STUDIES ON THE TISSUE DISTRIBUTION OF ^{125}I-IODOPROPAMIDE IN THE DOG

C. M. Boyd,* G. N. Holcomb, R. E. Counsell, W. H. Beierwaltes, and L. M. Lieberman

University of Michigan Medical Center, Ann Arbor, Michigan

Several methods for the external visualization of the pancreas using internally administered radionuclides have been devised, the most useful to date being the administration of ^{75}Se-selenomethionine (*1,2*) and its detection with gamma-imaging devices. A continuing program at this institution to develop scanning agents for specific localization in tumors has resulted in the study of several compounds for pancreatic scanning. One of these thought to be of potential value is ^{125}I-1-(p-iodobenzenesulfonyl)-3-n-propylurea. This compound has structural similarity to chlorpropamide, 1-(p-chlorobenzenesulfonyl)-3-n-propylurea, and other sulfonylurea compounds and will hereafter be referred to as ^{125}I-Iodopropamide. Although the exact mode of action is not known for the hypoglycemic action of the sulfonylureas, the most prominent effect appears to be insulin release from pancreatic beta cells (*3*). This action prompted the study of localization of ^{125}I-Iodopropamide in the pancreas.

METHOD

Four normal adult beagle dogs were slowly injected intravenously with 100 μCi of ^{125}I-Iodopropamide, which contained approximately 4 mg of the chemical dissolved in 90% ethanol. The four dogs were killed at 30 min, 4 hr, 24 hr, and 72 hr, respectively, by the intravenous injection of a rapidly acting lethal solution.

Immediately after sacrifice an autopsy was performed and 19 tissues were removed, from which duplicate small samples were obtained for counting. The samples were dissected free from surrounding fat and connective tissue. The adrenal cortex was separated from the adrenal medulla. Samples were weighed, placed in plastic tubes, and counted in an automatic well-counter (Picker Autowell II). Counts were accumulated for a period of time to insure less than 5% statistical counting error, and corrections were made for physical radioactive decay and machine counting efficiency. Standards of the original solution were made and counted identically to the tissues.

Synthesis of the ^{125}I-Iodopropamide was performed as reported elsewhere (*4*). Purity was checked by thin-layer chromatography. The radiolabeled compound was chromatographed against the stable iodinated compound. The radiolabeled compound had an identical R_f value as the stable compound, and radiochromatographs showed radioactivity only at the same R_f value. Specific activity of the compound was 25.5 μCi/mg.

Autoradiography was performed on fixed 5-micron-thick sections of tissue using Kodak NTB 2 photographic emulsion by a dipping technique. The incubation time was 7–10 days. Slides were stained with Mayer's hematoxylin and aqueous eosin.

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For reprints contact: C. M. Boyd, University of Arkansas Medical Center, Little Rock, Ark. 72201.

* Present address: See above.

TABLE 1. ^{125}I-IODOPROPAMIDE DISTRIBUTION IN DOG TISSUES (PERCENT DOSE/GM TISSUE)

	Pancreas	Blood	Spleen	Lung	Kidney	Liver	Bile	Adrenals	
								Cortex	medulla
30 min	0.008	0.079	0.043	0.020	0.024	0.018	0.011	0.011	0.008
4 hr	0.009	0.044	0.045	0.044	0.027	0.026	0.015	0.011	0.010
24 hr	0.019	0.056	0.081	0.053	0.051	0.031	0.020	0.030	0.110
72 hr	0.017	0.060	0.088	0.095	0.031	0.021	0.024	0.008	0.004

	Intestine	Heart	Thyroid	Ovary	Uterus	Thymus	Bladder	Urine	Muscle	Fat
30 min	0.008	0.006	0.006	0.005	0.009	0.008	0.008	0.007	0.005	0.002
4 hr	0.008	0.008	0.006	0.008	0.009	0.007	0.005	0.007	0.008	0.005
24 hr	0.017	0.023	0.016	0.019	—	0.012	0.023	0.080	0.014	0.010
72 hr	0.014	0.021	0.171	0.012	—	—	0.018	0.067	0.012	0.003

