Acta Oncologica Vol. 35, No. 7, pp. 925–933, 1996

ON THE SAFETY OF 5-[^{125}I]IODO-2′-DEOXYURIDINE

Preclinical evaluation in swine

JANINA BARANOWSKA-KORTYLEWICZ, GLENN V. DALRYMPLE, KATHERINE A. HARRISON, KAREN P. HOLDEMAN, J. GRAHAM SHARP, SAMUEL M. COHEN, ROBERT P. LIEBERMAN, MARTIN H. SCHNEIDERMAN, SYDNEY R. CLAUSEN, DEBRA HOFFMAN, JING LAI, G. SUE SCHNEIDERMAN and LYNN HELSETH

To increase tumor incorporation and minimize hepatic degradation of radio-IUdR, compartmental administration routes are being considered as an alternative to intravenous (i.v.) injections. Although there are significant data on the biodistribution and some reports on radiotoxicity of i.v.-administered ^{125}IUdR, similar results for other routes of delivery are not available. We have undertaken a series of experiments intended to examine radiation effects of ^{125}IUdR after intravesical (3 swine; eight 3 mCi doses at 4-day intervals), intracarotid (3 swine; two 10 mCi doses at 2-week intervals), and intra-aortic (5 swine, single dose of 10 mCi) administration in a swine model. Liver, renal functions, and complete blood counts were monitored throughout the duration of the experiment. Pharmacokinetics, systemic distribution of radioactivity and metabolites were measured. The normal tissue ^{125}IUdR uptake and histology were determined after necropsy. No adverse systemic effects were identified. Clinical observations, laboratory data, and necropsy results were within normal range.

Various uncertainties associated with the clinical use of radiopharmaceuticals, i.e., biodistribution and a cellular deposition of radionuclides, pharmacokinetics, metabolic fate of the agent and radiation doses delivered to normal tissues, must be evaluated prior to any clinical trial. Having planned several clinical trials with 5-radioiodo-2′-deoxyuridine (radio-IUdR), we were faced with the question of potential radiotoxic effects of this agent labeled with iodine-125 (^{125}IUdR) in normal tissues at doses contemplated for cancer treatment. We are also considering local administration routes (intra-aortic (i.a.), intracarotid (i.c.) and intrabladder (i.b.)) as an alternative to intravenous injections with the aim to increase tumor incorporation and minimize hepatic degradation of IUdR. There are significant data on the biodistribution (1, 2) and a few reports on dosimetry and radiotoxicity of ^{125}IUdR in mice (1, 3, 4) after i.v. or intraperitoneal (i.p.) injections, but similar results for other routes of delivery are not available. Some data on intrahepatic administration of ^{123}IUdR is available from clinical trials (5) but for obvious reasons, it is limited and lacking any information on the radiation effects in normal tissues.

It has been suggested (6) that the mouse is not a good model on which to study radiation effects and to extrapolate results to a clinical situation. The use of swine as an animal model in evaluation of radiation-related injuries has manifold advantages (7–11). Swine have many physiological similarities to humans. Anatomical likeness be-

Received 11 October 1995.
Accepted 26 February 1996.
From the Departments of Radiology (Nuclear Medicine) and Radiation Oncology (J. Baranowska-Kortylewicz, G.V. Dalrymple, K.A. Harrison, K.P. Holdeman, R.P. Lieberman, M.H. Schneiderman, S.R. Clausen, D. Hoffman, J. Lai, G.S. Schneiderman, L. Helseth), Department of Cell Biology and Anatomy (J.G. Sharp) and Department of Pathology and Microbiology (S.M. Cohen), J. Bruce Henriksen Laboratories, Omaha, Nebraska, USA. Correspondence to: J. Baranowska-Kortylewicz, University of Nebraska Medical Center, Department of Radiology, J. Bruce Henriksen Laboratories, Omaha, Nebraska 68198-1045, USA. Telephone 402-559-8906; Fax 402-559-4675.
E-mail jbaranow@mail.unmc.edu.
Paper presented at the Third International Symposium on Biophysical Aspects of Auger Processes, August 24–25, 1995, Lund, Sweden.

 ISSN 0284-186X

tween swine and human lung makes it an ideal model to study the radiation-induced damage to the lung (6, 12). The swine is unique among laboratory animals in possessing a multipapillate, multipyramidal kidney similar to that of humans (13). There are many functional and biochemical similarities between kidneys of the two species (14). Swine skin is a well established animal model for assessment of radiation effects on the epidermis and dermal vascular and connective tissues (15). Further advantages to using a swine model come from its size. Tissue volumes of swine are comparable with those of humans facilitating the study of radiation effects in clinically relevant volumes and allowing more realistic estimates of radionuclide biodistribution and doses to normal organs (16). For these reasons, we have chosen to utilize the pig as an animal model for the pre-clinical evaluation of ^{125}IUdR. A thorough examination of renal and liver functions, complete blood counts, metabolites, pharmacokinetics, radioisotope deposition and histopathology studies were conducted to determine any adverse effects associated with administration of radio-IUdR.

Material and Methods

Synthesis of ^{125}IUdR. Sodium [^{125}I]iodide was purchased from either ICN or NEN. No-carrier-added ^{125}IUdR was prepared using a kit method described previously (17) with the radiochemical yield of 100% and the yield of recovery >90%. Prior to administration, the identity and radiochemical purity of ^{125}IUdR was assayed on a C18 reversed phase HPLC column (80:20 v/v water/methanol) with dual detection (uv and gamma-counting) and on TLC (7:1 v/v $CHCl_3/CH_3OH$ and 1:6 v/v concentrated NH_4OH/1-butanol) with ^{127}IUdR and 5-[^{127}I]iodouracil (IU) as standards.

