
Radiotoxicity of Some Iodine-123, Iodine-125 and Iodine-131-Labeled Compounds in Mouse Testes: Implications for Radiopharmaceutical Design

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In this work, spermhead survival in mouse testis was used to investigate the radiotoxicity of several intratesticularly localized radioiodinated pharmaceuticals. Radioiodines that decay by electron capture and/or internal conversion (^{123}I , ^{125}I) as well as by β^- decay (^{131}I) were coupled to pharmaceuticals that selectively localize in different cell compartments. Dose response curves yield D_{37} values of 62 cGy, 75 cGy, 61 cGy and 7.7 cGy for ^{123}I IMP (N-isopropyl-p-iodoamphetamine), ^{131}I dU (iododeoxyuridine), H^{131}I PDM (N,N,N'-trimethyl-N'-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propanediamine) and ^{125}I dC (iododeoxycytidine), respectively. At 37% survival, the relative biological effectiveness (RBE) of these radiochemicals, when compared to the pure gamma-emitting radiochemical ^7Be -chloride ($D_{37} = 65$ cGy), are 1.0, 0.89, 1.1 and 8.4, respectively. Intratesticular ^7Be , with an effective half-life of 430 hr in the organ, was used as the source of reference radiation to determine the RBE values because it solely emits 477 keV gamma rays, and the dose to the testis is delivered chronically, as in the case of the other radiocompounds. Subcellular distribution studies show that all of the cellular activity is localized in the cytoplasm in the cases of ^{123}I IMP and H^{131}I PDM, while virtually all of ^{131}I dU and ^{125}I dC were bound to DNA in the cell nucleus. In agreement with our earlier in vivo studies, these data show that subcellular distribution plays a key role in the radiotoxicity of Auger electron emitters such as ^{123}I and ^{125}I , and has no role for beta emitters such as ^{131}I . These findings may have implications in the design of radiopharmaceuticals for both diagnosis (localize Auger emitter in cytoplasm of cell) and therapy (localize Auger emitter in cell nucleus).

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Radioiodinated pharmaceuticals are widely used in nuclear medicine for diagnostic and therapeutic applica-

tions. Of the radioiodines, ^{123}I , ^{125}I and ^{131}I have been most commonly used in medicine. The former two decay by electron capture followed by internal conversion and, as a consequence, emit numerous low-energy Auger electrons (1). These low-energy (~ 20 –500 eV) electrons have ranges of subcellular dimensions and therefore impart their energy locally (1). The favorable organ dosimetry for these radionuclides has led to their use predominantly in diagnosis. Although the low-energy nature of the photons emitted by ^{125}I has limited its utility as an in vivo diagnostic agent, it is the radionuclide of choice for radioimmunoassay. Because of its desirable physical properties and favorable dosimetry, ^{123}I is routinely used for thyroid uptake and imaging studies. Other promising radiopharmaceuticals such as the brain imaging agents H^{123}I PDM (N,N,N'-trimethyl-N'-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propanediamine) (2) and ^{123}I -Spectamine® (^{123}I IMP: N-isopropyl-p-iodoamphetamine) (3,4) are also finding a place in nuclear medicine. In contrast to the above radioiodines, the physical properties of ^{131}I favor therapeutic applications (5).

It is widely believed that the lethality of beta emitters of low linear energy transfer (LET) are reasonably independent of the subcellular distribution. Conversely, however, it is now well recognized that the radiotoxicity of Auger electron emitters depends strongly on their distribution within the cell (6–9). The most severe effects have been observed when the Auger emitter is localized in the cell nucleus and bound to DNA, while effects akin to beta emitters are observed when situated in the cytoplasm (6, 8,10). For DNA-bound Auger emitters in vivo and in vitro, the values of relative biological effectiveness (RBE) have been as high as those observed for high-LET alpha particles (9,11). Since the biological effects of Auger-emitting radiochemicals can not be predicted a priori, it is presently necessary to ascertain the biological effects of each radiocompound individually. Accordingly, in this work the well established mouse testis model is employed to investigate the lethality of the brain imaging agent ^{123}I IMP, as well as three additional radioiodinated products

