RADIOPHARMACEUTICALS FOR PANCREATIC IMAGING

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ABSTRACT

Over the past few decades, cancer of the pancreas has emerged as one of the most important neoplasias in human beings. It now accounts for approximately 20,000 deaths annually in the United States. Diseases of the pancreas are difficult to diagnose by standard clinical or medical imaging techniques. In spite of the introduction of the CT scanner and ultrasonography, there is a lack of suitable diagnostic agents for pancreatic carcinoma which is the most difficult abdominal tumor to diagnose, and in only 30% of autopsied cases the clinical diagnosis was correct. As the existing diagnostic procedures confirm the pathological condition too late for proper treatment, the prognosis of pancreatic carcinoma is poor.

In 1929 acid dyes such as acid fuchsin, fast yellow fluorescein and methyl orange, and basic dyes such as basic fuchsin, methylene blue, rhodomin B, safarino and safrin extra bluish were used to measure pancreatic function, as these dyes concentrated moderately selectively in the pancreas.

In this paper, radioisotope labeled agents such as ^{35}S-methionine, ^{75}Seselenomethionine, ^{11}C-methionine radioiodine labeled paraiodo-phenyl alanine, ^{99m}Tc-labeled methionine, ^{131}Cs-cesium acetate, etc. used to image the pancreas will be presented.

Diseases of the pancreas are difficult to diagnose by standard clinical or radiographic techniques. Klintrup[1] in his recent statistical, clinical and pathological survey report emphasized the lack of suitable diagnostic agents for pancreatic carcinoma which is the most difficult abdominal tumor to diagnose, and in only about 30% of autopsied cases the clinical diagnosis was correct. As the existing diagnostic procedures confirm the pathological condition too late for proper treatment, the prognosis of pancreatic carcinoma is poor.

In 1929, Crandall et al[2] used acid dyes such as acid fuchsin, fast yellow fluorescein and methyl orange and basic dyes such as basic fuchsin, methylene blue, rhodomin B, safarino and safarin extra bluish to measure pancreatic function test, as these dyes concentrated moderately selectively in the pancreas.

Wheeler et al[3] in 1949 reported high amino acid concentrations in the pancreas shortly after the intravenous administration of ^{35}S labeled amino acids, particularly ^{35}S-methionine, which was confined mainly to the exocrine part of the gland.

In 1959, Hansson[4], by means of whole body autoradiograms and Geiger-Muller tubes, clearly demonstrated the distribution of maximum activity of ^{35}S-L-methionine in the pancreas of the mouse 30 minutes after intravenous injection compared to other

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organs. Six hours after the injection the radioactivity fell rapidly and was distributed equally in most of the other organs. Like the pancreas, other organs with a substantial synthesis of protein, such as liver (serum albumin) and the mucosa of the small intesting (digestive enzymes) showed an uptake of labelled amino acids. Meschan et al[5] attempted to visualize the pancreas using ^{65}Zn compounds, but they found the pancreatic concentrations of the radionuclide were nsufficient to be of clinical value.

An analogue of methionine, namely selenomethionine labeled with ^{75}Se (half-life 120 days and principal gamma ray of 0.27 MeV) was prepared by Blau and Manske in 1961[6]. ^{75}Se-selenomethionine has high pancreatic specificity and since then it is the only agent being used for radioisotope scanning of the human pancreas. However,, scanning is complicated by the liver and pancreas always being closely adjacent, and the liver, due to its great size, accumulating more selenomethionine than the pancreas. This large source of activity can seriously interfere with visualization of the pancreas; if the two organs overlap, pancreatic visualization is normally impossible.

There have been several efforts[7-13] to overcome the difficulties due to the large amount of selenomethionine accumulating in the liver, but have not been very successful. Hence, the diagnosis of pancreatic disease by ^{75}Se-selenomethionine photo scanning is only 53% correct.[14]

This material is not recommended for clinical use on women of child bearing age as high concentrations have been observed in the placenta and fetuses of pregnant animals.[15,16] Also, it has a long biological half-life in man of 100 days[14], but different values have been reported in the literature.[17-20]

Sodee et al[20] have estimated the whole body radiation dose in man to be 2.2 rads from a standard diagnostic dose of 250 uCi, 2-5 rads to gonads and a much higher dose, 14 rads, to the kidneys; 0.6 rad to the pancreas and 0.5 rad to the liver. In view of the foregoing discussion there have been continuous efforts to find an ideal radiopharmaceutical for the scanning of the pancreas.