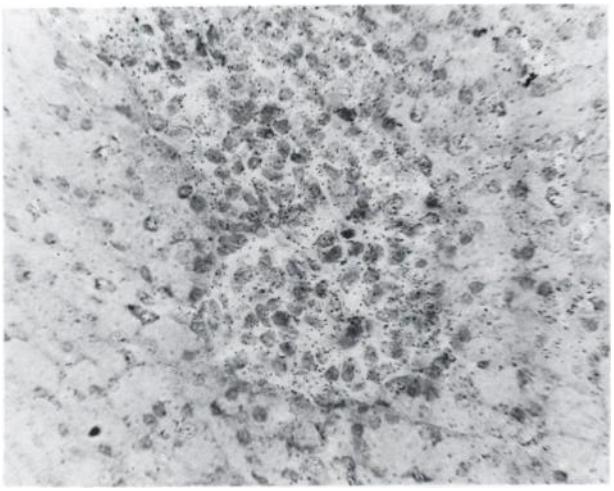

FIG. 1. Autoradiograph of section of dog pancreas showing islet of Langerhans and surrounding exocrine pancreas. Grain development is seen primarily in islet area (× 430; hematoxylin and eosin stain).

RESULTS

Table 1 shows the concentrations of the radioactivity in the various tissues removed. Results are expressed as percent of dose per gram of tissue. The pancreas and liver showed a rather low concentration of the compound compared with spleen, lung, kidney, and blood. At 72 hr 0.187 μCi was found in the total pancreas which weighed 17.5 gm.

Table 1 also shows that the highest pancreas-to-liver ratio of tissue concentration of the ^{125}I-Iodopropamide of 0.81:1 was obtained at 72 hr.

Autoradiography (Fig. 1) showed some radioactivity throughout the pancreas above that of background, but an increased concentration of radioactivity in the islets compared to surrounding exocrine cells. No toxic effects were seen in the routine H & E sections. Autoradiography of liver, spleen, kidney, lung, and muscle showed diffuse distribution of the radioactivity but no particular cellular concentration.

DISCUSSION

The proposed primary site of action of the sulfonylurea compounds on the beta cells of the pancreas suggested the possibility that chlorpropamide might concentrate in those cells of the pancreas. The ability to synthesize and radioiodinate an analog of chlorpropamide afforded us the opportunity to study the relative tissue concentration of this related compound in the normal pancreas compared with other tissues and organs.

The time intervals chosen in this study for the sacrifice of animals after dose administration apparently included the peak pancreatic tissue concentration present since previous studies have indicated a rather prolonged hypoglycemic action and excretion rate. A maximum hypoglycemic effect of chlorpropamide is seen at 3–6 hr with some residual effect to 24 hr. Also, studies with ^{35}S-labeled chlorpropamide have shown a 32-hr half-life for the major portion of excretion in the urine and 3–7 days for complete excretion (*5*). Our studies confirm the prolonged retention of this related compound since the concentration in most tissues peaked by 72 hr. The increasing concentration of radioactivity in pancreas compared to liver, which is highest at 72 hr, would suggest continued differential localization in the pancreas. The high thyroidal uptake at 72 hr is probably due to deiodination of the compound.

Experience with ^{75}Se-selenomethionine in pancreatic scanning has indicated that the concentration (percent dose per gram) in the pancreas of 8–9 times that of liver is perhaps the minimum target-to-nontarget ratio sufficient for scanning purposes (*1*). In this study we found that the maximum radioactivity from ^{125}I-Iodopropamide in % dose/gm of tissue in the pancreas is slightly less than that in the liver. However, the concentration of ^{125}I-Iodopropamide in islet cells as compared to adjacent acinar cells in the pancreas (as shown by autoradiography) is certainly high, even though the total amount of ^{125}I-Iodopropamide present in the pancreas as determined here is low. The latter observation may be due to the islet cells comprising only 1–4% of the total pancreatic weight normally (*6*). If, however, the patient had a neoplasm of the pancreas consisting of a large enough mass of functioning islet cells, the neoplasm might conceivably be detected by scanning using this compound.

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