Uptake, Localization, and Dosimetry of ^{111}In and ^{201}Tl in Human Testes

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This study concerns the testicular uptake and dosimetry of Auger electron-emitting radionuclides that are used during routine diagnostic nuclear medicine procedures. To consider the possible effects of these radionuclides on spermatogenic cells, a study has been undertaken to obtain in vivo data for quantification of ^{111}In chloride and ^{201}Tl chloride uptake into the human testis after intravenous administration. Values have been determined for uptake into the testis as a whole and to the seminiferous tubules where the germ cells are located. **Methods:** Data were obtained from patients with prostate cancer who opted for orchidectomy to effect hormone suppression. Patients were administered intravenously 1.5 MBq of either ^{111}In chloride or ^{201}Tl chloride at 24 or 48 h before orchidectomy. Upon removal, the testes were analyzed to assess uptake of radionuclide. Conventional dosimetry has been used to estimate testicular radiation doses using our values of percentage uptake. **Results:** Uptake of both ^{111}In chloride and ^{201}Tl chloride into the testes was seen at a level above that explained by simple homogeneous distribution of the radionuclide throughout the body; the testes as a whole demonstrated increased uptake by factors of 3.56 and 4.01 compared with nonspecific uptake for ^{111}In and ^{201}Tl, respectively, at 24 h after administration. Both radionuclides gained access to the seminiferous tubules. **Conclusion:** The results obtained indicate that the values of testicular radiation doses quoted by the International Commission on Radiological Protection for ^{111}In might be too low by a factor of 4, whereas those for ^{201}Tl might be too high by a factor of 4. No data were obtained for uptake by individual germ cells within the testis and, therefore, no consideration of dosimetry at the cellular level was possible. However, it has been demonstrated that uptake of diagnostic Auger electron-emitting radionuclides by male germ cells within the testis is possible after intravenous administration.

Key Words: radiation dosimetry; nuclear medicine; testes

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Both ^{111}In chloride and ^{201}Tl chloride are used in diagnostic nuclear medicine for imaging a range of diseases and medical conditions. Nuclear medicine scans have demonstrated localization of ^{111}In and ^{201}Tl in the genitalia, and possibly testes, of male patients after intravenous administration for diagnostic purposes (*1–5*). However, the resolution of γ-camera images is inadequate to determine the exact location of the radionuclides within this area, whether it is associated with germ cells within the testes or reproductive tract, or within the blood in local vessels. In addition, ^{111}In-labeled leukocytes have been used to image the epididymis (*6*) and localization in the epididymal region has been reported after intravenous administration of labeled cells, although once again imaging techniques cannot determine whether the ^{111}In is actually localized within the epididymis.

Animal studies have demonstrated uptake of ^{111}In (*7–10*), ^{114m}In (*11–13*), and ^{201}Tl (*14–16*) into the testes and onto developing germ cells in rodents. It is therefore possible that there is similar localization onto germ cells within the human testis. Currently, very little in vivo human data are available to accurately determine localization and quantity of ^{111}In and ^{201}Tl within the testes. The information used by the International Commission on Radiological Protection (ICRP) (*17*) to calculate dose equivalents assumes no selective testicular uptake of ^{111}In chloride and 0.8% of injected activity (%IA) uptake into the testis for ^{201}Tl chloride, after intravenous administration. The value of 0.8 %IA for ^{201}Tl is based on nuclear medicine images of the testicular or scrotal region (*15,18*). However, data from postmortems on 2 patients who died soon after intravenous administration of ^{201}Tl chloride (*19*) indicated uptake of around 0.11 %IA.

Within the testis, stem cells (type A spermatogonia) and developing germ cells (intermediate and type B spermatogonia, spermatocytes, and spermatids), as well as spermatozoa, are located within the seminiferous tubules. Access of blood-borne radionuclides to these cells is restricted by the so-called blood–testis barrier made up by the tight junctions between the Sertoli's cells within which the germ cells are embedded during development. Only the spermatogonia that are located close to the basal membrane of the seminiferous tubules are not excluded from contact with the extracellular environment. Any uptake of either ^{111}In or ^{201}Tl by germ cells within the testis (with the exception of spermatogonia) must therefore be via the Sertoli's cells. Ionic indium acts as an iron analog and several studies have demonstrated that uptake of ^{114m}In into rat testes is via

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transferrin-mediated endocytosis (*13,20*). In contrast, thallium acts as a potassium analog, using the Na^+/K^+ pump to gain access to the seminiferous tubules (*14,21,22*). Hoyes et al. (*20*) demonstrated passage of ^{137}Cs, another potassium analog that utilizes the same uptake mechanism, across the Sertoli's cell junction. Similar behavior of ^{201}Tl is likely and uptake of this radionuclide into the testis is possible.

The most radiosensitive cells in the seminiferous tubules are the type B and intermediate spermatogonia with a median lethal dose (LD_{50}) of the order of 0.2 Gy (in the mouse) (*23*). Stem cell spermatogonia show that the dose required to reduce survival to 37% is 0.97 Gy (in humans) (*24*). Spermatocytes are less radiosensitive (LD_{50} between 1.99 Gy and 8.1 Gy in the mouse), and further studies in mice have determined that spermatids and spermatozoa are less radiosensitive still and genetic damage is only shown after fertilization (*23*). Hoyes (*13*) has demonstrated mutagenic damage in the offspring of rats after paternal exposure to systemic ^{114m}In chloride, providing evidence for passage of indium through the blood–testis barrier. In addition, studies have shown damage to germ cells in animals after injection of both indium and thallium radionuclides directly into the testis (*25–27*).

