constant (rad cm^2/mCi hr), Ao is the initial activity (μCi), M is the tumor mass (g) and g is the geometric factor (cm). For spherical objects, g is estimated from 3π R ($R < 10$), where R is the tumor radius in cm. Ao is determined from the conjugate scintillation camera views as described above and the tumor mass is determined from the CT scans (Table 1). It should be noted that Eq. (3) is valid in so much as the size of the tumor was large compared to the mean range of the beta particle (0.4 mm).

RESULTS

The scintillation camera images acquired during the administration of [^{131}I]Ethiodol demonstrate that it is localized in the tumor on the first pass through the liver. Figure 1 shows the time-activity curve for a ROI located about the tumor in one of the patients. Note that the counts increase linearly as the activity is injected. The same behavior was found in other areas of the liver.

The distribution of the [^{131}I]Ethiodol was determined from the conjugate scintigraphic images, the CT scans, and the blood and urine samples from each of the four patients. Approximately 80–90% of the administered activity localized within the liver (including the tumor) and the remainder appeared to be in the lungs (10–20%) (Fig. 2). There was no selective tumor localization in the two patients with infiltrative tumors. However, in both these cases there was significant involvement of the tumor with the portal vein which probably created an effective shunt. Approximately 10–12% of the administered activity went to tumor in the patients with the massive and multinodular tumors (Patients 2 and

TABLE 2
Summary of the Initial Distribution

Patient	Tumor	Liver	Lung
1	*	90%	10%†
2	11%	78%	11%
3	12%	74%	14%
	10%	69%	21%
4	*	88%	12%

* No selective tumor uptake presumably because of portal vein involvement.

† This could not be directly measured because of the small amount of radioactivity which was administered (0.2 mCi). It represents the difference between the administered activity and that found in the liver.

3). This gave an initial tumor-to-liver concentration ratio of 12:1 for Patients 2 and 8:1 for Patient 3 (Table 2). The first blood sample which was acquired 2 hr postinjection had <0.1% of the administered activity in the entire blood volume.

No focal areas of [^{131}I]Ethiodol were imaged outside of the liver, lungs, or bladder. This is illustrated by Figure 3 which shows a posterior view of the spleen region and an anterior view of the pelvic region on Day 2. Even though the images are heavily thresholded to improve the low count contrast, one can detect neither the spleen nor the bone marrow. This finding is consistent with the low radioactivity found in the venous blood and suggests that there is minimal systemic circulation of Ethiodol.

The clearance of the [^{131}I]Ethiodol from the tumor and organs was fairly consistent from patient to patient. In the tumor, the effective half-life ranged from 4.7 to 5.7 days, while in the liver it ranged from 3.5 to 4 days. Figure 4 shows scintigraphic images obtained from one patient over a period of 2 mo which illustrate the selective concentration and retention in the tumor as compared with the normal liver. The lung activity increased from by 30% to 50% over the first two days, and then cleared with a 4 to 5 day effective half-life. The activity in the blood also increased from Day 1 reaching its maximum on Day 3 and then cleared with a 5-day effective half-life. The maximum activity in the total blood volume never exceeded 0.9% of the administered [^{131}I]Ethiodol. The effective half-lifes of [^{131}I] Ethiodol in the tumor, liver, and lungs are given in Table 3 and a sample plot of the time-activity curves in Figure 5. Approximately 1–3% of the radioactivity cleared through the urine each day.

The dose calculations were performed using Eqs. (2) and (3) along with the measured biodistribution and clearance data. The tumor radiation dose ranged from 3,250 to 6,400 rad in the patients with the massive and multinodular hepatoma, while the dose to the liver and lungs in these patients was well below 1,000 rad. The dose calculations for each patient are summarized in Table 4. Table 5 has the estimated dose per mCi administered based on the average uptake and clearance values found in this study.

