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Biodistribution and Kinetics of Holmium-166-Chitosan Complex (DW-166HC) in Rats and Mice

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The fate of ^{166}Ho-chitosan complex, a radiopharmaceutical drug for cancer therapy, was determined by studying its absorption, distribution and excretion in rats and mice. **Methods:** Holmium-166-chitosan complex [0.75 mg of $Ho(NO_3)_3 \cdot 5H_2O$ and 1 mg chitosan/head] was administered intrahepatically to male rats. Radioactive concentrations in blood, urinary and fecal excretion and radioactive distribution in tissues were examined. To determine the effects of chitosan in ^{166}Ho-chitosan complex, ^{166}Ho alone [0.75 mg of $Ho(NO_3)_3 \cdot 5H_2O$/head] was intrahepatically administered to male rats, and radioactive concentrations in blood, urinary and fecal excretion and radioactive distribution were examined. In B16 melanoma-transplanted nude mice, radioactive distribution after intratumoral administration of ^{166}Ho-chitosan complex [0.075 mg of $Ho(NO_3)_3 \cdot 5H_2O$ and 0.10 mg chitosan/head] was investigated also. **Results:** After administration of ^{166}Ho-chitosan complex, the radioactive concentrations in blood were low, and cumulative urinary and fecal excretions over a period of 0–72 hr were 0.53% and 0.54%, respectively. The radioactive concentrations in tissues and the whole-body autoradiography images showed that most of the administered radioactivity was localized at the administration site, and only slight radioactivity was detected from the liver, spleen, lungs and bones. On the other hand, results of intrahepatic administration of ^{166}Ho alone showed high radioactive concentrations in the blood, and the whole-body autoradiographs showed that the administered radioactivity was distributed in many organs and tissues. These results strongly suggest that ^{166}Ho is retained at the administration site only when it forms a chelate complex with chitosan. Autoradiographs after intratumoral administration of ^{166}Ho-chitosan complex showed that radioactivity was localized at the site of administration without distribution to the other organs and tissues. **Conclusion:** Administered ^{166}Ho-chitosan complex is retained at the administration site after either intrahepatic or intratumoral administration to rats or tumor-transplanted nude mice.

Key Words: internal radiotherapy; liver cancer; radiopharmaceutical drug

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There are several articles showing biodistribution after the administration of internal radiotherapeutic agents (*1–4*). These studies are focused on obtaining higher concentrations of the radioactivity and longer retention times in the tumor compared with normal tissues to show the therapeutic effects with high selectivity and to avoid radiation damage to normal tissue or organs. Many antibodies against tumors have been studied (*5–7*), and their selectivities to the tumor cells allow intravenous injection. The other approach uses a radionuclide-bound resin that is physically trapped in the blood vessels of the target tumor (*4,8–12*).

Holmium-166-chitosan complex (DW-166HC), in which chitosan is chelated with 166-holmium, is being developed as a radiopharmaceutical drug for cancer therapy by the Korea Atomic Energy Research Institute (Taejon, Korea) and Dong Wha Pharmaceutical Company (Kyunggi-do, Korea). Chitosan, a polymer of 2-deoxy-2-amino-D-glucose that is obtained by deacetylation of chitin, forms a chelate with the heavy metals (*13–15*). It is readily dissolved in water to make a clear solution under acidic conditions, but it converts to a solid state under basic conditions. Holmium-166 has many beneficial physical characteristics for internal radiation therapy, such as an appropriate half-life (26.8 hr), high beta-energy [maximum 1.85 MeV (51%), 1.77 MeV (48%); mean = 0.67 MeV) and low gamma-energy (0.081 MeV) that is easily detectable by gamma camera. Direct administration of DW-166HC in acidic solution into the lesion of the tissue percutaneously converts the solution to a gel in the tissue, and radioactivity of ^{166}Ho destroys the tumor.

When DW-166HC is applied for clinical therapy, the pharmacokinetic profile gives important information on both therapeutic efficacy and side effects. The objective of this study, therefore, is to determine the fate of DW-166HC by studying its absorption, distribution and excretion after intrahepatic, intravenous and intratumoral administration to male rats and nude mice.