A study has been undertaken to quantify the in vivo uptake of ^{111}In and ^{201}Tl into adult human testes after intravenous administration of radionuclide as the chloride. Values of uptake per gram of tissue have been determined as a percentage of the injected radionuclide for both gross testicular tissue as well as for the seminiferous tubules alone. The information obtained will enable more accurate calculation of absorbed dose to the testes using the MIRD system of dosimetry. In addition, the data will provide a first step to identifying cellular uptake of these Auger electron-emitting radionuclides by developing germ cells within the human testis, which would have significant implications for the form of dosimetry model required.

MATERIALS AND METHODS

Design of Experiment

An experiment was designed in which radionuclide, either ^{111}In or ^{201}Tl, was administered to patients who were to undergo orchidectomy (subcapsular or total) as a means of hormone suppression for the treatment of prostate cancer. The radionuclide was administered intravenously at either 24 or 48 h before the operation. Upon removal, the testes were used to assess the uptake and localization of radionuclide within testicular tissue as a whole and within the seminiferous tubules. In addition, a 2 mL blood sample was taken from the patient at the time of the operation to compare the amount of radionuclide in the blood with that in the testes.

The radioactivity administered to each patient was approximately 1.5 MBq (the value being based on the sensitivity of the radiation detection instrument and the requirement to be able to detect uptake into the testis down to the level that is considered nonspecific—that is, based on even distribution of radionuclide throughout total body weight (*28*)).

Twelve volunteers were recruited into the study, 6 being administered with each radionuclide. All were male patients with prostate cancer who had elected to undergo orchidectomy to achieve suppression of testicular hormones. None of the patients had undergone chemical hormone suppression treatment before recruitment. All volunteers were >64 y old and considered able to give informed consent. Patients who were unwilling or unable to give informed consent or were confused as to the nature of the study (or orchidectomy procedure) were excluded from the study. All information obtained from the study is reported in a strictly anonymous form.

The radionuclide (^{111}In or ^{201}Tl) was administered via intravenous injection.

Measurement of Testicular Uptake

Radiopharmaceuticals were obtained from Nycomed Amersham at typical specific radioactivities (Amersham Nuclear Medicine radiopharmaceutical catalog: Nycomed Amersham), approximately 1,850 MBq/mg for both ^{111}In and ^{201}Tl. Both ^{111}In and ^{201}Tl were injected as chloride.

The radioactivities of the administered radionuclide doses (and standards) were determined using an ionization chamber (CRC 15R; Capintec) dose calibrator that is calibrated annually against a traceable national standard.

Two syringes of radionuclide (both containing either ^{111}In chloride or ^{201}Tl chloride) were prepared for each volunteer. The radionuclide in 1 syringe was used to make a standard solution in 1 L of water containing enough stable metal (indium or thallium) to ensure that the ratio of stable to radioactive atoms was of the order of at least 10^6:1. This was to prevent any adhesion of the radioactive element to the container walls, which would produce inaccuracy when aliquots of the standard were assayed. Four 1 mL aliquots were placed into counting tubes and these were sealed as standards.

The second syringe contained the radionuclide to be administered to the volunteer by intravenous injection. A small amount (approximately 1 mL) of blood was drawn into the syringe immediately before injection and mixed with the radionuclide. The blood plus radionuclide was then injected back into the patient. The mixing of blood with the radionuclide is significant in the case of ^{111}In chloride as it allows labeling of serum transferrin before reinjection. The syringe was flushed several times with blood. The injection time and date were noted. The radioactivity remaining in the syringe was remeasured and, thus, the injected activity was calculated.

At the time of surgery, a blood sample was taken into a heparinized tube and, after removal, the testes were placed on ice until processed. The testes were weighed and if the operation was not a subcapsular orchidectomy, the capsule and epididymis were dissected free before weighing. Three 1 g samples were taken from each testis or paired epididymides (if available) and were minced and weighed into tubes for the determination of radioactivity.

A section of tissue (up to 5 g) was then taken from each testis for isolation of the seminiferous tubules. Eagle's Minimum Essential Medium (MEM) was used as the basis of a testis dispersion fluid (which removed the interstitial tissue from a sample, leaving only the seminiferous tubules intact). Bovine serum albumin was added to the MEM at 0.1%. Immediately before use, collagenase dispase (0.3 mg/mL) and deoxyribonuclease (20 μg/mL) were also added to the medium. The tissue was incubated at 34°C for 20 min with continuous agitation in dispersion fluid. The seminiferous tubules remained intact at the end of incubation and were washed twice in MEM. From this, three 1 g samples were taken for each

testis and processed for radioactivity determination as described above. Tissue samples processed for histology were preserved in Bouin's fluid. All of the above chemicals were obtained from Sigma Chemical Co.