1-aminochelopentane-^{14}C-carboxilic acid was reported as a pancreas specific agent by Berlinquet et al[21] in 1962. Aminocyclopentane carboxylic acid (ACPC) is an unnatural animo acid which is an anti-tumor agent, and is selectively concentrated by the pancreas, tumor tissues and the bone marrow which are very active tissues for protein biosynthesis and remain there unchanged; interestingly enough, it is to these tissues that ACPA is the most toxic. However, it is not known why regenerating liver in which protein biosynthesis is very active, does not concentrate ACPC.

Sherman, et al[22] reported that they were able to observe the concentrations of alpha aminocyclopentane-^{14}C-carboxlyic acid in the pancreas of the mouse, but not in that of dogs and rabbits. Based on the reports that phenylalanine-^{14}C[4] and p-fluorophenylalanine-^{14}C[23] have pancreatic specificity. Counsell, et al[24] synthesized ortho meta and paraiodophenyalanine-^{125}I and made their tissue distribution analysis. All three iodophenylalanine-^{125}I isomers showed a specificity for pancreatic tissue in mice but not in dogs.

Ullberg and Blomquint[25] working independently on the selective localization to pancreas of radioiodinated phenyalanine analogs pointed out two advantages of the use of these amino acids over ^{75}Se-selenomethionine: (a) higher degree of concentration in the pancreas and (b) short biologic half-life due to more rapid renal excretion.

Tubis and Endow[26] prepared ^{99m}Tc labeled cystine, methionine and a synthetic lepta-cosa-peptide amide hormone with secretin-like properties. They studied the distribution of these compounds in the organs of mice. At 5 minutes the ^{99m}Tc methionine radioactivity in the pancreas was less than that of liver at 5, 30 and 60 minutes. The ^{99m}Tc synthetic secretion of radioactivity in the pancreas remained about the same for 5-10 minutes, whereas there was a rise in the liver activity during this period.

While scanning the pancreas of a dog, they noticed a definite but somewhat diffuse uptake in the scintiscan of the pancreas.

The dye, toluidine blue O. (TBO) was observed to have preferential concentration in the parathyroid and pancreas.[27] It was suggested that radioisotopic labelling of this dye might permit the visualization of these organs by scanning procedures.[28]

Yeh, et al[29] succeeded in labelling TBO with ^{99m}Tc. However, they found the new complex was in an aggregated form, and hence, it was localized mainly in the liver rather than in the parathyroid and pancreas. There have been unpublished reports of labelling TBO with ^{113m}In and the complex being used for kidney scanning.[30]

Sodee[31] used ^{131}Cs cesium acetate in isotonic saline for scanning the pancreas in guinea pigs and dogs. The results were not encouraging and the author himself expressed doubt regarding the application of his finding to humans. After reading the reports of the localization of alloxan in the pancreas, Bedkik, et al[32] made an extensive study of the accumulation of ^{14}C-labeled alloxan in mice and dogs in order to develop it as a pancreatic scanning agent. However, they came to the conclusion that alloxan cannot be used as a pancreatic scanning agent.

Recent advances in pancreatic imaging by computerized tomography, or CT,[33] and by ultrasonography[34] have been promising, but development of new radiopharmaceuticals for the

diagnosis of pancreatic disease has been slow. ^{75}Se-selenomethionine has altered biochemical behavior compared with that of natural amino acids.[35] For this reason, natural amino acids labeled with ^{11}C (T ½ = 20.4 min) and ^{13}N (T½ = 10.0 min) are better choces for *in vivo* studies, since they follow normal metabolic pathways. Also, since both radionuclides are positron emitters, rectilinear scanning and positron tomography[36] can be used. ^{11}C-tryptophan and ^{11}C-valine were tried as a diagnostic modality for the detection and study of pancreatic diseases.[37] Adequate and prompt homogeneious concentration of a positron-emitting agent in the pancreas (i.ke., C-11 amino acids) tends to rule out pancreatic disease; on the other hand, nonvisualization or poor uptake would be compatible with pancreatitis and segmental defects. Parial or nonvisualization could indicate a neoplastic or cystic process. ^{11}C-methionine and positron computerized tomography was used to image the pancreas. Although no false positive or negative was observed, a differential diagnosis between cancer and pancreatitis was impossible.[38]