MATERIALS AND METHODS

Chemicals

Holmium-166-$(NO_3)_3 \cdot 5H_2O$ was produced at the Korea Atomic Energy Research Institute. Specific activities of $^{166}Ho(NO_3)_3 \cdot 5H_20$ were between 65 and 296 MBq/mg (1.75 and 8.0 mCi/mg). Chitosan was obtained from Korea CCR (Seoul, Korea), and its molecular weight was ~700,000. All other chem-

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icals were obtained from common suppliers and were reagent-grade.

Experimental Animals and Dosages

Male Sprague–Dawley rats (6-wk-old) and male ICR nude mice (5-wk-old) were purchased from Charles River Laboratories Japan, Inc. (Kanagawa, Japan). Animals were used after acclimation for ~1 wk. Tumor-transplanted nude mice were prepared with transplantation of a piece of B16 melanoma into the left lateral lobe of the mouse liver using the method reported previously (*15*). The transplanted mice were maintained for ~10 days and then used for the experiments.

In the intrahepatic or intratumoral administration, DW-166HC solution was injected directly into the liver or transplanted tumor by surgical techniques using a 27-gauge needle. The injection rate was ~10 μl/20 sec. In intrahepatic administration, DW-166HC was injected at two sites in the left lateral lobe of the rat liver, and the administered volume per site was 50 μl, whereas in intratumoral administration, 10 μl DW-166HC were injected into the transplanted tumor tissue. In intravenous administration, DW-166HC solution was administered via the caudal vein.

DW-166HC solution for intrahepatic and intratumoral administrations was prepared by the method of Korea Atomic Energy Research Institute to contain 10.0 mg chitosan and 7.5 mg/ml $Ho(NO_3)_3 \cdot 5H_2O$, and for intravenous administration, it was prepared to contain 1.0 mg chitosan and 0.75 mg/ml $Ho(NO_3)_3 \cdot 5H_2O$.

The radioactive concentrations of the drug solutions, which were recalculated at the time and date of administration, and administration volumes were 9–13 MBq (243–351 μCi)/100 μl/head (50 μl/site, two administration sites/head) in intrahepatic administration to rats and 1.5 MBq (41 μCi)/10 μl/head in intrahepatic and intratumoral administrations to mice.

Intravenous administration study was performed to determine the pharmacokinetic behavior of DW-166HC transferred into the blood flow from the administration site. Because we estimated that the amount of DW-166HC transferred into the blood flow would not exceed 25% of the injected dose (%ID) in the intrahepatic administration from the preliminary experiments, ~25% of the intrahepatic dose was administered via the caudal vein. The intrahepatic dosing solution has a high viscosity, and it is not suitable for intravenous administration. To avoid any problem caused by injection of the highly viscous solution, a 10-fold dilution of the intrahepatic dosing solution was used for intravenous administration. The radioactive concentration and volume were 7 MBq (189 μCi)/ml/kg body weight.

Determination of Radioactive Concentration

To determine the radioactive concentration in blood, blood was obtained from the jugular vein of the rats after intrahepatic or intravenous administration of DW-166HC or ^{166}Ho.

To determine the radioactive concentration in tissues, animals were exsanguinated from the inferior vena cava under diethyl ether anesthesia after intrahepatic administration of DW-166HC. Tissues and organs were dissected and weighed. They were mixed to homogeneity, and whole or aliquot of samples were weighed and measured for radioactivity.

To determine the radioactivity in urine and feces, animals were kept separately in their individual stainless metabolic cages after intrahepatic or intravenous administration of DW-166HC or ^{166}Ho. Urine and feces were collected separately, and at the final observation time, each animal was killed by diethyl ether, and residual radioactivity was measured.

Samples for radioactivity measurement were prepared, with or without digestion, by the tissue solubilizer. Radioactivity in samples was measured in a liquid scintillator and counted for 1 min with a three-channel liquid scintillation counter (LSC-1000; Aloka Co., Japan), with corrections made for background and counting efficacy. The obtained radioactivities were corrected for the time and date administered by the radioactive half-life of ^{166}Ho.