The radioactive content of the tissue samples, blood (1 mL), and standards, as well as a set of 4 tissue blanks (tubes containing 1 mL of unlabeled testicular tissue preserved in Bouin's fluid from a previous donor) were assayed using a Minaxi γ-Counter (5500 series Autogamma; Packard Instruments). Energy windows of 210–270 keV and 60–80 keV were set for ^{111}In and ^{201}Tl, respectively. A 2 min counting period was used and resulted in Poisson counting errors of <5% per sample tube. All values of counts per minute (cpm) were background corrected and decay corrected to the same time. Values of cpm were corrected to cpm/g or cpm/mL and the mean ± SE for each tissue type was found (gross testicular tissue, seminiferous tubules, epididymides, blood, and standards).

The percentage of injected radioactivity present per gram of tissue sample (or per mL blood) A_s was calculated using Equation 1:

$$A_s = \frac{I_{std}}{I_{inj}} \times \frac{C_s}{C_{std}D} \times 100, \qquad \text{Eq. 1}$$

where I_{std} is the radioactivity of the 1 L radionuclide standard (MBq), I_{inj} is the radioactivity of the injected radionuclide (MBq), C_s is the cpm/g (or per mL) recorded for the sample tissue, C_{std} is the cpm recorded for the 1 mL of standard, and D is the standard dilution factor (1,000).

Four volunteers were administered ^{111}In and 4 were administered ^{201}Tl at 24 h before orchidectomy (8 samples in total). A further 2 in each group were given the radionuclide at 48 h before surgery (4 in total). Mean values (±SEs when the number of samples ≥3) of percentage uptake per gram of tissue (gross testicular tissue, seminiferous tubules, epididymis) or per milliliter of blood were determined for all volunteers at each administration time and radionuclide. Where only 1 sample of a tissue or blood was obtained from a subject, a single result was recorded.

Mean values of nonspecific uptake per gram of tissue were calculated based on the weight of the volunteer, by considering homogeneous distribution of radionuclide throughout the body with no specific uptake mechanisms resulting in concentration within any organ or system. A factor for the amount of uptake above the nonspecific value was thus determined for the gross testicular tissue as uptake per gram of testicular tissue divided by uptake per gram throughout the body.

Dose Calculation

The MIRD system of organ dosimetry (*29*) was used to calculate the absorbed dose to the testes per MBq injected, using 3 different models for residence time in the testes as described:

I. We used the mean measured testicular uptake per gram in our 4 subjects at 24 h after injection, multiplied by a standard mass for 2 normal testes of 35 g (*28*), to obtain our own estimate of normal testicular uptake. This approach was used to minimize the effect of low testicular weight in some of our subjects. This uptake figure was then combined with the standard clearance times used by the ICRP (*17*) to give the testicular residence time. The SD of the uptake measurements was used as an estimate of the uncertainty on the residence time.

II. This model used the same testicular uptake as model I, but the pessimistic assumption of no biologic clearance from the testes was used instead of the ICRP clearance.

III. The 6 measured values of percentage uptake per gram at both 24 and 48 h were fitted to a falling exponential, taking into account the errors of each individual measurement. The area under the fitted exponential, combined with a standard testicular mass of 35 g, gave the estimate of testicular residence time. The uncertainty in the fit was used to estimate the uncertainty in the residence time.

For all 3 models, S factors for the testes (MIRDOSE3.1, Radiation Internal Dose Information Center, Oak Ridge Institute for Science and Education, Oak Ridge, TN, 1995) were used to calculate the self-absorbed dose to the testes from activity within the testes. We assumed that the dose to testes from other nearby organs would be the same as that calculated by the ICRP. The total testicular dose calculated by the ICRP for ^{111}In (*17*) and for ^{201}Tl (*30*) was used, from which the testicular self-dose calculated using the ICRP uptake figures (*17*) was subtracted and our own calculated values of testicular self-dose were added. We then used the modified values of testicular dose, together with (unchanged) ICRP data on doses to other organs for ^{111}In (*17,31*) and for ^{201}Tl (*30*; David Taylor, Secretary of ICRP Committee 2, written communication, 2001), multiplied by relevant tissue weighting factors, to calculate effective doses. No attempt was made to account for Auger electron emissions not included in S factors in MIRDOSE3.1.

RESULTS

The mean age and weight of volunteers were 70.5 y and 78 kg for ^{111}In and 77.8 y and 70.8 kg for ^{201}Tl. None of the volunteers was significantly anemic. Figures 1 and 2 are typical histology sections for the volunteers (Figs. 1A and 1B represent subjects In2 and In4, respectively, and Figs. 2A and 2B represent subjects Tl1 and Tl2, respectively). It can be seen that the testes from subject Tl2, in particular, contains few germ cells within the testes. This might have been expected from the low testicular weight (total for both testes, 15.0 g). The sections from subjects In2 and Tl1 indicate higher numbers of germ cells present (total testicular weights, 39.0 and 41.0 g, respectively). In general, all testes demonstrated spermatogenesis, although the level appeared to be associated with testis weight. As the individuals recruited into the study were all >64 y old and most were >70 y old, this was expected.

Tables 1 and 2 show individual results for ^{111}In and ^{201}Tl administered 24 and 48 h before orchidectomy. Results are shown as the percentage of injected radionuclide activity per gram of tissue (%IA/g) for gross testicular tissue, seminiferous tubules, and epididymis and per milliliter (%IA/mL) for blood. Percentage uptake representing nonspecific uptake (based simply on the weight of the individual) is also shown. Tables 3 and 4 are a summary of these results for all individuals undergoing the same administration protocol (for ^{111}In and ^{201}Tl, respectively). The mean percentage activity in the testes is also shown (based on a standard mass of 35 g (*28*) and our values of uptake per gram of gross testicular tissue).

