ministration should be taken into consideration. The authors illustrated this with a typical example of ^{131}I administrated patient, in which more than 90% of the gonad dose was given within the first 24 hours, but even in this case the simplified calculation by the equation (*) is a practically good approximation of the absorbed dose of the patient.

XIII. Invited Lectures by the Foreign Lecturers

Utilization of Radioisotopes in Nuclear Medicine

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Important Parameters

I only will cover those parameters which are important for radioisotopes in diagnostic applications. These are the energy of the gamma photon that is emitted, the effective half life, the decay scheme for the nuclide, the selectivity for a specific organ or tissue and production capabilities. Some information will be given for newer isotopes used in nuclear medicine. These include indium-113m, technetium-99m, xenon-133, iodine-125 and cesium-131.

Iodine-131 was the first important isotope used for scanning. This nuclide has a gamma photon energy of 360 kev, and this is still an excellent energy for diagnostic work. The energy range considered suitable for scanning with present equipment is 100 kev to 600 kev. Gamma photons with energies below 100 kev lack sufficient energy to effectively penetrate large thicknesses of tissue. Thus, anomalies deep within the body may be difficult to detect. However, for low energy species, such as cesium-131 (30 kev), or iodine-125 (27.4 kev), the use of newer devices, such as the image amplifier, produce good scans.(1)

If the energy is higher than 600 kev, collimation is poor and the trapping efficiency in the sodium iodide crystal also is low. In addition, the radiation dose to personnel may be high. For example, calcium-47 which would be useful for bone scanning work, has excellent properties other than the energy of its gamma photon. A 1.31 mev photon is too energetic and although its 4.7 day half life is attractive, calcium-47 is not widely used. (It is also a very expensive radionuclide.)

Half life must be considered, since it directly affects radiation dose. If a nuclide has a short physical half life or short biological half life, then the effective half life also is favorable. This is one of the advantages of technetium-99m, which is widely used for brain and liver scanning.(2,3) It has a short physical half life of 6 hours and the biological half life is not important. For bone studies with strontium, the biological half life is very long.(4) and if one uses strontium-85, then the effective half life is long, since the physical half life is 65 days. If possible, utilization of strontium-87m with a physical half life of 2.8 hours is highly desirable because radiation dose to the patient can be greatly reduced.(5) I believe that the trend is to utilize radioisotopes with short physical half lives.

This permits the use of large amounts of radioactivity (millicuries) in patients and still maintain reasonably low radiation to the subject. Increased number of photons leads to more useful information.

For example, indium-113m, which Dr. Wagner has described, can be used in large amounts—since its physical half life of 1.7 hours is so short that radiation damage to tissue is low. This radioisotope is obtained from a tin generator, but the product is too short lived for shipment.

There are practical limits for production of short-lived isotopes. Material of a radiopharmaceutical quality requires that pyrogenicity and sterility tests be initiated and the product shipped to the user's location. We produce ^{99m}Tc (6-hour half life) as a sterile solution and where feasible, this product is shipped to users. I think that an optimum physical half life for nuclides, other than those from a generator, would be 12-48 hours.

For diagnostic purposes, beta particles are a definite disadvantage. They contribute nothing to the information obtained and are easily absorbed by tissue resulting in excessive radiation to the patient. The absence of beta emission makes technetium-99m, indium-113m, and strontium-87m particularly attractive.

It will be difficult to find any biological system similar to the inorganic iodide-thyroid relation (inorganic iodide concentration in the thyroid is approximately 60,000 times the concentration in the remainder of the body).[6] For brain scanning, the tumor to non-tumor ratio is about 22 to 1, whether the isotope used is iodine-131, mercury-197, or technetium-99m. The spleen operates on a sequestering principle, and it is the organ which is responsible for removing degraded red cells. The specificity of the spleen for nuclides attached to damaged red cells is excellent and the compound, mercuri-hydroxypropane containing radioactive mercury, has been successfully used for scanning of the spleen.[7] Chromium labeled red cells that have been damaged by heat also have great selectivity for the spleen.

Colloidal systems, such as gold-98, or technetium sulfide are removed by the reticulo endothielial system, particularly the Kupffer cells of the liver and the distribution is extremely favorable, because particles are involved.

Selenomethionine concentrates in the pancrease, but the ratio is only 7 to 1, and there can be interference from the liver. The subtraction technique is certainly useful in pancreatic scans, but a compound with a more effective distribution is required.

Production Requirements

For many radiopharmaceutical preparations, the choice of target material is arbitrary. However, in many cases it is highly important due to specific activity requirements, volatility of the compound, or other criteria. For example, in production of iron-59, an enriched, stable iron-59 target purchased from Oak Ridge must be utilized. Production of species such as chromium-51, selenium-75, strontium-85 and several others require the use of enriched, stable material.

Strontium nitrate cannot be successfully irradiated, because radiation damage causes volatility with much loss of radioactivity. Strontium nitrate is purchased as an enriched material from ORNL, whether for ^{85}strontium or ^{87m}strontium production, but in either case, the material is converted to the carbonate prior to irradiation.