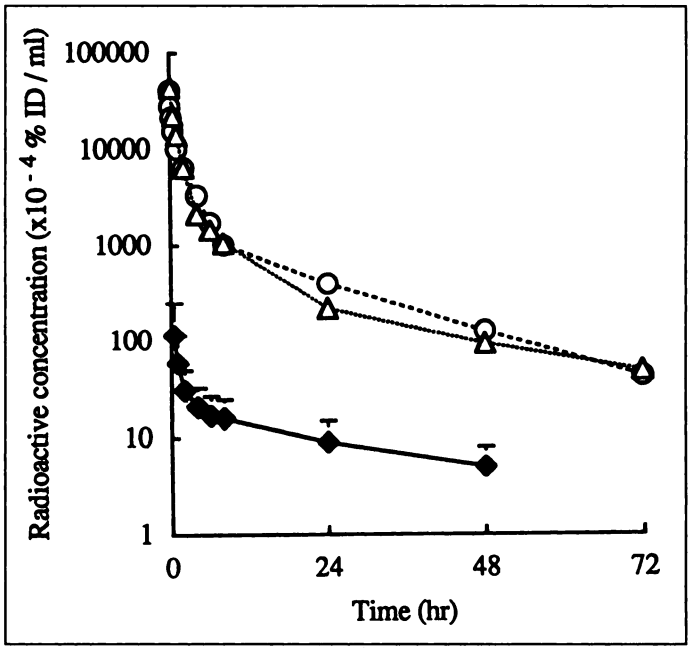

FIGURE 1. Radioactive concentration in blood after administration of DW-166HC or ^{166}Ho to male rats. ◆ = intrahepatic administration of DW-166HC; ○ = intravenous administration of DW-166HC; △ = intrahepatic administration of ^{166}Ho. All values were expressed as mean %ID/ml ($\times 10^{-4}$) ± s.d. (n = 3).

Whole-Body Autoradiography

The animals were killed by diethyl ether at the predetermined time. They were frozen in liquid nitrogen and then mounted for sectioning. From each animal, thin sections were prepared with the Cryomacrocut (Leica Instruments GmbH, Germany). The obtained sections were then freeze-dried at −20°C. The sections were exposed to the imaging plates (Fuji Photo Film Co., Ltd., Tokyo, Japan). After exposure, each autoradiography image was obtained and analyzed by BAS2000 (Fuji Photo Film Co., Ltd.).

Expression of Results

Radioactive concentrations in blood and tissues were shown as %ID/g tissue or organ, calculated with dpm/g and injected radioactivity (dpm).

Excretion data from urine and feces were expressed as %ID, calculated with dpm of total radioactivity in each period of urine or feces and injected radioactivity (dpm), and represented with cumulative values.

The doses absorbed in tissues and the administration site are calculated based on the Medical Internal Radiation Dose Committee method (*16*) of absorbed fractions.

Measured radioactivity, which was greater than twofold that of background, was represented as not detectable (ND). In the event that two individual values in three animals were ND, the mean value was represented as ND, whereas when only one individual value was ND, the mean value was calculated with two other values.

RESULTS

Radioactive Concentrations in Blood

Radioactive concentrations in blood were determined after intrahepatic or intravenous administration of either DW-166HC or ^{166}Ho alone to male rats (Fig. 1). After intrahepatic admin-

TABLE 1

Cumulative Urinary and Fecal Excretion and Residual Ratios of Radioactivity After Administration of DW-166HC or Holmium-166 to Male Rats

Sample	Observation period (hr)	% of dose DW-166HC (ih)	% of dose ^{166}Ho (ih)	% of dose DW-166HC (iv)
Urine	0~6	0.19 ± 0.02	1.34 ± 0.81	0.98 ± 0.55
	0~12	0.28 ± 0.03	2.42 ± 0.69	1.75 ± 0.51
	0~24	0.41 ± 0.01	3.20 ± 0.75	2.60 ± 0.70
	0~48	0.49 ± 0.04	4.41 ± 0.77	3.50 ± 0.87
	0~72	0.53 ± 0.07	5.30 ± 0.71	4.27 ± 1.05
Feces	0~24	0.15 ± 0.04	4.05 ± 0.58	1.13 ± 0.63
	0~48	0.35 ± 0.06	9.94 ± 0.96	3.49 ± 1.07
	0~72	0.54 ± 0.08	14.93 ± 1.32	4.86 ± 1.22
Carcass	72	7.24 ± 4.33	79.48 ± 0.93	90.59 ± 2.66
Administration site	72	92.11 ± 3.53		