L-3-iodo-a-methyltyrosine, labeled with either ^{131}I or ^{123}I, was found to have a high pancreatic specificity in mice, with a pancreas-to-liver ration of 8.6 during the first hour after I.V. injection.[39]

One study indicates that in pancreatic emergencies, CT is the method of choice and that in chronic pancreatitis, CT is not advisable.[40]

Radionuclide pancreatic imaging may supplement anatomic imaging with ultrasonography and computerized tomography (CT).

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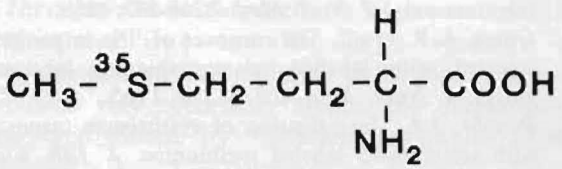
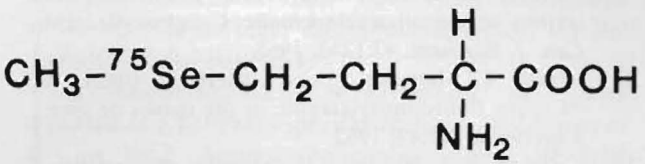


^{35}S-methionine

Figure 1: Chemical structure of methionine labeled with radioactive sulfur-35.

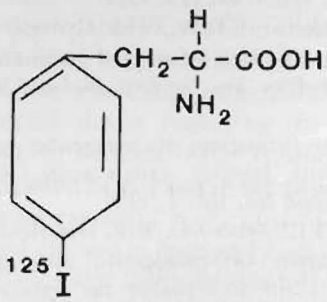


^{75}Se-selenomethionine

Figure 2: Chemical structure of methionine labeled with Selenium-75.

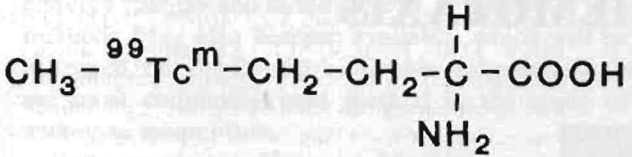
Alpha aminocyclopentane-^{14}C-carboxylic acid

Figure 3: Chemical structure of Alpha aminocyclopentane-^{14}C-carboxylic acid.



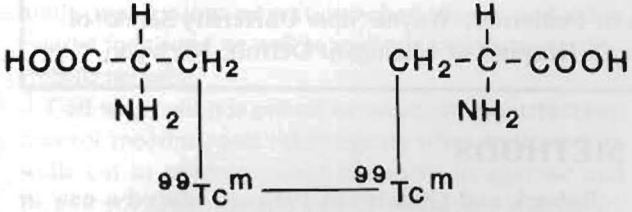
^{125}I-paraiodophenylalanine

Figure 4: Chemical structure of ^{125}I-paraidophenyl-alanine.



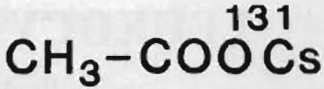
$^{99}Tc^{m}$- labeled methionine

Figure 5: Chemical structure of methione labeled with Technetium-99m.



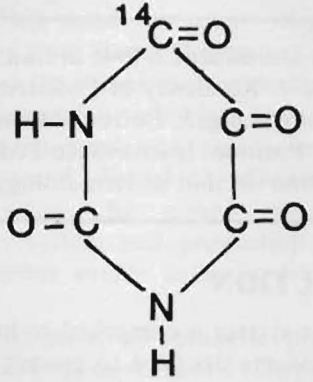
$^{99}Tc^{m}$-- labeled cystine

Figure 6: Chemical structure of cystine labeled with Technetium-99m.



^{131}Cs-cesium acetate

Figure 7: Chemical structure of cesium acetate labeled with Cesium-131.



^{14}C-labeled alloxan

Figure 8: Chemical structure of alloxan labeled with Carbon-14.