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including $H^{131}IPDM$, ^{125}I iododeoxycytidine (^{125}IdC) and ^{131}I iododeoxyuridine (^{131}IdU). Subcellular distribution of these radiochemicals is determined and correlated with the biological effects. These results, in conjunction with earlier studies (7,8,12), suggest that the design of diagnostic radiopharmaceuticals involving Auger emitters should take into account subcellular distribution in order to minimize risk. For the therapeutic use of Auger emitters, it is desirable to maximize the biological effect by directing the radiochemical to the tumor cell nucleus. Finally, the results confirm that in general subcellular distribution is not a determinant in the design of beta-emitting radiopharmaceuticals. However, it should be noted that there may be instances where subcellular distribution plays a role (13).

MATERIALS AND METHODS

Spermatogenesis in mouse testis was used as the experimental model with spermhead survival serving as the biological end point. This model has been used extensively to investigate the radiotoxicity of a variety of radiochemicals (7,8,11,14,15). The rationale for this model stems from the differential radiosensitivity of the various cells in the testis. The primary spermatogonial cells (types A₁-A₄, In, B) are the most radiosensitive with LD₅₀ ~40 cGy, while the remaining cell types (spermatocytes, etc.) have substantially higher LD₅₀ values ranging from 200-60,000 cGy (16,17). Therefore, irradiation of the testis with low doses results in a reduced spermhead count about 29 days postirradiation, the time required for the spermatogonia to become sonication resistant spermatids of Stages 12-16 (16,17). Further details regarding the model may be found elsewhere (7,8,15).

Anesthetized male Swiss Webster mice (8-9 wk) weighing about 30 g were intratesticularly injected with 3 μ l of a solution containing the radiochemical. In order to facilitate a reasonably uniform distribution of the radiochemical in the testis, a line injection was performed whereby the needle was continuously withdrawn during the injection (7,8,11,12). This mode of administration is preferred over intravenous and intraperitoneal injections because the radiobiological effect of particulate radiation (alpha, beta, Auger) can be ascertained without the interference of penetrating radiation emanating from the whole body.

Radiochemicals

Radioiodinated HIPDM was prepared and assayed according to the procedures of Lui et al. (18) using ^{131}I (New England Nuclear, N. Billerica, MA). Spectamine® (^{123}IMP) and 7Be -chloride were obtained from Medi-Physics (South Plainfield, NJ). The ^{123}IMP , also provided, had a 4.8% (by activity at time of use) ^{124}I contaminant which contributed about 16% of the total testicular absorbed dose. The radiochemical ^{125}IdC was obtained from ICN Radiochemicals (Irvine, CA). Finally, ^{131}IdU was prepared by an adaptation of the syntheses of Hadi et al. (19) and Bakker and Kaspersen (20). Briefly, a solution of chloramine T (400 μ g in 200 μ l of phosphate buffer (PB), 0.1 M, pH 6.95) 2'-deoxyuridine (400 μ g in 400 μ l of PB) was stirred at 105°C in an oil bath. One millicurie of Na ^{131}I (New England Nuclear, Billerica, MA), specific activity 770 Ci/mmol, was added and the heating continued for 25 min. Upon cooling to 25°C, K₂S₂O₅ (400 μ g in 40 μ l PB) was added, the mixture passed through a 0.4 μ m filter and purified by HPLC. The HPLC system consisted of an Ultremex® C18

column (150 \times 4.6 mm, 5 μ m, Phenomenex, Torrence, CA) equilibrated with 8% methanol in water at a flow rate of 1 ml/min. Pure radiolabeled ^{131}IdU was eluted after 12 min. One to two additional passes through the HPLC column afforded >98% radiochemical purity, 55% radiochemical yield, and specific activity 300 Ci/mmol.

Biological Clearance from the Testis

The right testis of mice were intratesticularly injected with small quantities of the radiochemicals. The mice then were killed under ether in groups of four at various times postinjection. The testes were removed and the radioactivity contained within each testis was determined with a NaI well counter. The fraction of activity retained in the testis was the ratio of average activity in the testes to that in the injection standard.