All values are expressed mean ± s.d. (n = 3). In intrahepatic administration of DW-166HC, radioactivity in the administration site was determined separately, whereas in the other cases, administration sites were not clearly defined and were included in the carcasses.

ih = intrahepatic administration; iv = intravenous administration.

istration, the concentration of DW-166HC gradually decreased as a function of time and remained at a low level up to 48 hr. In comparison, the concentration of ^{166}Ho alone after intrahepatic administration was ~200 times higher than DW-166HC within 2 hr after administration, and the profile of radioactive concentrations in blood after ^{166}Ho alone administration was similar to that after intravenous administration of DW-166HC. These data indicate that ^{166}Ho itself cannot be retained in the administration site unless it is administered in a chelate complex with chitosan.

Urinary and Fecal Excretion of Radioactivity

Urinary and fecal excretion of radioactivity was measured after intrahepatic or intravenous administration of either DW-166HC or ^{166}Ho alone to male rats (Table 1). Cumulative excretion ratios after intrahepatic administration of DW-166HC were 0.53% in urine and 0.54% in feces during 0- to 72-hr period. More than 90% of the radioactivity of the drug administered was recovered from the administration site. In the intravenous administration of DW-166HC, 4.27%, 4.86% and 90.59% of the radioactivity in urine, feces and residual carcass, respectively, was recovered. On the other hand, 5.30% and 14.93% of administered ^{166}Ho were excreted in urine and feces, respectively, within 72 hr of the intrahepatic administration of ^{166}Ho alone. These results indicate that >90% of administered DW-166HC is retained in the administration site after intrahepatic administration, and ≤10% was transferred into the blood flow.

Distribution of Radioactivity of Test Compounds in Tissues

Distribution of the radioactivity in tissues was determined by radioactivity counting and autoradiography after intrahepatic administration of DW-166HC (Table 2 and Fig. 2).

The examination of organs and tissues showed that >90% of the radioactivity was retained in the administration site for at least 144 hr after administration, and <10% was distributed in

TABLE 2

Radioactive Concentrations in Organs or Tissues After Intrahepatic Administration of DW-166HC to Male Rats

Organ or tissue	%ID/g (× 10^{-4}) 2 hr	24 hr	72 hr	144 hr
Blood	33 ± 21	10 ± 6	ND	ND
Plasma	44 ± 27	11 ± 6	ND	ND
Brain	5 ± 2	ND	ND	ND
Thymus	11 ± 6	42 ± 20	25 ± 2	ND
Heart	99 ± 57	104 ± 42	234 ± 296	146 ± 28
Lung	21,088 ± 19,043	28,235 ± 31,256	15,573 ± 24,456	4,540 ± 6,132
Liver	492 ± 397	695 ± 586	254 ± 186	173 ± 76
Kidney	180 ± 158	152 ± 121	72 ± 53	ND
Adrenal	58 ± 23	109 ± 72	66 ± 52	ND
Pancreas	45 ± 48	61 ± 37	48 ± 27	ND
Spleen	315 ± 252	291 ± 197	202 ± 106	227 ± 123
Skeletal muscle	7 ± 5	ND	ND	ND
Bone	485 ± 428	831 ± 326	1,060 ± 661	1,120 ± 469
Bone marrow	47 ± 39	82 ± 44	102 ± 79	ND
Skin	18 ± 13	16 ± 11	ND	ND
Testis	8 ± 4	9 ± 4	ND	ND
Carcass	33 ± 20	92 ± 56	143 ± 51	155 ± 21
Stomach	13 ± 7	26 ± 13	20 ± 0	ND
Small intestine	68 ± 77	29 ± 12	36 ± 21	ND
Large intestine	12 ± 6	44 ± 22	44 ± 28	ND
Administration site	645,660 ± 19,698	787,084 ± 116,591	679,717 ± 92,175	834,300 ± 25,707

All values are expressed as mean %ID/g (× 10^{-4}) ± s.d. (n = 3). ND = not detectable.