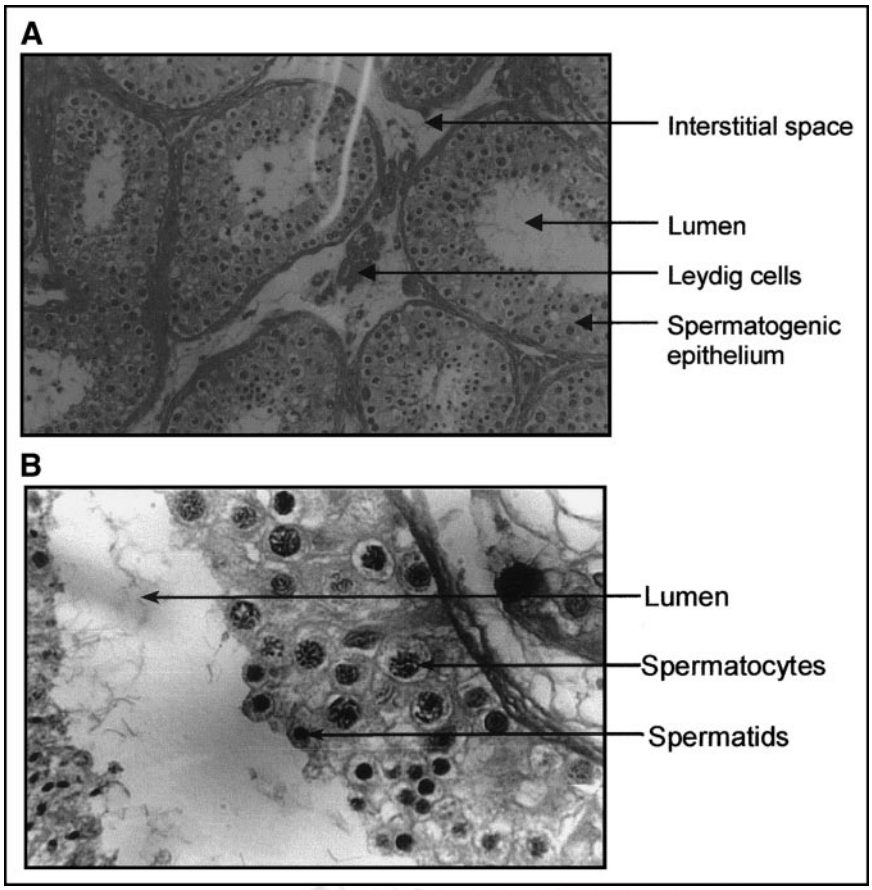

FIGURE 1. Typical testicular sections from subject In2 (A) and subject In4 (B), administered intravenously with ^{111}In chloride.

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The values of absorbed dose to the testes per MBq injected for each of the different models of clearance used and the resulting values of effective dose are given in Tables 5 and 6 for ^{111}In chloride and ^{201}Tl chloride, respectively. The quoted errors only take account of the uncertainty in our measurements of testicular uptake. There are many other sources of error in biologic data and S factors, but these are common to our results and those quoted by the ICRP.

DISCUSSION

As shown by Tables 1–4, uptake of both ^{111}In and ^{201}Tl into the testes was greater than that accounted for by simple homogeneous distribution of the intravenously injected radionuclide throughout the body according to organ weight (nonspecific uptake). The errors associated with the measurements are relatively large due to the limited number of subjects. This is especially significant for the 48-h measurements when only 2 subjects participated for each radionuclide and the data must be considered as preliminary.

Percentage uptake per gram into gross testicular tissue is $3.56 \pm 0.55 \times$ nonspecific uptake for ^{111}In at 24 h and 3.64 (4.40, 2.88) $\times$ at 48 h (where the values in parentheses [or brackets] are the individual results when only 2 samples were obtained). Though this is of a similar magnitude to the amount of ^{111}In in the blood at the same times ($3.49 \pm 0.85 \times$ and 3.41 [4.20, 2.62] $\times$ at 24 and 48 h, respectively), it is unlikely that the radioactivity associated with the testes is simply due to the blood within the tissue, because the content of blood in the testis is relatively small. The ICRP (*28*) reports the total blood content of both testes (combined total weight, 35 g) as being 5.8 g. Uptake of ^{201}Tl into gross testicular tissue is of a similar order ($4.01 \pm 0.09 \times$ and 3.32 [3.70, 2.94] $\times$ nonspecific uptake at 24 and 48 h, respectively). However, the amount of ^{201}Tl localized in the blood is very much smaller than for ^{111}In ($0.11 \pm 0.02 \times$ and 0.09 [0.07, 0.11] $\times$ nonspecific uptake values at 24 and 48 h, respectively). This result would be expected because ^{201}Tl is a potassium analog and would be expected to be removed from the blood into the urine, as well as being taken up by tissues such as muscle (*22*,*32*), whereas ^{111}In will be present in blood bound to serum transferrin and will have a much longer clearance time from the blood as it is taken up and retained by cells with a large iron requirement (*33*–*35*).