Subcellular Distribution

Subcellular distribution of the radiochemicals in the testicular cells was determined according to procedures described elsewhere (14). Briefly, one day following intratesticular injection of the radiochemical, the animals were killed and the testes removed. The testicular cells were isolated and the cytoplasmic and nuclear fractions separated. Aliquots of these fractions were counted for radioactivity and the fraction of total cellular activity found in the two compartments was obtained. The nuclei were further processed to obtain the fraction of nuclear activity bound to DNA.

Optimal Day to Perform Spermhead Survival Assay

Because irradiation of the testis with low doses primarily affects only the spermatogonia, the minimum testicular spermhead count is not observable until the time required for spermatogonia to become sonication-resistant spermatids (Stages 12-16). Hence, the optimal day to perform the spermhead survival assay (minimum spermhead count) was ascertained. Forty mice were intratesticularly injected with a fixed quantity of radiochemical. On various days postinjection, the animals were killed, the testis removed and placed in 1 ml deionized water, homogenized, sonicated, and the spermhead count determined according to procedures reported earlier (15). Using these data, the optimal day was delineated.

Spermhead Survival Assay

Spermhead survival as a function of testicular absorbed dose was obtained as follows. Various amounts of the radiochemicals were injected into the right testes of the animals (groups of four). On the optimal day postinjection as determined above, the animals in each group were killed, the spermhead counts obtained and the surviving fraction compared to controls (injected with normal saline or the nonradioactive compound) were determined.

RESULTS

Biological Clearance and Radiation Dose

Figure 1 shows the biological clearance of the radiochemicals from the testis following intratesticular administration. Similar elimination patterns have been consistently observed for all radiochemicals studied in this model (7,8,11,12). The biological clearance data were least squares fitted to a two-component exponential expression:

$$f = (1 - a) e^{-0.693t/T_1} + a e^{-0.693t/T_2}, \quad \text{Eq. 1}$$

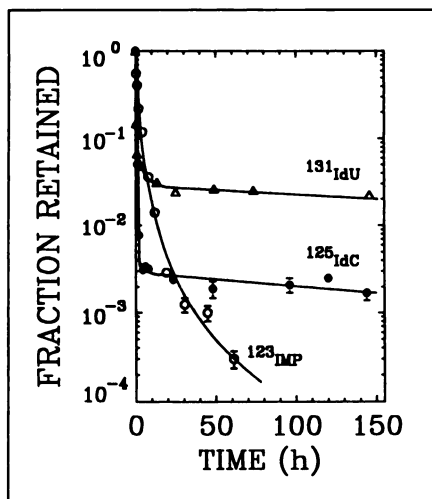


FIGURE 1. Biological clearance of the radiochemicals from mouse testis following intratesticular injection. The data for ^{131}IdU , ^{123}IMP and ^{125}IdC are represented by Δ , \square and \bullet , respectively. Clearance patterns were not affected by the amount of radioactivity injected over the range used in these studies. Representative standard deviations are indicated by the error bars.

where f is the fraction of injected activity remaining in the testis at time t (in hours) postinjection. The biological half-lives of the two components are given by T_1 and T_2 . The fitted parameters a , T_1 , and T_2 , are given for the various radiochemicals in Table 1. The biological clearance for $\text{H}^{131}\text{IPDM}$ was the same as that for $\text{H}^{125}\text{IPDM}$ and may be found elsewhere (8).

The absorbed dose D to the testis was calculated using conventional MIRD techniques (21) where $D = (A_0 \tau / m) \sum \Delta_i \phi_i$. The values of Δ_i (mean energy emitted per transition) for the radionuclides were taken from Weber et al. (22). Assuming uniform distribution of the radiochemical in the testis, the absorbed dose per unit cumulated activity was calculated (23). Finally, residence times τ were obtained by integrating the expressions for f (the biological half-lives being substituted with the appropriate effective half-lives) over seven days, the time over which the dose was delivered to the spermatogonia, that subsequently become spermatids 29 days later (7,8,14,15).