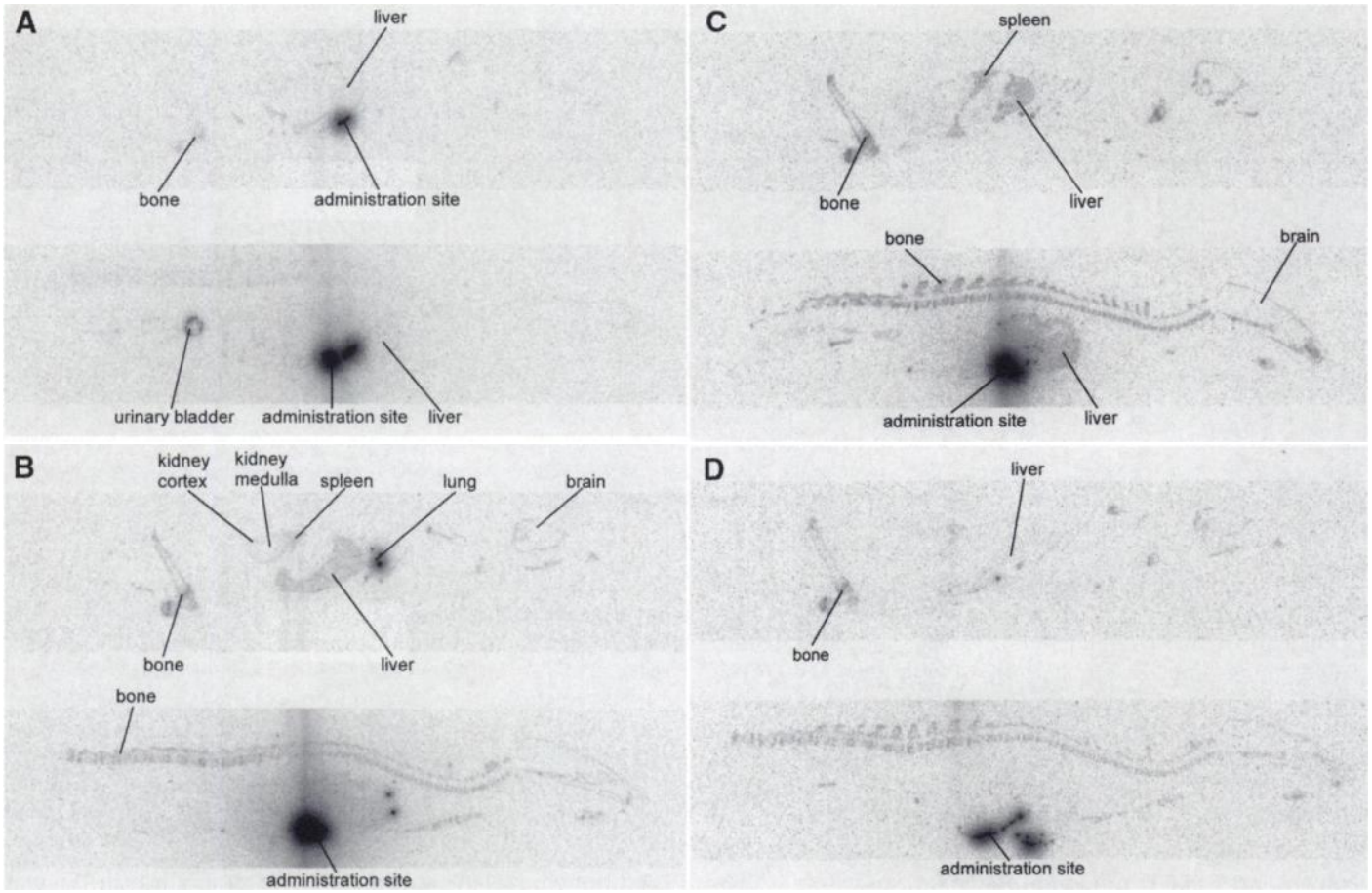

FIGURE 2. (A) Radioactive distribution at 2 hr after intrahepatic administration of DW-166HC to a male rat. (Upper) Dorso-ventral section including kidney. (Lower) Dorso-ventral mesion section. (B) Radioactive distribution at 24 hr after intrahepatic administration of DW-166HC to male rat. (Upper) Dorso-ventral section including kidney. (Lower) Dorso-ventral mesion section. (C) Radioactive distribution at 72 hr after intrahepatic administration of DW-166HC to male rat. (Upper) Dorso-ventral section including kidney. (Lower) dorso-ventral mesion section. (D) Radioactive distribution at 144 hr after intrahepatic administration of DW-166HC to male rat. (Upper) Dorso-ventral section including kidney. (Lower) Dorso-ventral mesion section.

the other tissues. Of these tissues, the radioactivity in lungs showed a relatively high concentration, although the %ID was relatively low (data not shown). Some radioactivity was detected in the liver, spleen and bones. The concentrations in the liver and spleen decreased gradually with time, but the concentration in bone increased.