Animals. All studies were conducted in mature female domestic swine with the approval of the UNMC Institutional Animal Care and Use Committee. Swine were acclimated at the UNMC Animal Facility for one week prior to any procedure. To assure the containment of radioactive urine and feces and to prevent inadvertent removal of the inferior vena cava catheter (IVC), swine were also acclimated to the romper room—a large padded metabolic cage—during the second week in the Animal Facility. Swine were gradually conditioned in a romper room from a few minutes to about 8 hours. Three days prior to and three days after ^{125}IUdR administration, swine received daily a saturated solution of potassium iodide (SSKI) at 1 ml/day injected into an apple slice.

Anesthesia. Prior to any procedure, swine received intramuscular pre-anesthetic Telazol mixture (Telazol 500 mg, Ketamine 250 mg, large animal Xylazine 250 mg) at the dose of 1 ml/50 kg under Halothane and oxygen mixture (4–5% Halothane in oxygen at 2.5–3 L via mask) until sufficient anaesthesia was accomplished to insert an endotracheal tube. After insertion of the tube, animals were maintained on 0.5–2.5% Halothane and oxygen at 2.5–3 l. At the conclusion of any procedure, the halothane was discontinued and animals were carried on oxygen until the endotracheal tube was removed. Animals were observed until fully awake.

Non-surgical placement of the inferior vena cava catheter. An 18-ga needle was introduced under fluoroscopic guidance from a right posterior-lateral approach to aid in positioning of a guide wire, and a 9.6 French single lumen catheter was placed. The IVC was flushed with approximately 5 ml saline and a volume of heparin (1 000 U/ml) slightly exceeding the volume of the catheter. The catheter was then closed, wiped with an alcohol swipe, curled up and placed under the bandage. After catheterization the swine were transferred into a romper room.

Blood collection. Blood for complete blood count (CBC), and renal and hepatic functions was withdrawn through the IVC at prescribed time points. Each time, a sterile 10-ml syringe was attached to the catheter and about 5 ml of fluid was removed and discarded. A fresh 3-ml syringe was attached to the IVC (clipping and unclipping the catheter closure as necessary) and 3 ml of blood was collected. The catheter was flushed with saline and heparin as described above.

Bone marrow biopsy. For the bone marrow biopsy, swine were anesthetized as described above. The skin over the anterior iliac crest was prepared as a sterile field. A skin puncture incision (1–2 mm) was made with a No. 11 scalpel blade. A sterile Lee Lok 4" needle was placed through the skin incision and inserted into the bone. A 2–5 ml sample of bone marrow aspirate was obtained. Using the same incision a core biopsy was removed.

Bladder instillations

After IVC catheter was placed and pre-procedure blood samples and bone marrow biopsies collected, an urinary French Foley catheter was inserted into the bladder. ^{125}IUdR (about 3 mCi) in 10 ml 0.9% saline was instilled via the urinary catheter and the catheter was clamped for about 30 min. A single blood sample was collected at 30 min. Bladder was irrigated 5 times with 30 ml sterile normal saline. All washes were collected and their radioactive content determined. Swine were transferred to the romper room and observed clinically at least twice a day for any changes in eating and bowel habits, stool consistency and any signs that might indicate infection or fever. The instillation procedure was repeated twice a week (Monday and Thursday) for the total of 8 doses per animal. Blood samples were regularly collected for CBC and renal/hepatic functions. Four weeks after the first treatment, swine were sedated with Halothane/oxygen and euthanized by an i.v. injection of sodium pentobarbital (150 mg/kg). Tissue samples (brain, thyroid, lung, heart,

liver, spleen, stomach, small bowel, large bowel, kidney, ureter, bladder, uterus, ovary, skin, and bone marrow) were collected and prepared for histological analysis (hematoxylin and eosin).

Aortic injections

With the swine under anesthesia employed to place the IVC (see above), a second needle was inserted into the descending aorta. Blood was withdrawn and a contrast medium (Hypaque50™, 50 ml) injected to confirm needle placement in the aorta. When the position of the needle was verified, about 10 mCi of ^{125}IUdR was injected. The needle was withdrawn and blood samples were collected from the IVC at 1, 2, 3, 4, 6, 10, 20, 30, 60, 90, 120 min, and 1 and 5 days. After the 60 min blood sample, swine were allowed to recover and were transferred into a romper room to contain any radioactivity. Swine were observed clinically at least twice a day. Blood samples were regularly collected for CBC, renal/hepatic functions (4 days intervals), and radioactive content determination (until at background levels). Urine was collected daily until radioactivity was at background levels. At 24 h, a bone marrow biopsy and aspirates for cytology were collected. Six weeks after the treatment, swine were sedated with Halothane/oxygen and euthanized by an iv injection of sodium pentobarbital (150 mg/kg). At necropsy, tissue samples of brain, thyroid, lung, heart, liver, spleen, stomach, small bowel, large bowel, kidney, ureter, bladder, uterus, ovary, skin, bone marrow and numerous samples of vessels, muscle and lymph nodes surrounding the injection site were collected, their radioactive content determined, and prepared for histological analysis.

