Advances in Nuclear Medicine Pose New Dosimetry Problems

Radiopharmaceutical Dosimetry Symposium Explores New Internal Dose Estimates

The questions that dosimetrists confront continue to expand as the field of nuclear medicine advances into more sophisticated imaging modalities with new radiopharmaceuticals. Last November, 130 scientists from nine countries gathered in Oak Ridge, TN, to discuss these questions at the Fourth International Radiopharmaceutical Dosimetry Symposium.

Over 50 speakers presented scientific papers on new models for calculating internal dose estimates, biokinetic and biodistribution data from new radiopharmaceuticals, and new quantitation methods using single-photon emission computed tomography (SPECT) and positron emission computed tomography (PET).

The four-day meeting also covered specific dosimetric problems encountered in different areas of nuclear medicine, including neuroreceptor-binding ligands, pediatric patients, renal pathology, variations in absorbed dose in different disease states, and the influence of radioactive contaminants.

Attendees also discussed dosimetry requirements of the US Food and Drug Administration (FDA) for the agency's approval of new radiopharmaceuticals, and ways to get clinical investigators to better understand the need for acquiring and publishing dosimetry data.

"Dosimetry's real goal is the clarification of the relationships between the interactions of radiation with matter and the biologic effects," said Roger J. Cloutier of the Radiopharmaceutical Internal Dose Information Center at the Oak Ridge Associated Universities (ORAU), which hosted and cosponsored the symposium. [The meeting was also cosponsored by the FDA and the US Department of Energy (DOE), and was supported by several radiopharmaceutical firms.]

Cellular Versus Organ Approach

S. James Adelstein, MD, of Harvard Medical School, presented data from estimates of absorbed dose using a cellular approach, or "microdosimetry." Traditional dosimetry assumes homogeneous distribution of radionuclides in organs of interest, while presuming that the ranges of particulate radiations are large relative to typical cell diameters, said Dr. Adelstein. "With the increasing utilization of intracellular agents such as thallium-201, however, it has become necessary to examine the microscopic distribution of energy at the cellular level," he explained.

There is an increasing need, continued Dr. Adelstein, to take into account the microscopic distribution of dose on the cellular level as radionuclides distributed in cells become more commonplace—especially if the decay involves electron capture or internal conversion. "As radiotracers are developed for the measurement of intracellular functions, these factors should be given greater consideration," he added.

Investigators presented eight papers on monoclonal antibodies, an area rife with microdosimetry problems. "For radiotherapy to be effective, one must be able to estimate the absorbed dose to both tumor cells and normal tissues in the body," said Darrell R. Fisher, of Batelle Pacific Northwest Laboratories. "Conventional methods for estimating absorbed doses and specific absorbed fractions for radiopharmaceuticals, however, do not apply to alpha emitters because of their short range and the resultant large variations in the local distribution of energy at the cellular level," he noted.

Ultrashort-Lived Radionuclides

The advent of ultrashort-lived radionuclide generators creates novel dosimetry concerns. "The half-life of the daughter is usually sufficiently short that it does not contribute significantly to the radiation burden," said H. William Strauss, MD, of Massachusetts General Hospital. "The half-life of the parent and associated radiocontaminants or the progeny, on the other hand, may contribute substantially to the patient's radiation burden," he added.

Carol S. Marcus, PhD, MD, of the University of California at Los Angeles (UCLA), noted that with the ultrashort-lived radionuclides there is no accurate method of determining how much activity is administered to the patient. "I would feel much more comfortable if there were an online dosimeter on these generators," she said. Prof. Dr. Gerhard F. Fueger, of the University of Graz Hospital in Austria, pointed out that while the generators deliver a small total dose, "the dose rate seems to be quite high."

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A group from the Texas A&M University and the King Faisal Specialist Hospital in Riyadh, Saudi Arabia, has developed a dosimetric model to describe the circulatory system. "The need for this model exists because of the increasing number of radiopharmaceuticals which are confined primarily to the blood, have short half-lives, and irradiate the body as they move through the system," explained the investigators.