To confirm the data obtained through radioactivity counting and to observe the detailed distribution of radioactivity in the organs, an autoradiographic study was performed. These data confirmed that the most of the radioactivity administered was retained in the administration site of the liver lobe. Low levels of radioactivity were observed in the liver adjacent to the administration site and in the kidneys, spleen and bones. Only the autoradiographic pattern of the individual rats 24 hr after administration showed high radioactivity in the spots in the lung, which is consistent with the counting study. Distribution of the radioactivity in the bone indicated that the periosteum has a higher radioactive concentration than the bone itself.

Compared with the tissue distribution of DW-166HC, autoradiographs after intrahepatic administration of ^{166}Ho alone showed that radioactivity had spread throughout the body, and no retention was observed at the administration site in the liver at 2 and 72 hr after administration (Fig. 3). A remarkable distribution of radioactivity was seen in the liver, spleen, kidneys and bones. These data further support that DW-166HC is retained in the administration site after intrahepatic administration, but ^{166}Ho is not retained in the administration site except in the chitosan chelate complex form. The data also indicated that ^{166}Ho has a high affinity for the liver, spleen and bones.

Table 3 shows the results of the internal radiation dosimetry studies. The total injected radioactivity was 13 MBq (351 μCi), and the mean doses in the blood, lung, liver, spleen and bone were 0.00319, 5.30, 0.0805, 0.0441 and 0.593 Gy, respectively, whereas the activity in the administration site was 160 Gy. Table 3 also shows the administration site-to-tissue dose ratios (Ad/Ti ratios), ranging from 30 to 50,157.

Distribution of Radioactivity in Tumor-Transplanted Mice

Because DW-166HC is being developed as a radiopharmaceutical drug for cancer therapy, an intratumoral administration study was performed using B16 melanoma-transplanted nude mice as models. DW-166HC was administered directly into the tumor, which had been transplanted into the liver lobe of the mice, and distribution of the radioactivity in tissues was studied by autoradiography. As a control, an equivalent dose and volume of DW-166HC was administered into the liver of the intact mice. Autoradiographs of the control mice showed that most of the radioactivity was retained at the administration site, with slight distribution to the liver, bones and spleen (data not shown), which is a very similar distribution pattern to that in rats subjected to intrahepatic administration (Fig. 2). In comparison, the tumor-transplanted mice showed higher radioactivity retained at the administration site than in the control mice and less distributed to the body (Fig. 4). The results indicated that much higher radioactivity of DW-166HC was retained in