Carotid injections

With the swine under anesthesia, the catheters were placed through the femoral veins in the common carotid artery, and in the ipsilateral and contralateral jugular veins. The veins were punctured with an 18-ga arteriotomy needle, an angiographic wire was passed into the vessel lumen and the needle was removed, a 5F catheter was passed over the guide wire into the vessel and the position of the catheter was verified under fluoroscopy by injection of radiographic contrast medium (Renografin 60™, 50 ml). About 10 mCi of ^{125}IUdR was injected into carotid artery and the carotid catheter was flushed with 10 ml saline. Blood samples were withdrawn from jugular veins at 10, 20, 30, 45 s, 1, 5, 10, 30, 60 min and from IVC (60 min) for clearance and metabolite determination. After 60 min blood sample, the jugular veins and carotid artery catheters were removed. Swine were allowed to recover and than transferred into a romper room to contain any radioactivity. Swine were observed clinically at least twice a day. Blood samples were regularly collected for CBC, renal/hepatic functions (4 days intervals), and radioactive content determination (until at background levels). Urine samples were collected daily. The second dose of ^{125}IUdR was administered 14 days after the first treatment. A bone marrow biopsy and aspirates for cytology were collected. Four weeks after the second treatment, swine were sedated with Halothane/oxygen and euthanized by an iv injection of sodium pentobarbital (150 mg/kg). At necropsy, tissue samples (brain, meninges, eyes, thyroid, lung, heart, liver, spleen, stomach, small bowel, large bowel, kidney, bladder, bone marrow) were collected, their radioactive content determined, and prepared for histological analysis.

Analyses of metabolites

Venous blood samples obtained either through the IVC or from jugular veins were stored on ice and worked-up within a few minutes after the collection. One-mL aliquot was counted in a gamma-counter to determine the total blood radioactivity. The remaining sample was centrifuged and a 0.1-mL aliquot of plasma was used for the radioactivity determination. The rest of the plasma sample was diluted with ethanol at 2:1 ratio (ethanol:plasma) to prevent enzymatic degradation during storage, vortexed and stored on ice until analyses. The identity of metabolites was determined in a chromatographic analysis of plasma samples on either a C_{18} HPLC column or TLC plates calibrated with non-radioactive standards of potential metabolites—IU, free iodide, iodine—and IUdR.

Results and Discussion

Bladder instillations

The bladder permeability barrier located in the apical membrane exhibits low permeabilities to water, urea, NH_3, H^+, and small nonelectrolytes (18). This property of the luminal surface of the bladder has been successfully exploited in the intravesical chemotherapy of transitional cell carcinoma (19) resulting in some tumor responses and lowered systemic toxicities. The objective of intravesical instillations of ^{125}IUdR into the urinary bladder is to maintain high concentrations of the radiotoxic agent at the site of the tumor, to bypass problems associated with a rapid hepatic dehalogenation of systemically administered radio-IUdR, and to avoid systemic distribution of the radioactivity. Because IUdR is a cell-cycle-dependent agent, our experimental protocol allows for repeated instillations which will be necessary to reach a maximum number of dividing cancer cells in any therapy/prophylactic clinical trial.

The diffusion of IUdR through the bladder wall was evaluated by IVC blood sampling at the end of each of the eight bladder instillations. Analyses of blood radioactivity levels revealed that the systemic distribution of radioiodine

after intravesical administration of ^{125}IUdR is minimal. The peak radioactivity levels at 30 min after the initiation of the experiment did not exceed 6×10^{-5}% injected dose (%ID) per ml blood which corresponds to less than 2 nCi/ml blood. The only radioactive species identified in blood was [^{125}I]iodide. With such a low leakage of radioactivity into the general circulation, an intravesical administration of IUdR appears to be an ideal way of avoiding high radiation doses to normal organs during the ^{125}IUdR-radiotherapy of bladder cancer. Total radioactivity distributed into the extracellular space of a 50-kg swine is less than 20 μCi. Renal and liver function tests indicate that such levels of ^{125}I are innocuous. Total bilirubin and alkaline phosphatase (ALP) were within normal range reported for domestic swine (20). The only parameter outside of the normal range was alanine aminotransferase (ALT). However, 2 and 3 days before the treatment ALT levels were also elevated (52 ± 7 U/l; mean and standard deviation) as compared to normal values (21.7 – 46.5 U/l). On the day of the procedure, ALT (44 U/l) was within the reported normal values range but it returned to pre-treatment levels (60 ± 7) on days 21, 24 and 25. The evaluation of ALT in all swine used in this study indicates that normal, pre-treatment values are uniformly higher than those cites in the literature. Indicators of renal function (urea nitrogen and creatinine) did not deviate from pre-procedure levels and stayed within the normal range reported in the literature (20). Similar results were observed for the complete blood counts (CBC). All hematological parameters, with the exception of hematocrit, were normal. Hematocrit determined in blood samples collected a few minutes before the beginning of the instillation was at 26.4% as compared to 26.1%, 27.4%, and 26.1% on days 21 (six 3 mCi doses of ^{125}IUdR), 24 (seven 3 mCi doses of ^{125}IUdR), and 25 (eight 3 mCi doses of ^{125}IUdR), respectively. There appears to be some discrepancy in 'normal' hematocrit levels depending on the source of reference. The Merck Veterinary Manual lists 36%–43% as an approximate hematocrit reference range (20, p. 967, Table 8), but it also cites 26%–35% as a normal range for this hematological parameter. It is possible that variations of the normal swine hematocrit levels are wider than in humans. We are building a database of normal hematological values for domestic swine based on animals used only in our Facilities.