The next slide is merely a picture of the various capsules used in irradiating materials at Sterling Forest. I have several samples of such containers with me, ranging from 1/4″ diameter to 3/4″ diameter. In most cases, the capsule or container must be of high purity. Contaminating elements, such as sodium, iron or cobalt must be avoided.

During the irradiation cycle, the closure or seal must be extremely reliable to prevent contaminating water from dissolving the target or removing it from the capsule. All capsules irradiated in the Sterling Forest reactor are carefully tested after sealing and prior to irradiation. This technique involves a test procedure in vacuum and under water.

Processing and Quality Assurance

All operations are carried out remotely, using Model 8 master slave manipulators. The capsules are opened in one hot cell, and these operations are facilitated by grooving the small capsules or uutilizing a cutting procedure for the large containers.

Subsequent processing steps involving dissolution, extraction, ion exchange, distillation and other chemical steps are carried out remotely. These operations produce a radiochemical grade product. All materials used in isotope production are pyrogen-free, but sterility and pyrogenicity tests are done only on radiopharmaceutical products.

Duplicate samples are taken for both qualitative and quantitative evaluation. Such tests on radiochemical products include determination of radioactivity, presence of contaminants, total solids, pH and others as required. For a radiopharmaceutical product, additional tests include chromatograms, biological evaluations (where required), pyrogenicity and sterility tests. No material or product sent from Sterling Forest is used, unless the pyrogenic tests are satisfactory. (Sterility tests cannot be completed before use for short lived material, since such tests require 7 days.)

Newer Radioisotopes

Tin-Indium Generators

Dr. Wagner has already indicated to you the many investigations he and his group at Johns Hopkins carry out with indium-113m. Reprints of this work are available here.[8,9,10] This nuclide is highly satisfactory for several reasons:

1. Its 1.7 hour half life minimizes radiation to the patient, and a gamma photon emission of 390 kev makes it superior for scanning.
2. It can be successfully eluted from a generator containing its parent, tin-113.
3. Since the parent is long-lived—119 days—the cost of indium is very low per patient dose. One unit would be suitable for many months eliminating weekly deliveries as required for the molybdenum-technetium generator.

Our results with the generator have been excellent. Greater than 90% of the available indium-113 can be recovered in 5 or 6 ml of 0.1 N HCl.

We have developed a rapid, effective test for tin contamination (breakthrough) of the indium product. This test uses the sensitive color reaction between tin in acid solution and hemotoxylin to form a lake. The absence of color indicates that the product (eluent) contains less than 0.003% tin-113 in indium-113m.

Before being shipped, each generator is eluted five times and each eluent checked for tin breakthrough and the first and fifth elutions checked for pyrogens. Both tests must be satisfactory before the generator is shipped.

Indium-113m also has been used successfully for production of a colloid suitable for liver scanning. Again, only a few routine chemical steps are required and the product can be sterilized by autoclaving.

When indium-113m is injected at pH 4, it remains in the bloodstream for several hours. Because of this, blood pool scanning can be satisfactorily done and the heart and placenta have been studied. An advantage in placental scanning is that indium does not concentrate in the bladder, while pertechnetate (as albumin) does. This interference may make diagnosis of placenta praevia more difficult.

Technitium-99m

The usual way of obtaining this radioisotope is elution of a molybdenum generator. Excellent separations are possible since the molybdate has a valence (or charge) of 2 and is held on the resin. The technetium as pertechnetate with a charge of 1 can be recovered in isotonic saline. A long-lived cobalt-57 (267 days) has found wide use as a standard for ^{99m}Tc. The advantages of the ^{99m}Tc are primarily physical ones: a 6-hour half life and a gamma photon of 140 kev.

Although ^{99m}Tc can be obtained from either a sterile or non-sterile generator, it is also available as a sterile, pyrogen-free system ready for injection.

It is widely used for brain scanning.[2] Although large amounts of activity (15,000 microcuries) are used, the radiation dose to the patient is only 1/5 to 1/50 of that resulting when 700 microcuries of mercury-197 or mercury-203 is used.

It is easy to convert the technetium into a sterile, pyrogen-free technetium sulfide suitable for injection. Since a colloidal system is involved, the liver will remove the

material and excellent liver scans can be obtained.[3] The nuclide, as a colloid, also has been used for zone marrow scans.

Xenon-133

A recent development at Sterling Forest permits production of vials with Xenon-133 dissolved in saline with no vapor space ppresent. This has found wide acceptance in the United States, since there is no transfer of activity from the liquid to the gaseous state. Xenon has been widely used for regional cerebral blood flow, pulmonary studies, including perfusion and ventilation work, extremity blood flow and intramuscle blood flow.[11,12,13,14]

The advantage of Xenon-133 are tis inertness, both chemically and physiologically, and its short biological half life. Much work has been done using reliable, inexpensive counters and very little hazard is involved in handling this isotope.