Both ^{111}In and ^{201}Tl gained access to the seminiferous tubules (uptake of both radionuclides being approximately twice that due to homogeneous distribution according to weight). This indicates that both radionuclides can pass across the blood–testis barrier formed by the Sertoli's cells and thus might be available for uptake by developing germ cells within the seminiferous epithelium. The result for ^{111}In is consistent with the work by other authors (*11*,*12*,*20*), who

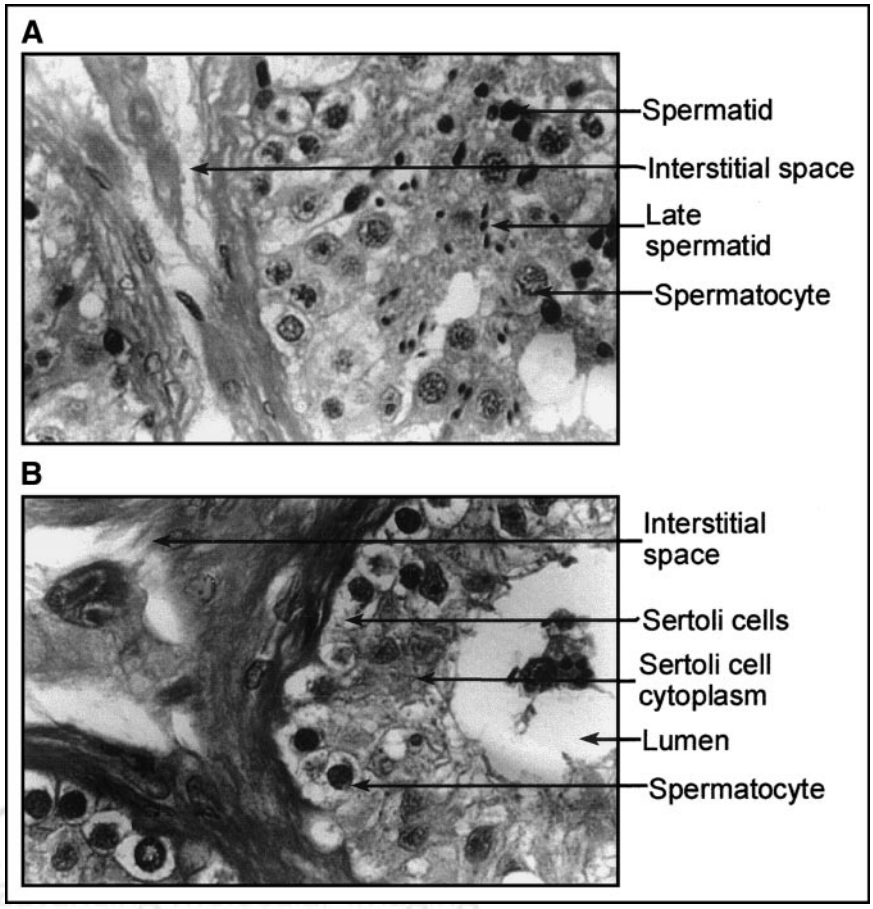

FIGURE 2. Typical testicular sections from subject Tl1 (A) and subject Tl2 (B), administered intravenously with ^{201}Tl chloride.

have demonstrated transferrin-mediated passage of the radionuclide (or ^{114m}In) through the Sertoli's cell layer in animals. Thallium is thought to use the Na^+/K^+ pump to gain access to the seminiferous tubules (*21*,*22*), and the possibility of leaching out of tissue samples during the washing process means that these results for ^{201}Tl must be viewed as a lower level of uptake only. Uptake of Auger electron-emitting radionuclides by developing germ cells

TABLE 1
Uptake of ^{111}In Chloride: Results for Individual Subjects

Subject	Time of administration before orchidectomy (h)	Total subcapsular testis weight (g) (both testes)	Subject weight (kg)	%IA/g (nonspecific)	%IA/g (mean ± SE) gross testis	%IA/g (mean ± SE) seminiferous tubules	%IA/g (mean (1, 2))* epididymis	%IA/mL (mean (1, 2))* blood
In1	24.5	17.8	55	0.0018	0.0070 ± 0.0007	0.0050 ± 0.0005	0.0025 (1 sample)	0.0080 (0.0078, 0.0082)
In2	25.0	39	73	0.0014	0.0069 ± 0.0001	0.0036 ± 0.0002	0.0032 (1 sample)	0.0074 (0.0072, 0.0076)
In3	24.0	27.6	46	0.0022	0.0052 ± 0.0002	0.0022 ± 0.0004	0.0039 (0.0036, 0.0042)	0.006 (0.0059, 0.0061)
In4	25.0	28.2	71	0.0014	0.0043 ± 0.0013	0.0031 ± 0.0003	0.0018 (0.0017, 0.0019)	0.0021 (0.0019, 0.0023)
In5	46.5	20.6	103	0.0010	0.0044 ± 0.0022	0.0022 ± 0.0001	0.0031 (0.0027, 0.0035)	0.0042 (0.0040, 0.0044)
In6	47.0	42.0	120	0.0008	0.0023 ± 0.0001	0.0010 ± 0.0001	0.0017 (1 sample)	0.0021 (0.0021, 0.0021)

*(1, 2) are individual of 2 samples for each subject when only 2 samples were obtained.