The uptake of ^{125}I in tissues collected during the necropsy performed after the eighth ^{125}IUdR administration was less than or about 1×10^{-5}%ID/g (0.3 nCi/g). Thyroid levels of ^{125}I were at about 20 nCi/g (Fig. 1). The histologic appearance of tissues considered at risk from ^{125}IUdR did not indicate any changes related to radiation injuries (Table 1). Bladder and ureter sections showed signs of a mild to acute inflammation of mucosa and submucosa most likely related to multiple emplacements of the urinary catheters. Chronic peribronchial inflammation of the lungs and mild fatty changes in the liver are not related to the administration of ^{125}IUdR. At present the cause of these abnormalities has not been determined.

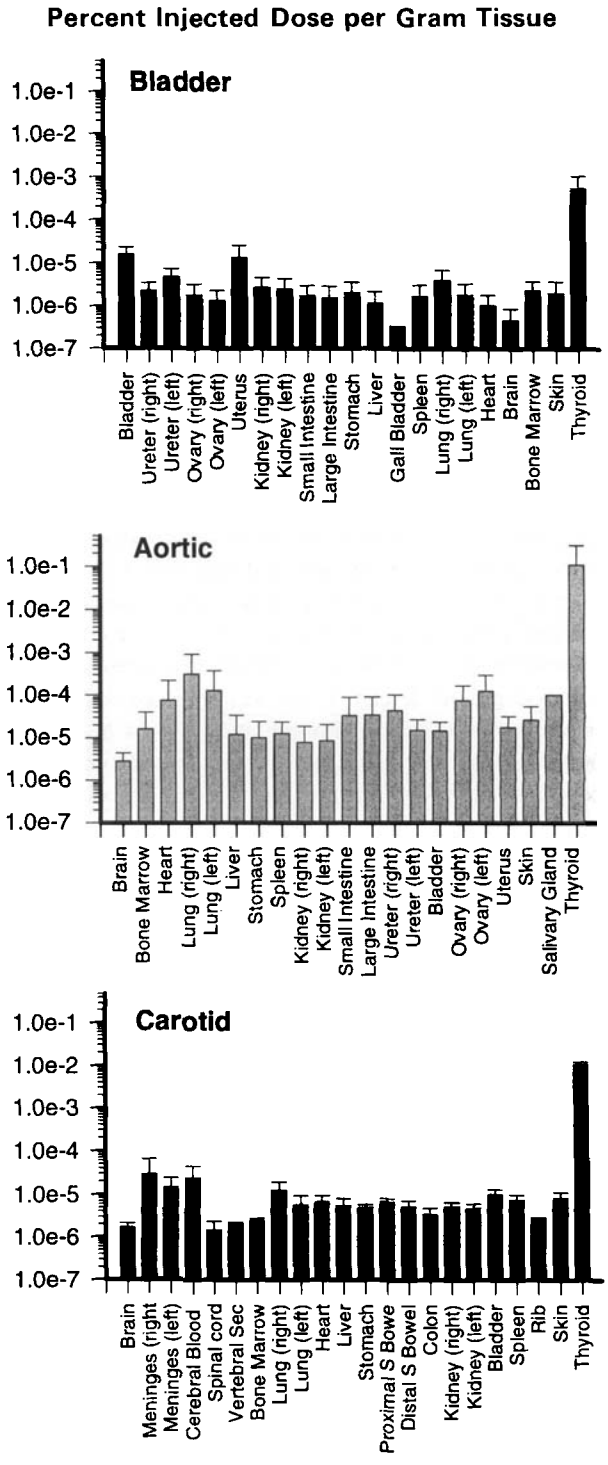

Fig. 1. Biodistribution of ^{125}I after intravesical (upper panel; n = 3), intra-aortic (middle panel; n = 4) and intracarotid (lower panel; n = 3) administration (mean and standard deviation) of ^{125}IUdR.

Table 1

Histopathology data for swine treated with eight fractionated intravesical doses of ^{125}IUdR every four days. Total administered doses are indicated under the research number of each animal

Site	Research No./Total dose		
	Pig 94001/23.54 mCi	Pig 94003/22.47 mCi	Pig 94006/19.52 mCi
Brain	Not available	Not available	Normal
Thyroid	Not available	Not available	Normal
Lung	Congestion; chronic peribronchial inflammation	Congestion; chronic peribronchial inflammation	Congestion; chronic peribronchial inflammation
Heart	Normal	Not available	Normal
Liver	Mild fatty change; focal chronic inflammation	Normal	Mild fatty change
Spleen	Not available	Congestion	Congestion
Stomach	Not available	Not available	Normal
Small bowel	Not available	Normal	Numerous eosinophils in lamina propria
Large bowel	Not available	Normal	Normal
Kidney	Normal	Normal	Normal
Ureter	Chronic inflammation in wall	Vacuolization; mild acute inflammation	Dilated
Bladder	Mild chronic inflammation	Accute inflammation of mucosa and submucosa with focal erosion	Focal, mild submucosal chronic inflammation
Uterus	Not available	Not available	Normal
Ovary	Cystic follicles	Cystic follicles	Cystic follicles
Skin	Normal	Normal	Normal
Bone marrow	Normal	Not available	Normal