DISCUSSION

The results of this study suggest that [^{131}I]Ethiodol has the potential to deliver a curative radiation dose to hepatic tumors in which it concentrates. The [^{131}I] Ethiodol is accumulated in the vascular hepatomas, liver, and lungs during the first pass of the tracer. Although little selective uptake was observed in the infiltrative hepatomas because of presumed portal vein involvement, the concentration in the massive and multinodular tumors was an order of magnitude greater than that of the surrounding normal tissue. In addition, the effective half-life of the [^{131}I]Ethiodol in the tumors was 20–25% longer than in the liver. As a result, large

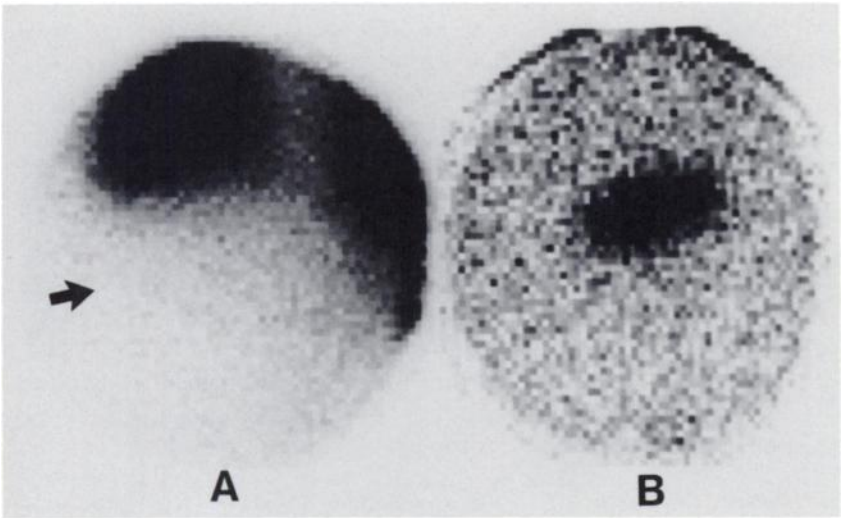

FIGURE 3
Scintigraphic images of (A) posterior spleen region and (B) anterior pelvic region. The images are displayed with a 10% upper threshold to increase the contrast in the areas with decreased counts. Note that no uptake is observed in the spleen (indicated by arrow) or pelvic bone marrow. The hot object in the center of image B is the bladder.

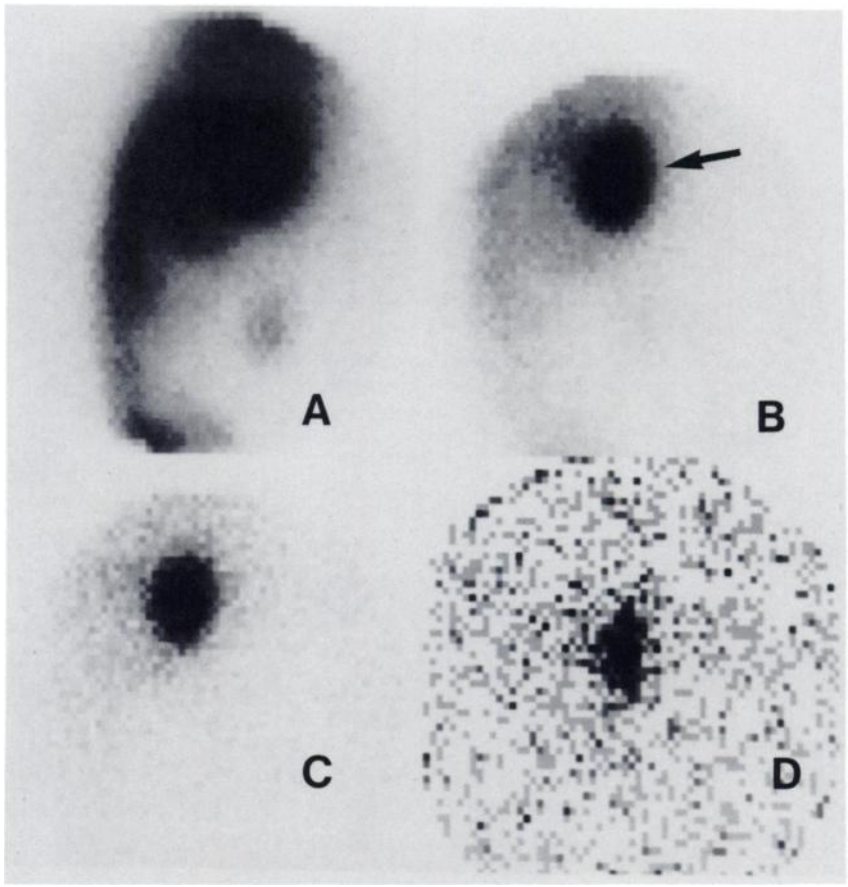

FIGURE 4
Anterior scintigraphic images of the distribution of [^{131}I]Ethiodol in the liver as a function of time. The images were acquired on day 1 (A), Day 16 (B), Day 30 (C) and Day 58 (D). The arrow indicates the location of the tumor.

