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RECENT DEVELOPMENTS IN RADIOPHARMACEUTICALS

Lecture presented

By

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I am grateful for the invitation to speak to this audience which represents many diverse disciplines. I come to talk as a radiobiochemist and radiopharmaceutical chemist in the area of Nuclear Medicine which encompasses many interdisciplinary sciences.

I have had the pleasure of associating previously with Turkish scientists, Drs. Tömek and Özker; Drs. Akcay and Renda of Ankara, nuclear physicians, so I really do not come as a stranger.

Firstly, we will discuss the research and development of new radiopharmaceuticals designed with specific properties for definite purposes.

How do these labeling problems arise? Firstly, by my recognition or that of one of my associates of the need for a specific new agent for a specific purpose. We then attempt to fulfill that need.

What are the desired characteristics for these new agents? Obviously there are "ideal" characteristics for radiopharmaceuticals for assessing the function, the structural breakdown or malfunction of an organ or the presence of a space-occupying lesion such as a tumor.

Let's look at some examples. What characteristics should a brain tumor scanning agent have?

1. It should define the presence, site, extension and nature of the lesion, at the same time cause minimal discomfort and hazard to the patient.

2. It should contain a gamma-emitting radionuclide with little or no beta emission which is undesirable and contributes internal dosage. The principle gamma energy should be between 100 and 500 keV and preferably be monoenergetic. Technetium 99m is almost ideal with the primary gamma of 140keV, a 6 hr. $T_{1/2}$ and no beta radiation. Lower energies are absorbed by the skull, higher energies pose problems in collimation.

3. The radionu^cclide should be stably bound in the agent, Na TcO₄ Tc 99m or In 113M DTPA are quite suitable.

4. The tumor/brain counts and tumor/muscle count ratios should be high so that the lesion will be differentiated from the surrounding tissue. The blood/tumor count ratio should be low so the level falls rapidly after injection, so as to minimize background radiation.

5. The radioactivity in the tumor should be high.

6. The biological and physical half-lives should be short so rescanning may be premitted and radiation dosage so minimized.

7. The distribution should be uniform throughout the body and the excretion should be rapid and not concentrated so as to cause excessive exposure in any organ or system.

8. The dose has to be larger than for other organs because of the low percentage of the administered activity which localize in the intercranial bed.

As is generally known, a frequently used brain-tumor scanning agent was human serum albumin labeled with I 131. This agent achieves a tumor/brain ratio of 30:1. Other agents used are chlormerodrin (Neohydrin) labeled with Hg 197 or Hg 203. These drugs concentrate in ratios of 22:1, also quite satisfactory. The Hg 203 is less desirable because of its physical properties, long physical $T_{\frac{1}{2}}$ (47 days), long biol. $T_{\frac{1}{2}}$ (28 days), energetic beta radiation and high irradiation of the kidneys. However the high energy photons have better bone and tissue penetration.

Presently, the most widely used radiopharmaceutical is sodium pertechnetate Tc 99m with a short half-life of 6 hrs., favorable emission of 140keV, good counting rates, and permissability of the use of large doses with minimal target organ and whole body radiation.

Instrumentation

New compounds are designed with an appropriate radionuclide in mind and the probable instrumentation that may be used.

Previously there was only the older type of scanner with a single moving probe, now we have dual probe scanners, with one above and another below the supine patient and more recently we have triple probe scanners. The usual scanner is seen in (Slide 1).

The next slide shows the organs that can be scanned. (Name the organs). (Slide 2)

The next two slides show the coordination of instrumentation, the color scanner, with the use of a radiopharmaceuticals, Selenomethionine containing radioactive Se 75. This shows the scanning in color using the "subtraction" method for imaging the pancreas Slide 3 shows the liver, and Slide 4, the pancreas.

The Anger scintillation camera is ideal for demonstrating dynamic processes such as will be seen in the later slides on the accumulation of the agent TPAC in the dog or human kidney. (Slide 5) Describe briefly in the Anger Camera.

Another example of the development of a new agent is that of Technetium 99m - Penicillamine. In 1968, we found that the Tc 99m in Tc O4 pertechnetate could be reduced by the SH group in Penicillamine to a valence of 4 and in this state would chelate with the excess Penicillamine (1). (Slide 6) Formula of Penicillamine - (Slide 1-Greece)

More recently, in our laboratory we found that TPen accumulates and concentrates in the gallbladder, serving to demonstrate the morphology of that organ and permit visualization by the Anger Camera (2). It appeared that this might be the compound we wanted for cholescintigraphy (explain) to substitute for cholecystographic

agents because these radiopaque agents used in the latter technique frequently cause toxic symptoms. TPen seems to fulfill these requirements. (3)

The next slide show a technique for creating an artificial lesion in the dog gallbladder where a simulated lesion of 1-5 cm³ is produced (Slide 7) and in the next slide () is seen the emptying of the gallbladder due to the effect of fat administration in the form of milk (Slide 8).