Aortic injections

A local bolus injection into hepatic artery appears to be the route of choice for delivery of ^{123}IUdR (5) and ^{127}IUdR (21, 22) in patients with liver metastasis in an attempt to delay deiodination. The tumor uptake is reported to be specific and easily measurable with the SPECT and planar imaging, but pharmacokinetics and metabolite data is lacking, particularly for radio-IUdR (35). To fill these gaps in our knowledge of IUdR behavior, five swine received ia doses of 10 mCi ^{125}IUdR. One dose of IUdR was misadministered and about 70% of the radioactivity was deposited in the interstitial space surrounding the aorta. The half-life of the α phase, calculated as a mean from four swine, is 0.4 ± 0.048 min. The elimination half-life is 144 ± 35 min. All points up to 24 h fit into a bi-exponential clearance curve. The analysis of metabolites showed that the rate of IUdR disappearance (0.27 ± 0.035 min^{-1}) and the rate of free iodide appearance (0.31 ± 0.036) are nearly identical with the half-life for IUdR deiodination of 2.6 ± 0.34 min. There was a transient appearance of iodouracil (up to about 20 min post-injection). An unidentified radioactive species, less than 8% at 60 min, was also detected in some blood samples. The analyses of urine samples collected daily for 9 days after the i.a. dose indicate that all radioactivity was eliminated in the form of free iodide and that the excretion was finished 4 to 5 days post-administration.

The summary of renal and liver function studies and CBC are shown in Figs 2 and 3. All values appear to be within normal range indicating that a 10 mCi i.a. dose of ^{125}IUdR does not pose any radiation-related hazards. A similar evidence was obtained from the histologic analysis of tissue samples obtained during the necropsy (Table 2). With the exception of the congestion and chronic peribronchial inflammation of the lung observed in all animals housed in our facilities, all other tissues were normal and did not exhibit any radiation-related injuries. Two swine (94005 and 94007) had abnormal epithelial vacuolization and submucosal edema/inflammation of the bladder. These two animals in addition to the 10 mCi i.a. dose also received a 3 mCi i.b. dose of ^{125}IUdR. Due to difficulties with the placement of the urinary catheter they were removed from the bladder protocol and enrolled in the i.a. study. The changes in the appearance of bladder mucosa and submucosa are most likely the result of multiple, unsuccessful attempts to place the catheter. Other observations, such as congestion of the spleen and cystic follicles in the ovary, are not related to radiation. The uptake of radioactivity in various tissues was about 50 times higher than in animals enrolled in the intravesical study (Fig. 1). Thyroid and right lung had the highest uptake, 0.11 ± 0.10%ID/g (11 μCi/g) and $3.07 \times 10^{-4} \pm 0.59 \times 10^{-4}$%ID/g (0.03 μCi/g) respectively.