radiation doses can be delivered to the tumor with acceptable radiation burdens to normal tissues. Using the values in Table 5, 50 mCi of [^{131}I]Ethiodol would deliver more than 11,000 rad to a 35-g tumor while delivering only 1,500 rad to the liver, 1,100 rad to the lungs and <100 rad to the whole body. These are well below the reported tolerance dose for external beam irradiation of the liver (3,000 rad) (*19*) and the lungs (2,500 rad) (*20*).

It should be noted that this technique will be most successful for small tumors with good blood flow. Poorly perfused tissues will not receive enough Ethiodol for a therapeutic effect. Large hepatic tumors often have anastomoses which allows Ethiodol to be shunted past the tumor vasculature. In addition, the radioactivity required to obtain a given dose increases with increased tumor volume. For these reasons, it may not be possible to deliver a therapeutic dose to large tumors without exceeding the tolerance level of the critical organ.

TABLE 3
In Vivo Clearance Times For [^{131}I]Ethiodol

Patient no.	Effective half-life (days)		
	Tumor	Liver	Lung
1	*	4	†
2	4.7	3.7	5.1
3	5.7	4	5.2
	5.3	4	4
4	*	4	5

* No selective tumor uptake presumably because of portal vein involvement.
† Measurement of lung clearance was not performed.

The accuracy of the dose calculation is on the order of ±15%. The reason for this large uncertainty stems from many factors but is primarily a result of the uncertainty of the ROI encompassing the tumor and the correction for activity in the surrounding tissue. SPECT studies would perhaps have significantly improved this aspect of the study particularly since the tumor had such a high contrast. Unfortunately, we were not able to perform SPECT studies with ^{131}I at the time the patients were presented to us.

There was no significant accumulation of [^{131}I]Ethiodol in the region of the spleen and bone marrow on the scintigraphic images. However, it would be difficult to image small amounts of ^{131}I if it were diffusely distributed especially in the vicinity of organs that had high concentrations such as the liver. The possibility of [^{131}I] Ethiodol localizing in other organs cannot be excluded, but it is not expected to be large for the following reasons. First, most of the activity can be accounted for

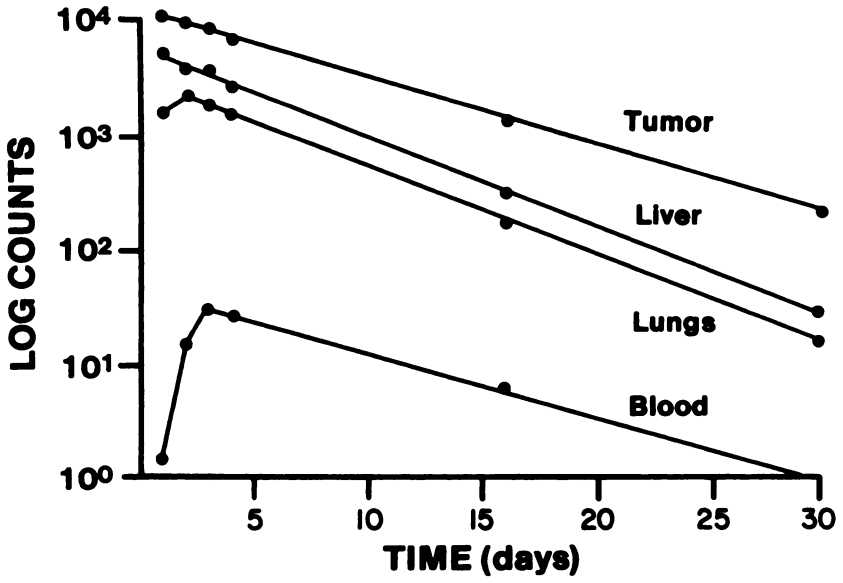

FIGURE 5
Semilog plot of the time activity curves of [^{131}I]Ethiodol in the tumor, liver, lung, and blood. Note that the tumor and liver have their maximum on Day 1 while the lung and blood reach their maximum 1–2 days later.