Iodine-125

Iodine-125 is the longest half-life radioisotope of that element, if iodine-129 with a half life of 10^7 years is considered stable. Iodine-125 has several advantages over iodine-131; no beta particles, lower energy radiation, and longer useful life because of the physical half life of 60 days.[15] Although its physical half life is 7.5 times that of iodine-131, the radiation dose to tissue is only one-half that of iodine-131 for equal microcurie amounts. The lower energy of the iodine-125 radiation reduces the shielding requirements and makes possible the utilization of small, light weight detectors.

Iodine-125 has a half value layer of 2.5 cm for tissue. However, this is an advantage in surface scans of the thyroid or liver, since the "soft" radiation from underlying tissue is absorbed while the strong gamma photons from iodine-131 pass through.[16] When optimal collimators are used, smaller nodules on the surface of the liver can be detected with iodine-125 than with iodine-131. Such collimators are two to three times more efficient than units designed for iodine-131.[17]

Porath and colleagues have studied the physical and clinical advantages when using iodine-125 for thyroid diagnosis.[18,19]

Production:

Iodine-125 decays by electron capture and the principal radiations are a 27 kev x-ray and a 35 kev gamma photon of tellurium.[15] The production reaction for neutron bombardment is:

$$^{124}\mathrm{Xe} + \mathrm{n} \longrightarrow {}^{125}\mathrm{Xe} \xrightarrow{\mathrm{ec}} {}^{125}\mathrm{I}$$

Although the abundance of Xenon-124 is only 0.096% of natural xenon, the cross-section of about 200 barns is high, therefore, large quantities of iodine-125 can be produced in nuclear reactors.

Short-Lived Radionuclides

The development of radiopharmaceuticals labeled with short-lived nuclides will be an area of increasing importance.

Several radioisotopes can easily be produced in nuclear reactors from enriched stable isotopes. These include strontium-87m, zinc-69m, high specific activity copper-64, palladium-109, promethium-149, samarium-153, ytterbium-175, osmium-193 andplatinum-195. The obvious advantage of all these species in diagnostic work is short physical half-life, which minimizes radiation damage to tissue. All of the enriched target isotopes are available from Oak Ridge National Laboratory with irradiations carried out in our reactor at Sterling Forest.

Strontium and calcium compounds localize in actively metabolic bone and bone tumors. Bauer and Ray have considered the kinetics of strontium metabolism in man.[20] There are several radioisotopes of both elements. Calcium-45, a pure beta emitter, has a long physical half-life and is not suitable for scanning. Calcium-47, although having a suitable half-life (4.7 days), is extremely costly and emits a 1.3 mev gamma ray. Strontium-85 does not emit beta particles, but it has a long physical half life (64 days). The biologic half life of strontium is extremely long, so the effective half life is the same as the physical half life, precluding repetitive applications to evaluate therapeutic treatment.

Charkes and Sklaroff carried out bone scans in 90 patients utilizing strontium-85 and report that photoscans can detect early

metastatic bone cancer.[21]

Myers pointed out the advantages of using strontium-87m.[5] Charkes and co-workers used strontium-87m and concluded that it can be used to detect metastatic cancer to bone even prior to observable roentgenographic changes. Strontium-87m should be particularly useful in evaluating non-malignant disorders of bone including those of children.[4] Meckelnburg concluded that studies in children can be performed without undue exposure.[22]

Wagner and associates have worked with reactor produced strontium-87m for several months. They measured the rate of accumulation of radioactive strontium in the epiphyses and metaphyses of growing bones. A paper, "Accumulation of Strontium-87m as a Parameter of Skeletal Growth", was presented at the Society of Nuclear Medicine Meeting in June 1966.[23] Scanning for tumor of the bone using ^{87m}Sr has been done.[24]

Cesium-137—Barium-137m Generator

Although the ^{137m}Ba has an extremely short half life (2.6 min.), it may find much use for studying vascular dynamics in nuclear medicine.[25] Multimillicurie amounts can be given with very little radiation dose to the patient and repeat studies can be safely done. Determination of circulation time and cardiac output are relatively simple.

Cesium-131

Cesium, element number 55, is one of the alkali metals and its chemistry (valence of plus one) is similar to that of sodium, potassium and rubidium. Each of these elements has radionuclides with certain disadvantages, and cesium apparently has a greater selectivity for muscle. Only three radioisotopes of cesium can be produced in large quantities: cesium-134, cesium-137 and cesium-131. The first two are long-lived nuclides (2.1 years and 30 years, respectively) and both emit beta particles or high energy gammas. These are critical disadvages for diagnostic applications in medicine and leave cesium-131 as the only really useful radioisotope of cesium.

Cesium-131 has been used in studying myocardial infarcts by Carr.[26] Charkes and colleagues studied 20 patients with a variety of neoplastic diseases using 0.134 to 2.2 mc of cesium-131 acetate given intravenously.[27] Cesium acetate has also been used experimentally for detection of cancer of the breast, cervical nodes, and lymphomas. The rationale is the greater alkali metal con tent of tumors.[28] Scintillation scanning in such cases may be started 10 minutes to 3 hours following intravenous injection.

I have presented some information on important factors for uutilization of radioisotopes in nuclear medicine. I am certain that many new important nuclides will be developed and used in the next several years.

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