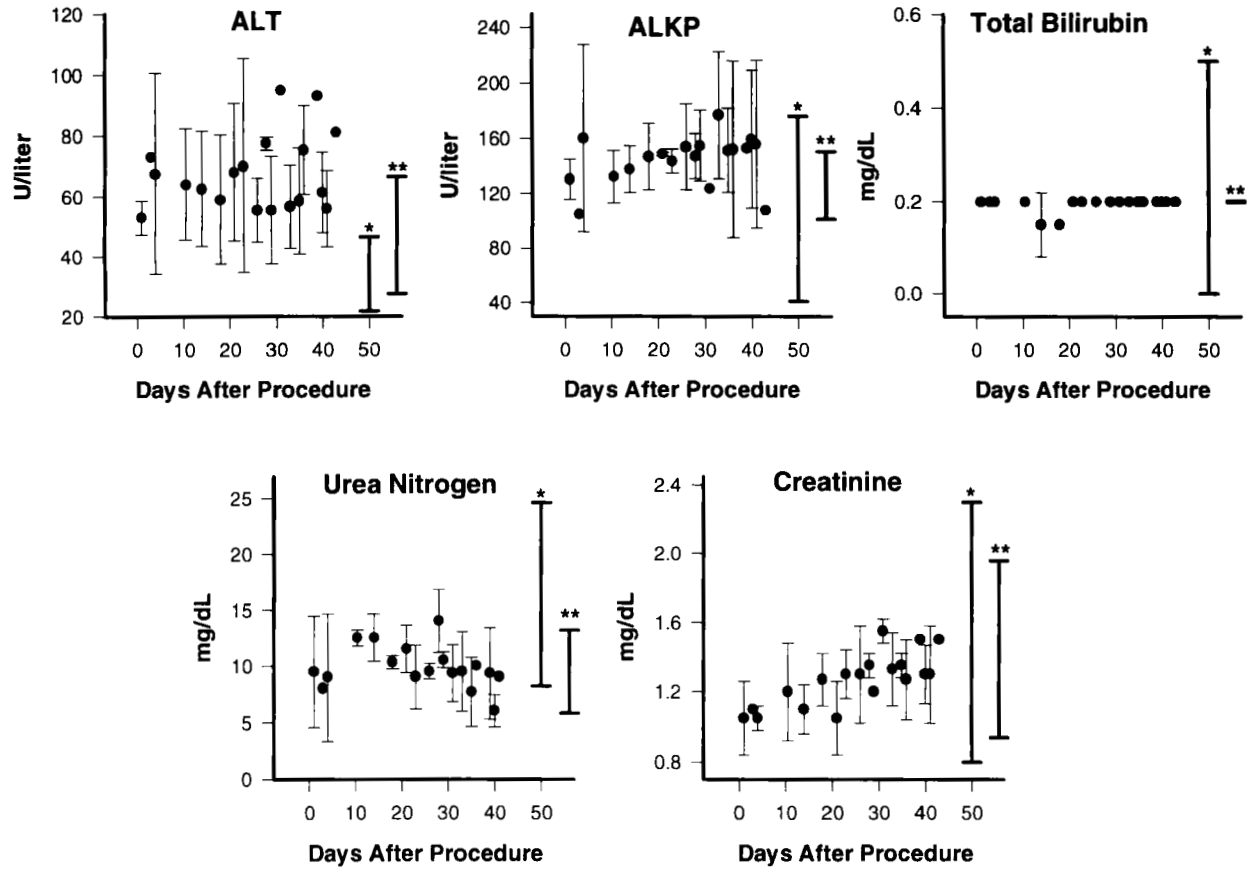

Fig. 2. Liver and kidney functions in swine from the intra-aortic study. Each animal received approximately 10 mCi of ^{125}IUdR. Data shown as means (symbols) and standard deviations (bars). *Literature values (20); **range of pre-treatment values collected 30, 12, 9, 2 and 0 days before administration.

Carotid injections

Intracarotid administration of IUdR is anticipated to have the advantage of increasing drug concentration reaching brain and brain tumors. Neurons and glial cells have a low, if any, mitotic rate and thus they are not expected to incorporate IUdR. The regional advantage calculated for 5-bromo-2′-deoxyuridine (BUdR)—an estimated local concentration for i.c. versus i.v. administration—is between 6 and 16 (23). In addition to increased local concentrations of IUdR after i.c. administration, an enhanced uptake should be gained from the higher lypophilicity of ^{125}IUdR (partition coefficient $K_p = 0.32 \pm 0.011$ as determined by partition experiments in phosphate buffered saline/1-octanol and by the reversed phase HPLC). Intracarotid 5-[^{125}I]iodovinyl-2′-deoxyuridine (24) was found to be totally excluded from the central nervous system probably due to the poor lipid solubility ($K_p = 83$). BUdR uptake in brain tumors, particularly when modulated with 5-fluorouracil, was found to be at the therapeutically significant levels (23, 25).

Pharmacokinetics of ^{125}IUdR injected in the common carotid artery in swine are similar to i.v. or i.a. administrations. The clearance half-lives in right and left jugular veins were identical ($t_{\frac{1}{2}z} = 0.16 \pm 0.009$ min) and comparable to i.a. values (0.4 ± 0.035 min). The elimination half-life was only 21 ± 7.5 min as calculated from combined results of two i.c. doses ($n = 6$; three pigs with two doses each). A separate analysis of blood clearance curves for each of the i.c. two doses have shown that there is no statistical difference between the first and the second administration. It is possible that insufficient number of samples collected between 30 to 180 min after the i.c. injection introduced this difference in the elimination half-lives for the i.c. and i.a. routes of administration. The metabolic fate of IUdR after the i.c. injection is similar to that observed after other means of administration. However, there appears to be about 1 min lag time before the first traces of free iodide are detected in blood samples collected from jugular veins. This is unlike the case of i.a. administrations where the appearance of free iodide is nearly instantaneous with about 7% I-detected in less than 30 s post-injection. The rate of IUdR disappearance (0.19 ± 0.021 min^{-1}) and I-appearance (0.23 ± 0.051 min^{-1}) are similar to these calculated from the i.a. metabolite analysis. There is a substantial amount of the unidentified 'oxidized' form of radioiodine (up to 40% after 1 h) in the blood from the left