We have used TPen as a gallbladder - visualizing agent in comparison with oral cholecistographic agents, ^{we found} that 75% of the cases they were equivalent and in 1 case the gallbladder was not visualized by either technique, however, in another case, cholecystography revealed a cholesterol stone in the bladder which was not revealed by cholecintigraphy (3).

From our studies we conclude that TPen is a useful agent for visualizing the gallbladder and we can reveal a filling defect of almost 1 cm in size. The agent is easy to prepare and there have been no reactions.

The present trend is toward the development of new radio-pharmaceuticals containing short-lived radionuclides for organ scintigraphy, due to their favorable characteristics.

I would therefore, to present the research and development of two new agents devised in our laboratories for specific purposes, utilizing Iodine 123, Technetium ^{99m}, and Indium ^{113m}

The Development of "TAPC"

The most universally Tc ^{99m} was used to prepare Tc ^{99m}-Penicillamine-Acetazolamide Complex abbreviated as TPAC, using acetazolamide which is a renotropic, carbonic anhydrase

inhibitor and diuretic, excreted largely by tubular secretion (4). We reasoned this would yield a high target organ-to-background-ratio and produce adequate scans even in patients with severe renal disease. Several years ago the speaker found that Tc 99m per-technetate can be reduced to Tc(IV) by D-Penicillamine which is β,β -dimethyl cysteine and that the "reduced" Tc 99m was available to be chelated by other compounds (1). Moreover, the slight excess of D-Penicillamine provided a milieu to maintain the Tc(IV) at that valence.

In the preparation of TPAC, the technetium 99m was complexed with the D-Penicillamine and acetazolamide by autoclaving in a medium of 2 to 3 N HCl, neutralizing the acid and sterilizing by membrane filtration.

The TPAC was shown to be virtually all located in the cortex of the dog kidney. (Slide 9--also shows the accumulation of TPAC with time).

TPAC is only very slowly cleared from the circulation with a plasma half-time of 90 minutes but is rather retained by the kidneys yielding excellent images. (Slide 10)

The new agent has been very successfully used in cases of various renal pathology such as hydronephrosis, (Slide 11), Hyperplasia, (Slide 12), renal cell carcinoma (Slide 13) and a comparison with DTPA (Slide 14) (Ref. 5).

The Development of a New Lung Scanning Agent ^{113m}In Indium Sulfide Macroaggregate (InSMA)

The objective was to develop an agent for lung perfusion which was easy to prepare, using the long life ^{113m}In - ^{113m}In generator obviating the need for frequent shipments of Tc 99m for its

preparations. In addition, the agent was to be usable with the present instrumentation, be biodegradable, and to leave no metallic residues (6).

The agent InSMA is prepared by precipitating ^{113m}In sulfide and sulfur in the presence of gelatin as a protective colloid, then denaturing the gelatin with glutaraldehyde and dispersing to the desired particle size. The maximum number of particles were 20-25 μm in size (85%) with a range of 5 to 50 μm . One hour after injection, 92 to 96% of the injected particles were found in the lungs of mice.

The InSMA was shown by trials in mice and rabbits using many times the comparable human dose, to be entirely safe and tolerated with no adverse reactions.

Clinical trials were made on a diverse group of patients with various lung pathologies using doses of 2 mCi for lung scanning (Slides 15 & 16-same as Greeklect). The estimated radiation dose to the total body was estimated to be 0.04 rads. The lung receive about 1.2 rads, representing a tenfold reduction of the dose received from ^{131}I macroaggregated albumin. The quality of the scans obtained were compared and found to be better than with ^{131}I MAA and comparable to those with ^{99m}Tc MAA. No reactions associated with InSMA occurred.

InSMA, in contrast to other lung scanning agents containing ^{113m}In , contains no other metallic compounds which might be a nidus-forming particle, also it is biodegradable.

In summary, InSMA is an excellent perfusion lung scanning agent, easily prepared and contains a radionuclide from the long-life ^{113m}In generator making it available where ^{99m}Tc compounds are not.

The Development of ^{131}I and $^{99\text{m}}\text{Tc}$ -Labeled Metronidazoles as New Agents for Amebic Hepatic Abscess Imaging

Our objective was to develop an agent to differentiate amebic hepatic abscesses from other space-occupying lesions by gamma-ray scintigraphy. The agent chosen was Metronidazole, also known as Flagyl, a synthetic amebicide and trichomonacide which is reputed to concentrate in the pus of these abscesses (Slide 17).

The halogen-substituted Flagyl derivatives have shown high trichomonacidal action and may exhibit similar amebicidal activity.