Spermhead Survival as a Function of Testicular Absorbed Dose

The optimal day to perform the spermhead survival assay was determined to be the 29th day postinjection for all of the radiochemicals studied in the present work (data

TABLE 1
Parameters for Least Squares Fit of Testicular Clearance Data

Radiochemical	a	T_1 (hr)	T_2 (hr)
^{131}IdU	0.044 ± 0.0047	0.16 ± 0.068	108 ± 40
^{125}IdC	0.0030 ± 0.00043	0.18 ± 0.005	172 ± 39
^{123}IMP	0.42 ± 0.056	0.34 ± 0.044	2.3 ± 0.31
$^7\text{Be-chloride}$	0.20 ± 0.029	0.27 ± 0.033	648 ± 102

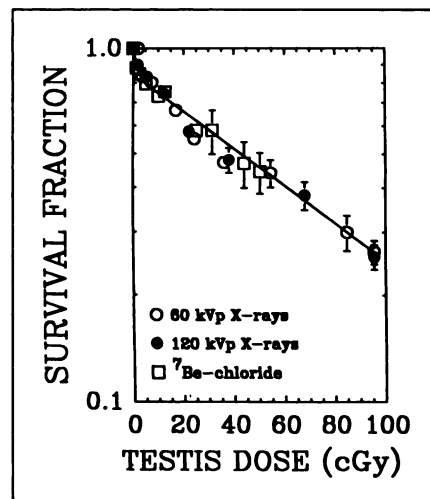


FIGURE 2. Dependence of spermhead survival on the testicular absorbed dose delivered by photons. The survival following selective acute irradiation of the testis with external 60 kVp (\circ) and 120 kVp x-rays (\bullet) (7) are shown. Similarly, the survival following intratesticular injection of the pure gamma emitter $^7\text{Be-chloride}$ (\square) is presented. Error bars are representative standard deviations.

not shown). Figure 2 shows the spermhead survival as a function of the testicular absorbed dose from acute external x-ray irradiation and from chronic internal gamma irradiation with $^7\text{Be-chloride}$. Similarly, Figure 3 shows the spermhead survival on the 29th day postinjection as a function of the testicular dose for ^{123}IMP , ^{125}IdC , ^{131}IdU and $\text{H}^{131}\text{IPDM}$. The survival data were least squares fitted to a two-component exponential expression

$$S = (1 - a) e^{-D/D_1} + a e^{-D/D_2}, \quad \text{Eq. 2}$$

where S is the survival fraction, D is the absorbed dose in cGy and D_1 and D_2 are the slopes of the two components.

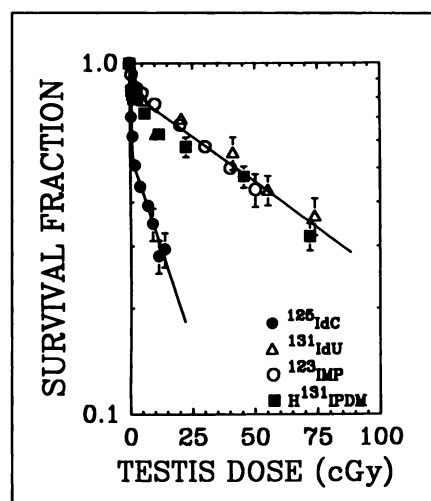


FIGURE 3. Spermhead survival as a function of absorbed dose to the testis from intratesticularly injected radiochemicals. ^{123}IMP (\circ), ^{125}IdC (\bullet), ^{131}IdU (Δ) and $\text{H}^{131}\text{IPDM}$ (\blacksquare). Representative standard deviations are shown.