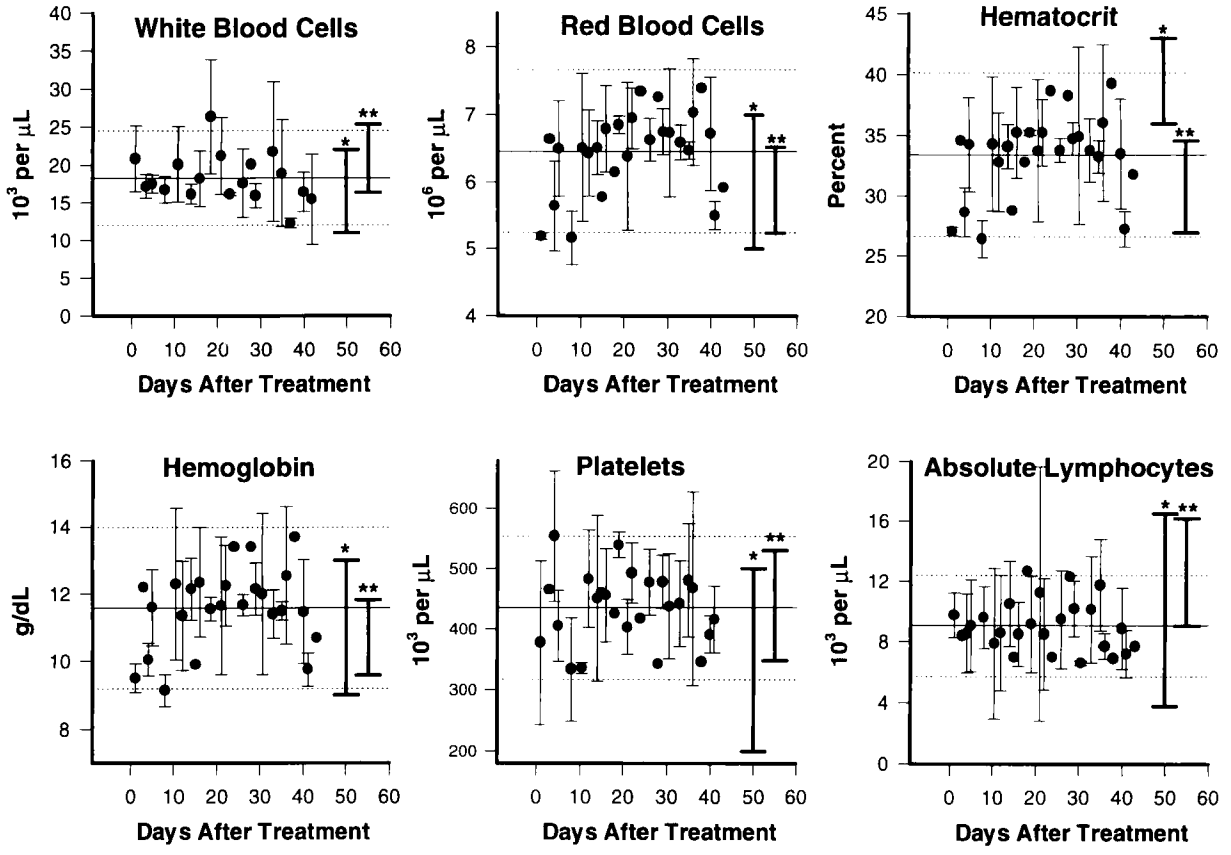

Fig. 3. Hematological data for swine treated with a single 10 mCi intra-aortic dose of ^{125}IUdR. *Literature values (20); **range of pre-treatment values collected 30, 12, 9, 2 and 0 days before administration.

Table 2

Histopathology data for swine treated with one intra-aortic dose of ^{125}IUdR

Site	Research No./Total dose			
	Pig 94002/9.1 mCi	Pig 94005/9.77 mCi	Pig 94007/11.25 mCi	Pig 94008/8.46 mCi
Brain	Normal	Normal	Normal	Normal
Thyroid	Not available	Normal	Normal	Normal
Lung	Congestion; chronic peribronchial inflammation	Congestion; chronic peribronchial inflammation	Congestion; chronic peribronchial inflammation	Peribronchial lymphocytic aggregates
Heart	Normal	Normal	Normal	Normal
Liver	Normal	Normal	Normal	Normal
Spleen	Congestion	Normal	Congestion	Normal
Stomach	Normal	Normal	Normal	Normal
Small bowel	Normal	Prominent lymphoid follicular hyperplasia	Normal	Normal
Large bowel	Normal	Normal	Normal	Normal
Kidney	Normal	Normal	Chronic inflammation of medullary interstitium	Cystic dilation of calyx, possibly hydronephrosis with thinning of medulla and cortex; fibrosis and chronic inflammation
Ureter	Not available	Normal	Normal	Focal clusters of lymphocytes in muscle wall
Bladder	Normal	Focal epithelial vacuolization and submucosal edema	Focal mucosal vacuolization and chronic inflammation of mucosa and submucosa	Normal
Uterus	Normal	Normal	Not available	Normal
Ovary	Cystic follicles	Cystic follicles	Not available	Cystic follicles
Skin	Normal	Normal	Normal	Not available
Bone marrow	Normal	Normal	Normal	Normal

Table 3

Histopathology data for swine treated with two intracarotid doses of ^{125}IUdR administered at two-week intervals

Site	Research No./Total dose		
	Pig 94014/20.52 mCi	Pig 94015/23.77 mCi	Pig 95001/16.84 mCi
Brain (Meninges)	Normal	Normal	Normal
Thyroid	Normal	Normal	Normal
Lung	Congestion; focal mild chronic inflammation and edema	Congestion; focal mild chronic inflammation and edema	Congestion; focal peribronchial lymphoid aggregates
Heart	Normal	Normal	Normal
Liver	Normal	Congestion	Normal
Spleen	Normal	Normal	Normal
Stomach	Normal	Not available	Normal
Small bowel	Normal	Normal	Normal
Large bowel	Not available	Normal	Not available
Kidney	Normal	Focal mild chronic corticomedullary inflammation	Normal
Bladder	Normal	Not available	Focal vacuolization of urothelium; no inflammation
Bone marrow	Normal	Mildly hypocellular	Normal

jugular vein. Also, a slightly higher amount of ^{125}IU was detected. It is difficult to reconcile these differences in the metabolite content of the left versus right jugular vein. A possible explanation is the contamination of 30- and 60-min samples with blood retained in the catheter.

As seen for i.a. and i.b. administration, the CBC and renal/liver functions are within normal range. The amounts of radioactivity retained after two i.c. injections is less than 2×10^{-5}%ID/g in all collected tissues with the exception of the thyroid (Fig. 1). The histology of bone marrow indicated one case of mild hypocellularity (Table 3; Res pig 94015). Although this animal received the highest total dose of ^{125}IUdR other tissues, CBC, and hepatic/renal functions tests did not indicate any radiation-induced abnormalities.

Combined results from the i.a., i.c. and i.b. administration of ^{125}IUdR indicate that regardless of the route of administration, the clinical observations, laboratory data and necropsy results are within normal range. This lack of any identifiable radiation-related systemic effects led us to conclude that local administration of ^{125}IUdR at the dose levels applied in these studies is safe.

ACKNOWLEDGEMENTS

This research was sponsored by the grant from the State of Nebraska (LB595) and Developmental Funds provided by Departments of Radiology and Radiation Oncology.