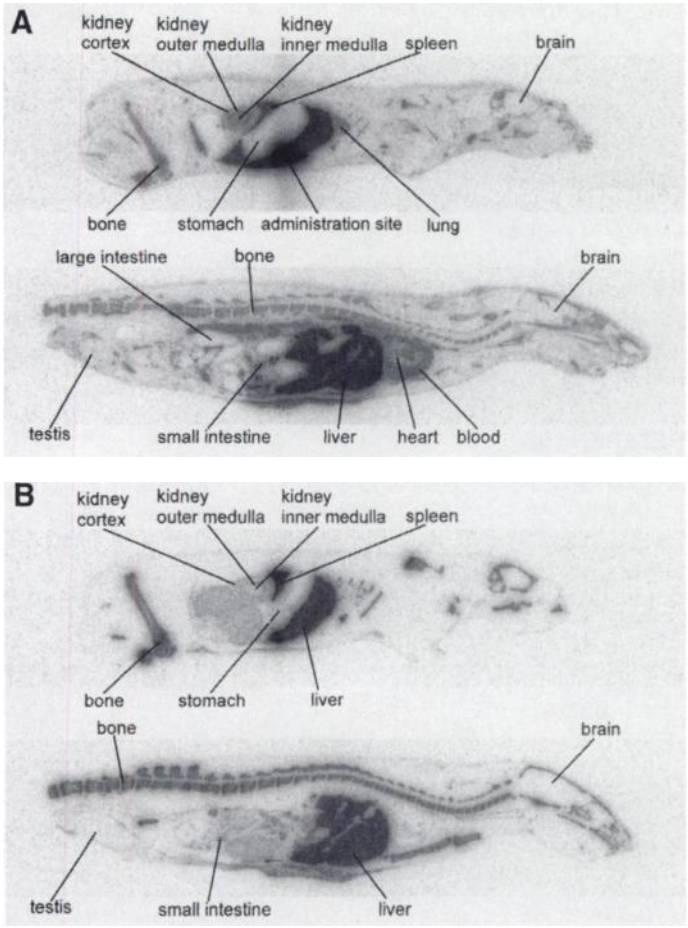

FIGURE 3. (A) Radioactive distribution at 2 hr after intrahepatic administration of ^{166}Ho to male rat. (Upper) Dorso-ventral section including kidney. (Lower) Dorso-ventral mesion section. (B) Radioactive distribution at 72 hr after intrahepatic administration of ^{166}Ho to male rat. (Upper) Dorso-ventral section including kidney. (Lower) Dorso-ventral mesion section.

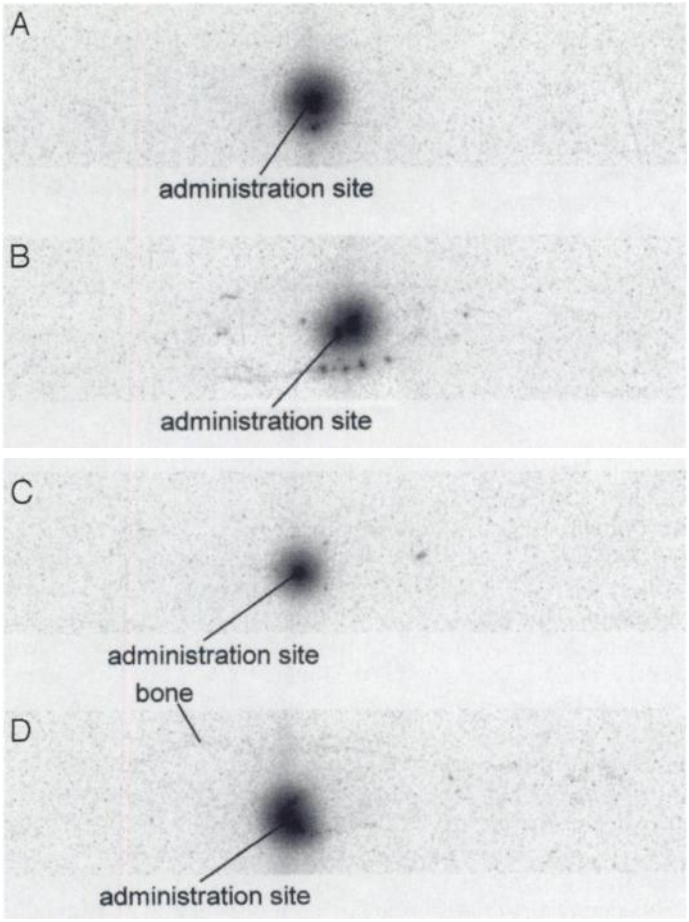

FIGURE 4. Radioactive distribution after intratumoral administration of DW-166HC to tumor-transplanted nude mice, 2 (A), 24 (B), 72 (C) and 144 hr (D) after administration.

the livers of tumor-bearing mice than in those of the control mice.

DISCUSSION

The physical properties of chitosan change with the environmental pH. Under acidic conditions, it is a clear and viscous solution, whereas it becomes an opaque gel under neutral conditions. When chitosan in acidic solution is injected into the tissue directly, the neutral environment surrounding the chitosan changes it to gel form. Because of these characteristics, chitosan has the potential to be retained at the injected site for a long period of time. In addition to this chemical characteristic, chitosan is known to form a chelate with heavy metals (*14,15*).

TABLE 3
Mean Dose of Major Tissues and Administration Site-to-Tissue Ratios

Administration site	Mean dose to tissue (Gy) 160	Ad/Ti ratio
Blood	0.00319	50,157
Lung	5.30	30
Liver	0.0805	1,988
Spleen	0.0441	3,628
Bone	0.593	270

Injection dose was 13 MBq (351 μCi).