Positron Emitters

Several papers documented radiation absorbed dose estimates for positron emitters such as rubidium-82, copper-64, and nitrogen-13. "Because much of the future of nuclear medicine will deal with metabolism, the field of radiopharmaceutical dosimetry will have to follow," said Mr. Cloutier.

In line with this prediction, a group from the University of Chicago presented a simple dynamic model for calculating radiation absorbed dose to the bladder wall, "an important factor to consider in designing experimental procedures for rapidly excreted radiopharmaceuticals such as fluorine-18 2-fluoro-deoxyglucose."

Roger Cloutier joined the Oak Ridge Associated Universities in 1959, and is also a former chairman of the SNM Medical Internal Radiation Dose (MIRD) Committee.

Evelyn E. Watson, program manager of the ORAU Radiopharmaceutical Internal Dose Information Center, discussed the influence of contaminants on radiation dose estimates. "Several popular radiopharmaceuticals contain low levels of radioactive contaminants, which increase the patient's radiation dose without any increased benefit and, in some cases, with a decrease in image quality," said Ms. Watson. She presented dose estimates, "assuming reasonable contaminant levels," for iodine-123, indium-111, thallium-201, technetium-99m, iridium-191m, rubidium-81, and gold-195m.

Marshall Islands Fallout

A. Bertrand Brill, MD, PhD, of Brookhaven National Laboratory in Upton, NY, presented data comparing internal versus external irradiation of the thyroid. From a group of 82 Marshall Islands children who were exposed to internal and external radiation of the thyroid, at a level of 1,400 rad, the Brookhaven group found that "dose from internal irradiation of the thyroid with radioiodine produces several times less thyroid cancer than does the same dose of radiation given externally." The children were accidentally exposed to fallout shortly after a nuclear weapons test in the western Pacific Ocean on March 1, 1954.

In his summary of the meeting highlights, Mr. Cloutier mentioned priorities for future work. "The dosimetry of radiopharmaceuticals in pregnant women and children needs to be of high priority because of the long life expectancy of a fetus or child," he said. He also warned, however, that failure to use a radionuclide study could lead to a shortened life expectancy because of a misdiagnosis. "Radiation dose is frequently the key to whether a diagnostic test is performed, and it behooves us to be careful with our dosimetry."

Dr. Marcus said that research needs to be directed toward the question of the effects of Auger and Coster-Krönig electrons on deoxyribonucleic acid (DNA). "I'd really like to know a little more about molecular radiobiology and what the microdosimetry means," she said.

James S. Robertson, MD, PhD, chairman of The Society of Nuclear Medicine's (SNM) Medical Internal Radiation Dose (MIRD) Committee, said that this committee's activities in the past have concentrated on the average dose to an organ. "I think we'll probably move toward dose estimates on the centimeter or millimeter level that are affected by beta and alpha particles," he said, adding that this is not microdosimetry, but rather small-scale or "millidosimetry."

"We still lack data on distribution and retention," said Mr. Cloutier. "I believe that several centers need to be established for the sole purpose of collecting this data," he added. "Since our last symposium, the positron camera and SPECT have come into their own. In the past, the instrumentation for this type of data collection was not available. It is available today." [The previous radiopharmaceutical dosimetry symposia were held in 1969, 1976, and 1980.]

Concerted Data Collection Needed

Katherine Lathrop, who was chairwoman of the MIRD Committee from 1977–1985, said that serious thought should be given to the funding of these data acquisition centers.

According to Michael G. Stabin, of the ORAU Radiopharmaceutical Internal Dose Information Center, however, a more practical and efficient approach might be to organize a group of dosimetry experts who could coordinate their efforts with investigators who are already acquiring this data. "This group of dosimetrists could work with investigators, teach them how to quantitate their data, and provide a mechanism for

centralizing this information," he explained.