TABLE 2
Parameters for Least Squares Fit of Spermhead
Survival Data

Radiochemical	a	D ₁ (cGy)	D ₂ (cGy)
¹³¹ IIdU	0.80 ± 0.035	0.73 ± 0.66	97 ± 14
H ¹³¹ IPDM	0.78 ± 0.022	0.67 ± 0.26	82 ± 7.8
¹²⁵ IIdC	0.55 ± 0.023	0.56 ± 0.073	19 ± 2.1
¹²³ IMP	0.88 ± 0.010	0.68 ± 0.22	71 ± 2.7
⁷ Be-chloride	0.88 ± 0.037	0.70 ± 1.1	76 ± 11

The parameters a, D₁ and D₂ are given in Table 2 for the various radiopharmaceuticals. The two-component nature of the survival curves, also observed by other authors (24–26), is a characteristic of this model, and it is most likely due to the differential radiosensitivities of the spermatogonial cells (24,27). The absorbed doses required to achieve 37% survival (D₃₇) are given in Table 3 along with the RBE value of each radiochemical compared to both acute external 60 or 120 kVp x-rays and chronic internal ⁷Be gamma rays. It should be noted that with the exception of ¹²³IMP, there were no chemotoxic effects observed with the unlabeled compounds in the amounts used in these studies. The chemical IMP was slightly chemotoxic, causing an 8% reduction in the spermhead count when the highest concentration was injected. Corrections to the dose response curve were made accordingly.

Subcellular Distribution of the Radionuclides

These results are summarized in Table 3. In agreement with our earlier results for H¹²⁵IPDM (8), our subcellular distribution studies for H¹³¹IPDM indicate that virtually all of the radionuclide is localized in the cytoplasm. The same distribution was found for ¹²³IMP. In contrast, as in the case of ¹²⁵IIdU (11), both ¹²⁵IIdC and ¹³¹IIdU were entirely localized in the nucleus and bound to DNA.

DISCUSSION

The mouse testis model employed in this work entails intratesticular injection of small amounts of radioactivity

(a few microcuries) and is a highly suitable in vivo model to ascertain the biological effects of radionuclides that emit particulate radiation. The reasons for this are twofold. First, there is no testicular irradiation by low-LET photons emanating from the whole body. Both intraperitoneal and intravenous modes of administration, which involve administration of large amounts of activity, result in a significant nontarget (whole body) to target (testis) dose from penetrating radiation. Second, most of the absorbed dose delivered to the testis from intratesticularly injected activity is from the particulate radiation. Due to their small absorbed fractions, photons contribute only minimally to the total absorbed dose. For example, for ¹²⁵I, our absorbed dose calculations indicate that photons deposit only 10.5% of the total testicular dose. Even smaller contributions were found for ¹²³I, ¹²⁴I and ¹³¹I where the photon component was only about 7%, 7.2% and 1.4%, respectively. These small fractions indicate that the survival curves largely reflect the radiotoxicity of the electrons emitted by the radioiodines and support the notion (7,11,14,15) that this model is well suited to studying the dependence of the lethal effects of Auger electron emitters on the subcellular distribution of the radiochemicals.

The possibility exists that the intratesticular line injection may lead to a highly nonuniform activity distribution and a correspondingly nonuniform energy deposition, thereby causing distortions in the survival curves. Our macroscopic distribution data (7,8,14,15) show that there is a reasonably uniform distribution of activity in the testis (within 10%–15%). The present data for ⁷Be-chloride, ¹²³IMP, ¹³¹IIdU, and H¹³¹IPDM, in conjunction with our earlier data for H¹²⁵IPDM (8), support the presence of uniform distribution for the following reasons:

1. Uniform irradiation of the testis with acute external x-rays is as effective as chronic irradiation of the testis with gamma rays from intratesticularly injected ⁷Be.
2. All low-LET type electron emitting radiochemicals (e.g., β[−] emitters and cytoplasmically localized Auger emitters) including ¹²³IMP, ¹³¹IIdU, H¹³¹IPDM, and H¹²⁵IPDM (8) produce survival curves equivalent to