TABLE 2
Uptake of ^{201}Tl Chloride: Results for Individual Subjects

Subject	Time of administration before orchidectomy (h)	Total subcapsular testis weight (g) (both testes)	Subject weight (kg)	%IA/g (nonspecific)	%IA/g (mean ± SE) gross testis	%IA/g (mean ± SE) seminiferous tubules	%IA/mL (mean (1, 2))* blood
Tl1	25.0	41.0	72	0.0014	0.0060 ± 0.0002	0.0050 ± 0.0002	0.00010 (0.0001, 0.0001)
Tl2	24.5	15.0	69	0.0015	0.0060 ± 0.0010	0.0020 ± 0.0001	0.00020 (0.0002, 0.0002)
Tl3	22.3	23.8	78	0.0013	0.0050 ± 0.0006	0.0040 ± 0.0001	0.00010 (0.00009, 0.00011)
Tl4	25.7	29.2	76	0.0013	0.0051 ± 0.0001	0.0030 ± 0.0002	0.00020 (0.00017, 0.00023)
Tl5	45.0	21.4	70	0.0014	0.0052 ± 0.0002	0.0032 ± 0.0001	0.00010 (1 sample)
Tl6	47.0	12.4	60	0.0017	0.0050 ± 0.0009	0.0026 ± 0.0007	0.00020 (1 sample)

*(1, 2) are individual of 2 samples for each subject when only 2 samples were obtained. No results for epididymis.

(and stem cells) might have biologic consequences necessitating dosimetric reevaluation (*9*,*10*,*26*,*27*,*36*–*38*).

Values for uptake into the epididymis are only available for ^{111}In, because all orchidectomies performed after administration of ^{201}Tl were subcapsular. There appears to be uptake into the epididymis, being of the order of twice the value obtained for nonspecific uptake only. The age of the patients and their medical condition mean that the number of sperm within the epididymi were likely to be lower than for a healthy young male. It is not known to what extent the number of spermatozoa present in the lumen affects the amount of radionuclide within.

The small number of samples for the 48-h measurement ($n = 2$) prevents any statistical analysis of these results. However, the SEs in Tables 1 and 2 give an indication of measurement error. The biologic variation between patients would be expected to be of the same order as for the 24-h data and, thus, associated errors would be estimated to be of a similar magnitude. Based on 48-h concentration factors, it does not appear that there has been significant clearance of either radionuclide from the testis between the 2 time points. This may indicate that an equilibrium has been reached by 24 h after administration and that both radionuclides are retained by the testes. The uncertainties in clearance rates have been addressed by using 3 alternative models to calculate absorbed and effective doses, as described in the Dose Calculation section and shown in Tables 5 and 6. Values of concentration factor for seminiferous tubules also appear to demonstrate retention of both radionuclides (2.14 ± 0.40 and 2.57 ± 0.49 at 24 h and 1.73 [2.21, 1.26] and 1.9 [2.28, 1.52] at 48 h for ^{111}In and ^{201}Tl, respectively), although once again small sample sizes prevent statistical analysis.

It is worth noting that the value for nonspecific uptake into the testis does not take into account the fact that the radionuclide is likely to be excluded from regions containing little fluid, such as cortical bone. This consideration can be included by assuming nonspecific distribution to be through the compartment of the body that consists of water. Of total body weight, 60% is considered to be water, whereas, in the testis alone, the value is 81% (*28*). Thus, the

TABLE 3
Summary Results for ^{111}In Chloride: Concentration Above Levels Expected for Nonspecific Uptake as Proportion of Body Mass

Mean injection time before surgery (h)	%IA/g of gross testicular tissue (mean ± SE)	%IA into testes* (mean ± SE)	Multiple of nonspecific %IA/g of tissue (mean ± SE or (1, 2)†)			
			Gross testicular tissue	Seminiferous tubules	Epididymis	Blood
24.6	0.0058 ± 0.0007	0.20 ± 0.02	3.56 ± 0.55	2.14 ± 0.40	1.68 ± 0.23	3.49 ± 0.85
46.8	0.0033 (0.0044, 0.0023)	0.12 (0.15, 0.08)	3.64 (4.40, 2.88)	1.73 (2.20, 1.26)	2.61 (3.10, 2.12)	3.41 (4.20, 2.62)

*In Tables 3 and 4, values of percentage uptake into testes as a whole are based upon mean values of uptake per gram of gross testicular tissue, combined with standard weight of 35 g.

†(1, 2) are individual of 2 samples for each subject when only 2 samples were obtained.

TABLE 4
Summary Results for ^{201}Tl Chloride: Concentration Above Levels Expected for Nonspecific Uptake as Proportion of Body Mass

Mean injection time before surgery (h)	%IA/g of gross testicular tissue (mean ± SE)	%IA into testes* (mean ± SE)	Multiple of nonspecific %IA/g of tissue (mean ± SE or (1, 2)†)		
			Gross testicular tissue	Seminiferous tubules	Blood
24.4	0.0055 ± 0.0003	0.19 ± 0.01	4.01 ± 0.09	2.57 ± 0.49	0.11 ± 0.02
46.0	0.0051	0.18	3.32	1.9	0.09
	(0.0052, 0.005)	(0.18, 0.17)	(3.70, 2.94)	(2.28, 1.52)	(0.07, 0.11)

*In Tables 3 and 4, values of percentage uptake into testes as a whole are based upon mean values of uptake per gram of gross testicular tissue, combined with standard testicular weight of 35 g.
†(1, 2) are individual of 2 samples for each subject when only 2 samples were obtained.

value of nonspecific uptake into the testis would be corrected by a factor of 0.81/0.6 (1.35), which is smaller than our measured concentrations factor for either ^{111}In or ^{201}Tl.