REFERENCES

1. Baranowska-Kortylewicz J, Makrigiorgos GM, Van den Abbeele AD, Berman RM, Adelstein SJ, Kassis AI. 5-[^{123}I]Iodo-2'-deoxyuridine in the radiotherapy of an early ascites tumor model. Int J Oncol Biol Phys 1991; 21: 1541–51.
2. Commerford SL. Biological stability of 5-iodo-2'-deoxyuridine labelled with iodine-125 after its incorporation into the deoxyribonucleic acid of the mouse. Nature 1965; 206: 949–50.
3. Bloomer WD, Adelstein SJ. Therapeutic application of iodine-125 labeled iododeoxyuridine in an early ascites tumor model. Curr Top Radiat Res Q 1978; 12: 513–25.
4. Humm JL, Bagshawe KD, Sharma SK, Boxer G. Tissue dose estimates following the selective uptake of ^{125}IUdR and other radiolabelled thymidine precursors in resistant tumors. Br J Radiol 1991; 64: 45–9.
5. Mariani G, Di Sacco S, Volterrani D, et al. Tumor targeting with 5-[^{123}I]iodo-2' deoxyuridine infused into the hepatic artery of patients with liver metastases from colorectal cancer. J Nucl Biol Med 1994; 38: 265–7.
6. Rezvani M, Hopewell JW. The response of the pig lung to fractionated doses of X rays. Br J Radiol 1990; 63: 41–50.
7. Miot E, Hoffschir D, Pontvert D, et al. Quantitative magnetic resonance and isotopic imaging: early evaluation of radiation injury to the brain. Int J Radiat Oncol Biol Phys 1995; 32: 121–8.
8. Novotny J, Otoupal P, Mika J, Hrusovsky J. Dose measurement in animal experiments. II. Dose distribution in ^{60}Co irradiated pigs. Strahlentherapie 1972; 144: 430–4.
9. Ragan HA, Palotay JL, Clarke WJ. Effects of radioiodine in sheep and swine. BNWL Rep 1966; 1: 38–40.
10. Young CM, Hopewell JW. The isotope clearance technique for measuring skin blood flow. Br J Plast Surg 1983; 36: 222–30.
11. Hopewell JW, Berry RJ. Radiation tolerance of the pig kidney: a model for determining overall time and fraction factors for preserving renal function. Int J Radiat Oncol Biol Phys 1975; 1: 61–8.
12. McLaughlin RF, Styler WS, Canada RO. A study of the subgross pulmonary anatomy in various mammals. Am J Anatomy 1961; 108: 149–65.

13. Sperber I. Studies on the mammalian kidney. Zoologiska Bidrag från Uppsala 1944; 22: 249–431.
14. Terris JM. Swine as a model in renal physiology and nephrology: a review. In: Tumbleson ME, ed. Swine in biomedical research. New York: Plenum Press, 1986: 1673–89.
15. Douglas BG, Grulkey WR, Chaplin DJ, Lam G, Skarsgard LD, Denekamp J. Pions and pig skin: Preclinical evaluation of RBE for early and late damage. Int J Radiat Oncol Biol Phys 1986; 12: 221–9.
16. Scharl A, Beckmann MW, Artwohl JE, Holt JA. Comparison of radioiodoestradiol blood-tissue exchange after intravenous or intraarterial injection. Int J Radiat Oncol Biol Phys 1995; 32: 137–46.
17. Baranowska-Kortylewicz J, Helseth LD, Lai J, Schneiderman MH, Schneiderman GS, Dalrymple GV. Radiolabeling kit/generator for 5-radiohalogenated uridines. (Baranowska-Kortylewicz J, U.S. Patent 5,468, 853; 1995) J Labelled Compds Radiopharm 1994; 34: 513–21.
18. Chang A, Hammond TG, Sun TT, Zeidel ML. Permeability properties of the mammalian bladder apical membrane. Am J Physiol 1994; 267: 1483–92.
19. Horn Y, Eidelman A, Walach N, Waron M, Barak F. Intravesical chemotherapy of superficial bladder tumors in a controlled trial with cis-platinum versus cis-platinum plus hyaluronidase. J Surg Oncol 1985; 28: 304–7.
20. Siegmund OH, editor. The Merck Veterinary Manual. Rahway, NJ: Merck and Co, 1986: pp 966–70.
21. Speth PA, Kinsella TJ, Chang AE, Klecker RW, Belanger K, Collins JM. Selective incorporation of iododeoxyuridine into DNA of hepatic metastases versus normal human liver. Clin Pharmacol Ther 1988; 44: 369–75.
22. Remick SC, Benson AB, Weese JL, Phase I trial of hepatic artery infusion of 5-iodo-2′-deoxyuridine and 5-fluorouracil in patients with advanced hepatic malignancy: biochemically based combination therapy. Cancer Res 1989; 49: 6437–42.
23. Gebarski HS, Chandler WF, Diaz RF. Intra-arterial bromodeoxyuridine radiosensitization and radiation in treatment of malignant astrocytomas. J Neurosurg 1988; 69: 500–5.
24. Klapper PE, Cleator GM, Bruce JM, Longson M. Penetration of the blood-brain barrier by the antiviral drug E-5-(2-vinyl)-2′-iodo-deoxyuridine in a rat model of herpes encephalitis. Drug Des Deliv 1988; 3: 57–67.
25. Greenberg HS, Chandler WF, Ensminger WD, Radiosensitization with carotid intra-arterial bromodeoxyuridine ±5-fluorouracil biomodulation for malignant gliomas. Neurology 1994; 44: 1715–20.