We were able to prepare the ^{131}I -labeled Bromometronidazole by exchange with sodium iodide ^{131}I , to very high specific activity (Slide 18). A $^{99\text{m}}\text{Tc}$ -labeled Flagyl has been prepared by reducing pertechnetate with D-Penicillamine and coupling the complex to the Flagyl or its halogen substituted analogs (8). (Slide 19)

The lack of toxicity of the ^{131}I -labeled Bromometronidazole and the Tc-Pen-Flagyl has been demonstrated in laboratory animals using 2000-4000 times the comparable human dose.

Distribution studies in animals show rapid clearance by way of the liver and kidneys.

Anger camera scintiphotographs of dogs using both compounds show high liver concentration and indicate the feasibility for human use. (Slide 20)

In the future we plan to replace the ^{131}I with ^{123}I so as to increase the dose and reduce the radiation to the patient.

Cooperative studies in humans are being conducted now in areas of the world where these abscesses are endemic, such as India, Mexico, Taiwan and Thailand.

The Use of Complex Phosphate and Phosphonates Labeled
with ^{99m}Tc Technetium as Bone Scanning Agents

In recent years, there have appeared in rapid succession, various agents containing phosphates and labeled with Tc^{99m} . They are polyphosphates, phosphonates and pyrophosphates in metal complexes and they attach themselves by chemical binding to the surface of the bone crystals. Their exact chemical composition is not known.

They are easy to prepare, have a good shelf-life, can be prepared in lyophilized form as kits and produce excellent scans with both scanners and scintillation cameras.

These compounds are shown in the next slide (Slide 21). Pyrophosphates containing the P_2O_7 radical, (not shown) and the phosphonates with P-C-P bonds are more stable in vitro and in vivo than the polyphosphates. These compounds have largely replaced F 18 for many applications because of their longer half-life, ready availability, reduced radiation dose and much lower cost, being about 1/10 that of F 18 (9).

There are special cases when the clinician may choose F 18 over the Tc^{99m} phosphates provided F 18 is available from a nearby reactor or by immediate air delivery.

Radioimmunoassay

Finally, let us look at some of the directions in which Nuclear Medicine is moving. Let us consider the area of Radioimmunoassay, the subject of the recent Symposium here in Istanbul.

There assays are being used not only assess hormone production and degradation but also drug toxicity due to overdosage or therapeutic intake, and the number of assays is increasing daily. Any compilation is soon to be superceded by many new additions. In addition, competitive binding assays are being used to show the presence of fetal proteins and carcinoembryonic antigens as diagnostic tests for cancer.

The next slide illustrates the scope of the assays for some hormones and drugs. (Slide 22)

New methods of Testing for Sterility and Pyrogenicity

The rapid growth of the preparation of radiopharmaceuticals in the radiopharmacy or nuclear medical clinic has led to the development of rapid testing for sterility and pyrogenicity. While it is true that even with these methods it is not possible to complete the test before the shortest life radiopharmaceuticals are used, it is useful with moderate half-life agents and serves as a check on the quality control and techniques.

For testing sterility there is a rapid, automated system called "Bactec" which measures the bacterial contamination automatically by analyzing for the C^{14} carbon dioxide produced by the growth of bacteria. This system is shown in the following slides. ()

For testing preparation for pyrogens, a new system has been proposed.

Pyrogen^s are very large molecules of glycoproteins or glycolipoproteins, metabolites of bacteria or their dead bodies. Presently, their presence is determined by injection of the pharmaceutical into rabbits and noting the rise in rectal temperature.

The new method is to determine the presence of pyrogens by their action of clotting a blood cell lysate derived from the horseshoe crab, limulus (describe). This material is prepared by lysing the colorless amebocytes of the blood of the Limulus. Quantities as small as 0.0001 ug or less of endotoxin cause the clear solution of the lysate to form a gel. The test is extremely sensitive to endotoxins and pyrogens, correlates well with the pharmacopeial tests and, in some instances is even more sensitive. The lysate is commercially available from several U. S. companies.

Let us now review the slides (Slides 3). Again, as in the case of fast sterility tests, these may not be completed before a final preparation is administered but they can serve to test the solutions used in the final preparations as well as even some short-lived preparations. Their nature also serves to check on the adequacy of the quality control procedures.

The Development of Generators

We have discussed the use of radionuclides Tc^{99m} and In^{113m} which are produced in generators and since these are eluted or milked out, we sometimes refer to these as "cows". In the next slide we see the simplest model of the generator or "cow". (Slide)

New Developments

Who develops the newest radiopharmaceuticals? Mostly radiopharmaceutical chemists, radiopharmacists, clinical scientists and teams of these, and manufacturers, although they do make available the materials, develop them least frequently.

We try to train scientists and not leave the situation chaotic like the three witches from Shakespeare's Macbeth (Slide).

In summary, I have presented some of the recent developments in research for new specific radiopharmaceuticals, the trends and quality control procedures.