Hoyes et al. (*20*) reported a value of 0.2 %IA uptake into the testes of rats at 24 h after systemic administration of ^{114m}In. The typical body weight of the rats used by Hoyes et al. was 200 g, with a testicular weight of approximately 1.8 g (*12*). Localization as a proportion of body mass would result in 0.9 %IA uptake into the testes. Their result of 0.2 %IA therefore demonstrates uptake at values lower than nonspecific (concentration factor, 0.22). Our study has demonstrated a concentration factor of 3.56 for ^{111}In at 24 h (testicular uptake, 0.2 %IA), which is significantly larger than that of Hoyes et al. Studies have shown (*23,39*) that the human testis has an increased ratio of parenchymal tissue to spermatogonia compared with the rat testis and contains twice as many transferrin-synthesizing Sertoli's cells. Therefore, transferrin-mediated uptake of indium into the human testis might be expected to be relatively larger than that in the rat, as demonstrated by this study. Values of uptake observed by other researchers (as above) are shown in Table 7, alongside the results from our work.

The values of ^{201}Tl uptake determined here are significantly less than most of those previously determined using nuclear medicine images; values of 0.46 %IA, 0.15 %IA, 0.8 %IA, and 1.0 %IA total testicular uptake at 24 h have been reported by Rao et al. (*5*), Atkins et al. (*14*), Hosain and Hosain (*15*), and Gupta et al. (*18*), respectively (Table 7). As discussed earlier, the resolution of such images does not enable accurate location of the radionuclide within the scrotal sack. However, Atkins et al. (*14*) reported 0.7% uptake of injected radionuclide into the 33-g testis of a 12-kg dog at 24 h after administration. This relates to a concentration factor above nonspecific uptake (based on the above testis and body weights) of 2.55. Our value of the concentration factor for ^{201}Tl at 24 h after administration was 4.01 (testicular uptake of 0.19 %IA for both testes), which is a similar order of magnitude. In addition, the postmortem values of testicular uptake determined by Samson et al. (*19*) were around 0.1 %IA. It should be noted that ICRP Publication 53 (*17,30,31*; David Taylor, Secretary of ICRP Committee 2, written communication, 2001) uses a value of 0.8 %IA (0.4 %IA per testis) based on the nuclear medicine imaging work of Hosain and Hosain (*15*) as a worst-case value.

The weight of testes used in this study (12–42 g for both testes) was often lower than the average value for young healthy males (35 g total for both) (*28*), and it can be seen from Figures 1 and 2 that they contained fewer than the normal numbers of germ cells. This might be expected due to the age of the patients (all >64 y). In addition, the function of the Sertoli's cells in these individuals is likely to be lower than average due to age (*40*). Uptake into the testes is related to germ cell numbers and Sertoli's cell function (*12*). Testicular uptake for the subjects in the study is thus

TABLE 5
Values of Absorbed Dose to Testes and Effective Dose for ^{111}In Chloride Using Different Models of Biologic Clearance from Testis

Model	Testicular self-dose (mGy/MBq)	Total testicular absorbed dose (mGy/MBq)	Effective dose (mSv/MBq)
ICRP (*17,30,31*)	0.015	0.053	0.21
This work			
Model I	0.134 ± 0.013	0.172 ± 0.013	0.22 ± 0.001
Model II	0.168 ± 0.017	0.206 ± 0.017	0.22 ± 0.002
Model III	0.096 ± 0.014	0.135 ± 0.014	0.22 ± 0.001

TABLE 6
Values of Absorbed Dose to Testes and Effective Dose for ^{201}Tl Chloride Using Different Models of Biologic Clearance from Testis

Model	Testicular self-dose (mGy/MBq)	Total testicular absorbed dose (mGy/MBq)	Effective dose (mSv/MBq)
ICRP (*30,32*)	0.442	0.45	0.17
This work			
Model I	0.105 ± 0.006	0.113 ± 0.006	0.14 ± 0.001
Model II	0.136 ± 0.007	0.144 ± 0.007	0.14 ± 0.001
Model III	0.111 ± 0.016	0.118 ± 0.016	0.14 ± 0.002

TABLE 7
Comparison of Results for Uptake of ^{111}In and ^{201}Tl From Our Research with Those Reported in Other Studies

Reference	Radionuclide	Measurement time after administration (h)	Model	No. of subjects	%IA into testes
Hoyes et al. (*20*)	^{114m}In	24	Rat	6	0.2
This work	^{111}In	24	Human	4	0.20
This work	^{111}In	48	Human	2	0.12
Rao et al. (*5*)	^{201}Tl	24	Human (imaging)	4	0.46
Atkins et al. (*14*)	^{201}Tl	24	Human (imaging)	3	0.15
Hosain and Hosain (*15*)	^{201}Tl	24	Human (imaging)		0.8
Gupta et al. (*18*)	^{201}Tl	24	Human (imaging)		1.0
Samson et al. (*19*)	^{201}Tl	Unknown	Human (postmortem)	2	0.11
Atkins et al. (*14*)	^{201}Tl	24	Dog	1	0.7
This work	^{201}Tl	24	Human	4	0.19
This work	^{201}Tl	48	Human	2	0.18

likely to have been lower than average. Values of uptake obtained from this study should therefore be viewed as lower limits only. However, we have attempted to allow for this effect as much as possible by using uptake values corrected to standard 35-g testes.