in the tumor, liver, and lungs, although errors in these estimates on the order of 10% are possible. The total blood radioactivity estimated from venous blood samples obtained in our study was never more than 0.9% of the administered ^{131}I. Although chemical analysis was not performed, it is likely that most of the radioactivity in the blood and urine was no longer attached to the Ethiodol. There have been reports of the accumulation of activity in the bone marrow and spleen of animals injected either intraarterially or through the lymphatic system, but the uptake in these organs was small (*13,21*). In our investigation, the [^{131}I]Ethiodol was injected into the hepatic artery. Although the liver and lungs Efficiently filter the ethiodol, ~2% of the cardiac output bypasses the pulmonary capillary bed (*22*). Ethiodol that is shunted past the lungs will be distributed to the body tissues proportionate to blood flow. If it is conservatively assumed that as much as 5% of the administered activity follows this route, the increase to the total body dose will be on the order of 0.15 rad per mCi administered.

The total-body dose per mCi is estimated to be 1.9 rad. More than 90% of this dose results from the gamma rays emitted in the liver and lungs. As a result, the whole-body dose should be significantly reduced if a pure beta emitter such as yttrium-90 (^{90}Y) were used as the radiolabel instead of ^{131}I. This appears feasible. Yttrium-90 would have several other advantages including its shorter half-life (67 hr) and high-energy beta (2.27 MeV). Yttrium-90 has the disadvantage that scintigraphic imaging is difficult. A comparison of the estimated radiation dose to tumor and normal organs from ^{131}I and ^{90}Y-labeled Ethiodol is given in Table 5.

The amount of Ethiodol administered to the patients is ~3–5 ml. This volume is significantly less than that given in lymphangiography studies. Reports from groups which have performed a large number of intraarterial injections of Ethiodol indicate that the most common adverse reaction is mild fever or nausea and that many patients are unaware of any effect (*3–10*). None of the four patients who participated in this study had any significant complaints resulting from the Ethiodol administration. However, because Ethiodol microembolizes in tissue, caution should be exercised in

TABLE 4
Summary of Estimated Patient Doses (rad) from [^{131}I] Ethiodol

Patient no.	Administered activity (mCi)	Tumor	Liver	Lungs	Total body
1	0.2	*	7	1.2	0.5
2	8.2	6400	575	70	15
3	12	3250	370	264	25
	21	5010	750	647	44
4	24	*	870	422	50

* No selective tumor uptake presumably because of portal vein involvement.

TABLE 5
Summary of Radiolabeled Ethiodol Dosimetry

Organ	Percent of administered activity*	^{131}I (rad/mCi)	^{90}Y (rad/mCi)
Tumor	10%	239†	477†
Liver	75%	31	58
Lungs	15%	22	31
Total body		1.9	0.02

* The percentages refer to the initial distribution.
† Assuming a 4-cm-diameter spherical tumor.

treating patients with severely depressed liver or pulmonary function.

Because Ethiodol is a contrast agent, it is visible on CT scans if the concentration is high. As a result, the deposition of Ethiodol in the tumor, liver and lungs can be quantified. This provides an alternate means of determining the dose to the tumor which will be especially useful if the Ethiodol is labeled with a pure beta emitter. The scintigraphic images are more sensitive in monitoring low concentrations of [^{131}I]Ethiodol through out the body. However, if dosimetric calculations on the sub centimeter scale are desired, that information can be obtained from the CT images.

In summary, [^{131}I]Ethiodol has been shown to localize in vascular hepatoma in high concentration. As a result, a high radiation dose can be delivered to the tumor with an acceptable radiation burden to liver, lungs, and total body. The use of a high energy pure beta emitter such as ^{90}Y will improve the uniformity of dose to the tumor and will decrease the whole-body dose to the patient.

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