TABLE 3
D₃₇ Values and Subcellular Distribution for Iodinated Radiochemicals

Radiochemical	Subcellular distribution	D ₃₇ (cGy)	RBE compared to acute x-rays*	RBE compared to chronic ⁷ Be gamma rays	Reference
¹³¹ IIdU	100% N, 100% D	75 ± 12	0.89 ± 0.15	0.87 ± 0.19	this work
H ¹³¹ IPDM	100% Cy	61 ± 6.3	1.1 ± 0.12	1.1 ± 0.20	this work
¹²⁵ IIdU	100% N, 100% D	8.5 ± 2.1	7.9 ± 2.0	7.6 ± 2.2	11
¹²⁵ IIdC	100% N, 100% D	7.7 ± 1.2	8.7 ± 1.4	8.4 ± 1.8	this work
H ¹²⁵ IPDM	100% Cy	68 ± 6	1.0 ± 0.10	0.96 ± 0.17	8
¹²³ IMP	100% Cy	62 ± 3	1.1 ± 0.07	1.0 ± 0.16	this work
⁷ Be-chloride	54% N, 46% Cy	65 ± 10	1.0 ± 0.16	—	7 and this work

* External 60 kVp or 120 kVp x-rays where D₃₇ is 67 ± 3 cGy (7). N = nucleus, Cy = cytoplasm and D = DNA.

those obtained by uniformly irradiating the testis with external x-rays. These consistent results would not be observed if significant inhomogeneities were present.

The primary aim of this work is to examine the dependence of the toxicity of radioiodinated pharmaceuticals on their subcellular distribution in an in vivo experimental model. The survival curves in Figure 3, along with other data in the literature (6–8,10,12), point to the strong dependence of the radiotoxicity of Auger emitters on this key parameter. In this work, ^{125}IdC , which covalently binds to the DNA in the cell nucleus, produces damage akin to high-LET alpha particles (9,11) with an RBE value of 8.7 ± 1.4 compared to x-rays. This is in reasonable agreement with our value of 7.9 ± 2.0 for ^{125}IdU (11), and it compares favorably with our in vitro data (9). In contrast, the radioiodinated compounds that emit Auger electrons and localize in the cytoplasm, including ^{123}IMP , $\text{H}^{123}\text{IPDM}$ (unpublished data) and $\text{H}^{125}\text{IPDM}$ (8), are much less lethal with RBE values of about 1. Finally, the RBE values for the ^{131}I compounds are essentially equal to one, within experimental errors. This is in keeping with earlier reports (10,28–30) that the subcellular distribution of ^{131}I plays no role in determining its lethality. It should be further noted that the above conclusions which are based on results from the mouse testes model, seem to be independent of the nature of the irradiation (i.e., chronic internal versus acute external) as evidenced by the ^7Be -chloride and x-ray data shown in Figure 2.

It has been a common practice to base the risk associated with diagnostic nuclear medicine procedures on the average absorbed dose to the organ. Macroscopic nonuniformities in organ activity distribution may result in significantly different local absorbed doses (23,31). Similarly, when specific cells within an organ selectively accumulate the radiochemical, the absorbed dose to these cells may be higher than the average organ dose (32–34). Accordingly, the risk may be higher than expected (35). Further complicating the issue of risk assessment is the dependence of the biological effects of incorporated radionuclides on subcellular distribution (6–10). This is particularly important for Auger electron emitters (e.g., ^{123}I , ^{201}Tl). While it is increasingly being recognized, this aspect is not yet folded into the design of diagnostic radiopharmaceuticals. Our data for a variety of radioiodinated compounds (Table 3) suggest that those compounds intended for diagnosis should be directed to the cytoplasm of cells in order to minimize the risk. In this context, our recent discussion on the dose equivalent for ^{125}I , which incorporates subcellular distribution (9,27), may be of some value. For therapeutic uses, however, the Auger emitter must be directed to the tumor cell nucleus (preferably DNA) in order to achieve maximal therapeutic efficacy (36). Since most nuclear medicine radionuclides are copious emitters of Auger electrons (1,37) [e.g., $^{99\text{m}}\text{Tc}$ (4 Auger electrons), ^{111}In (8 Auger electrons), ^{123}I (11 Auger electrons), ^{201}Tl

(20 Auger electrons)], the findings reported here may be of value for future radiopharmaceutical development.

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