Using the MIRD system of dosimetry, the absorbed dose to the testes has been estimated using the uptake values determined in this study and 3 alternative clearance models described earlier in this article: model I, ICRP clearance rates (*17*); model II, no biologic clearance; and model III, an exponential fit to our own measurements. Use of these different models allowed us to address the uncertainty associated with the results at 48 h. In the case of ^{111}In, testicular absorbed doses of 0.17 ± 0.013, 0.21 ± 0.017, and 0.14 ± 0.014 mGy/MBq were obtained for models I, II, and III, respectively (Table 5). These are all significantly higher than the ICRP value of 0.053 mGy/MBq (*17*,*30*,*31*), which assumed no specific testicular uptake. Our estimates of testicular absorbed dose for ^{201}Tl are 0.11 ± 0.006, 0.14 ± 0.007, and 0.12 ± 0.016 mGy/MBq for models I, II, and III, respectively (Table 6). These are all significantly lower than the ICRP value of 0.45 mGy/MBq (*30*), which assumed a value of 0.8 %IA testicular uptake (*17*).

It can be seen that our results show significant differences from the published data. The differences all arise from our figures for testicular uptake. The differences between our 3 clearance models are small when compared with the difference between our results and those quoted by the ICRP. Our estimates of the testicular dose from ^{111}In are a factor of between 2.6 and 4.0 larger than the ICRP values, and our estimates for ^{201}Tl are a factor of between 3.2 and 4.1 smaller than the ICRP values.

After intravenous administration of 80 MBq ^{111}In chloride for joint imaging (*41*) or 80 MBq ^{201}Tl chloride for myocardial studies (*14*), the calculated radiation dose to the testes, using the figures as determined in this work (from model III), would be 11 and 10 mGy, respectively. However, depending on the subcellular localization of both ^{111}In and ^{201}Tl, studies have demonstrated an increased radiobiologic effectiveness (RBE) of up to 4.2 for ^{111}In oxine (compared with x-rays) and 3.3 for ^{201}Tl chloride (compared with the β-analog ^{204}Tl) when injected into the testis of mice (*38*). Although the subcellular distribution of ^{111}In chloride will differ from that of ^{111}In oxine, the increased RBE for ^{201}Tl chloride would increase the equivalent dose to the testes to 32 mSv. These doses are considerably below the levels (at least 80 mGy, x-ray) that have been shown to produce measurable oligospermia (*20*); however, the possibility of genetic damage cannot be excluded (*27*,*42*).

The choice of clearance model has no effect on the value of effective dose (Tables 5 and 6). For ^{111}In, the effective dose calculated using any of our models is 0.22 mSv/MBq, which is similar to the ICRP value of 0.21 mSv/MBq (*30*). For ^{201}Tl, our calculated effective dose is 0.14 mSv/MBq, which represents a 36% decrease in the published ICRP value of 0.22 mSv/MBq (*30*). However, the ICRP has now recognized that the effective dose from ^{201}Tl published in ICRP Publication 80 (*30*) contained an error in transcription of the dose to the ovary. This has subsequently been corrected and the effective dose is now recalculated as 0.17 mSv/MBq (David Taylor, Secretary of ICRP Committee 2, written communication, 2001), although this corrected figure is still not widely known. Relative to this, our value of 0.14 mSv/MBq represents a decrease of 18%.

The number of samples (especially for the 48-h data) is rather limited. The reason for this was a change of preferred treatment protocol for prostate cancer within the department, which resulted in very few orchidectomies being performed. However, the study does provide a significant addition to the available data for in vivo testicular uptake of ^{111}In and ^{201}Tl, from the chloride form.

It should be noted that all data obtained in this study were from patients with prostate cancer who opted for orchidectomy to effect hormone suppression. None of the patients had previously undergone hormone treatment. The age of the patients (>64 y old) means that Sertoli's cell function is likely to have been lower than average and, thus, translation of the results obtained to the general male population should be viewed with caution. However, because in vivo data

could not be obtained from healthy young men, we believe that the results obtained provide a valuable extension to the data regarding uptake and localization of these commonly used diagnostic radiopharmaceuticals.

CONCLUSION

The results of this in vivo study indicate that there is uptake of both ^{111}In and ^{201}Tl into the human testis after systemic administration in the chloride form, though it is likely that the uptake mechanisms are different for the 2 radionuclides. Values of the percentage uptake into the testis as a whole are consistent with previous data obtained from animal studies, the uptake of ^{111}In being larger than that used by the ICRP in dose calculations and that of ^{201}Tl being smaller. In addition, both radionuclides appear to traverse the blood–testis barrier and, thus, can gain access to the developing germ cells within the seminiferous epithelium. Further work should be undertaken to localize the radionuclide within the seminiferous tubules and to quantify uptake onto the intratubular germ cells.

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