What the FDA Needs

Neil Abel, a reviewing pharmacist with the FDA's Center for Drugs and Biologics, explained the agency's dosimetry requirements for the review and approval of new radiopharmaceuticals. "Up to this time, it has been rare for radiopharmaceuticals to exhibit any toxicity other than that produced by the radiation hazards; therefore, the evaluation of the safety of these products is sometimes restricted to the radiation dose alone," explained Mr. Abel. (The FDA is currently reevaluating the criteria for preclinical data required for initiating a study.)

The most common errors or omissions in investigational new drug (IND) submissions, according to Mr. Abel, include: not listing all contaminants; not accounting for 100% distribution in preclinical studies; not utilizing the worst case situation; using calculation methods that lead to a lower radiation dose estimate; listing the radiation dose in rads/μCi instead of rads/dose administered; and not listing assumptions used in calculations. Mr. Abel noted that some investigators list activity/unit in inconsistent ways, such as per gram of organ, per gram of body weight, per gram of organ in relation to body weight, "per gram with no explanation, and per anything without a step-by-step explanation of how this per unit of activity was selected."

The most disconcerting problem, said Mr. Abel, is when IND sponsors do not adequately explain their methods, assumptions, and calculations. "In many cases where an FDA reviewer cannot follow the pathway of reasoning used by the IND sponsor, it results in the study being delayed or stopped until further explanation is received," he added.

Mr. Abel said that the FDA also needs to see this logic behind the methods and results published in scientific journals. "I find it very disturbing to read an article that does not clearly explain how the investigators came to their results. I would ask publishers and authors to at least allow me to understand how they got from A to Z," he said.

Publishing in Scientific Journals

Getting dosimetry results published is extremely important, noted Mr. Cloutier, who urged authors to include this information in their manuscripts. "I have heard of cases where authors are asked to shorten their manuscripts, and they elect to delete the dosimetry. I would urge them to keep the dosimetry and find something else to delete," he said.

Concerns Over Worker Exposure

Although the aim of medical dosimetrists is to calculate radiation absorbed dose estimates in patients, Allen Brodsky, ScD, a health physicist for the US Nuclear Regulatory Commission (NRC), pointed out his concern over worker exposure in nuclear medicine procedures. "The last real study of exposure to hospital workers who administer radionuclides was published ten years ago," said Dr. Brodsky, who added that he was concerned about worker exposure to new radiopharmaceuticals and short-lived radionuclides.

Dr. Marcus of UCLA said that Dr. Brodsky had an "excellent point," and other attendees agreed that worker exposure should be given serious thought, particularly for workers who handle short-lived radionuclide generators and radiochemists who prepare fluorine-18 deoxyglucose.

In addition to new approaches to dosimetry, Mr. Cloutier noted that conventional dosimetry also moved ahead at this symposium. "Each improvement we make in the anthropomorphic model or kinetics moves us closer to the right answer. But remember also that the model gives us just the dose to the model, and only suggests the possible dose to the patient," he said.

The ORAU Radiopharmaceutical Internal Dose Information Center staff, (left to right) Audrey T. Schlafke-Stelson, Evelyn E. Watson, and Michael G. Stabin, which received an award for excellence last year from the Federal Laboratory Consortium, organizes international symposia on radiopharmaceutical dose calculation.

Dr. Robertson, who is also director of the DOE Human Health and Assessments Division, explained that his group promotes the development of new instrumentation and radiopharmaceuticals, and dosimetry "is at the heart of the utilization of new procedures that will result from these developments."

[Unlike this meeting, which used both conventional and the international system (SI) radiation units, the next symposium will use only SI (sievert, gray, and becquerel) units. For information on proceedings of the Fourth International Radiopharmaceutical Dosimetry Symposium, contact: Evelyn E. Watson, Radiopharmaceutical Internal Dose Information Center, Oak Ridge Associated Universities, PO Box 117, Oak Ridge, TN 37831-0117 (615) 576-3448.]

Linda E. Ketchum