Because ^{166}Ho has many beneficial characteristics for internal radiation therapy, such as its half-life, high beta-energy and low gamma-energy, DW-166HC, a ^{166}Ho-chitosan chelate complex is being developed for use in internal radiotherapy.

The most important conclusion from the pharmacokinetic study on DW-166HC administered into the liver lobe of the rat is that most of the administered radioactivity was exclusively retained at the administration site for over 72 hr. This conclusion was supported by the results of the whole-body autoradiography and the radioactive distribution in tissues. On the other hand, intrahepatic administration of ^{166}Ho alone showed higher radioactive concentrations in the blood from the early period, and it had also spread to many tissues. These results strongly suggest that DW-166HC is retained in the administration site, being a good therapeutic agent.

In this study, the autoradiographic images and tissue distribution of DW-166HC after intrahepatic administration revealed that the most of the radioactivity was retained at the administration site, and only slight radioactive concentrations were detected in the liver, spleen and bone. The Ad/Ti ratio showed that the radioactive concentrations in these tissues were at least three orders of magnitude lower than that of the administration site (Table 4). Moreover, the Ad/Ti ratios, except that of bones, increased with time, indicating that the biological half-life of radioactivity at the administration site is longer than that in the other tissues. The autoradiograph for 24 hr after intrahepatic administration showed uneven distribution, with grains of high radioactive concentration in the lung. These results suggest that the radioactive compound transferred into the blood vessels is likely to be DW-166HC and that DW-166HC was transferred

TABLE 4
Administration Site-to-Tissue Ratios of Radioactive Concentrations

Ratio	Time			
	2 hr	24 hr	48 hr	72 hr
Administration-to-blood	19,565	112,441	—	—
Administration-to-liver	1,312	1,511	2,676	4,823
Administration-to-lung	31	37	44	184
Administration-to-spleen	2,050	3,610	3,364	3,675
Administration-to-bone	1,331	1,263	641	745

All values were calculated from the data indicated in Table 2. Liver refers to liver tissue not including the administration site.
— = incalculable.

into the hepatic vein, passed through the liver and heart and clotted in the capillary vessels of the lung. The radioactive distribution to the lung must be the result of direct administration of DW-166HC to the liver of a small animal. For clinical use, however, it should be possible to avoid the large blood vessels in the liver by medical administration techniques.

The administration of ^{90}Y microspheres to primary or secondary liver cancer has been studied (*4,8–12*). After intraarterial or intraperitoneal administration of ^{90}Y microspheres, the enhanced tumor blood flow transports ^{90}Y microspheres preferentially to the resident tumor. Because of the size of the microsphere, it gets trapped in the tumor and provides extensive radiation exposure. These studies showed a tumor-to-liver ratio of ≤45, showing that the Ad/Ti ratio of DW-166HC is remarkably high.

Nakajo et al. (*17*) reported the biodistribution of ^{131}I-lipiodol infused via the hepatic artery of patients with hepatic cancer. They determined that the radioactive concentration in blood after administration of ^{131}I-lipiodol had been kept as low as 10×10^{-4} %ID/ml for 8 days after administration. Our results presented here reveal that the radioactive concentration in blood 30 min after administration was ~10 times higher than in their results. However, the concentration decreased rapidly and became 10×10^{-4} %ID/ml within 2 days. Overall radioactivity in the blood suggested that DW-166HC is similar to ^{131}I-lipiodol. More than 50% of the administered ^{131}I-lipiodol was transferred into systemic circulation, passed through the kidney and excreted in urine. On the other hand, only 1% of the DW-166HC was excreted in urine and feces for 3 days. These results strongly suggested that irradiation to the whole body after DW-166HC administration should be much smaller than that after ^{131}I-lipiodol administration.

CONCLUSION

This pharmacokinetic study of intrahepatic or intratumoral administration of DW-166HC revealed that:

1. The effective biological half-life at the administration site is much longer than that at other tissues;
2. The Ad/Ti ratios are extremely high; and
3. The activity in the organs other than the administration site is very low.

These data strongly suggest that DW-166HC is a good candidate for a radiotherapeutic agent. In addition, our data suggest that DW-166HC is retained in the liver as well as tumor. By taking advantage of the characteristics of chitosan, DW-166HC may be applied to other tissues and organs that require treatment with radiotherapy.

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