COMMENTS

LINES FROM THE PRESIDENT: RADIODOGnostics, DRUGS, AND THE FDA

The date is some time in early October, 1987. Clinical trials of a new iodine-123-labeled brain perfusion agent began in the summer of 1981, more than six years ago. As of today, not one iodine-123- or technetium-99m-labeled tracer has been approved by the United States (US) Food and Drug Administration (FDA) for imaging brain perfusion, metabolism, or receptor function. At this point, the US may be the only nation in the world that does not allow physicians to order state-of-the-art brain scans except as investigational studies.

In 1984, the isonitriles became the first technetium-99m-labeled complex to successfully image the human heart. Since that time, at least three generations of isonitriles have been tested in humans, each with progressively superior biologic characteristics. The isonitrile complex can be altered by an almost limitless number of chemical twists and turns. But each time the chemical form is changed, each time the complex is altered in the slightest, studies of toxicity, dosimetry, biodistribution, and safety—as expensive and exhaustive as for the first isonitrile—must be performed if the new complex is to be tested clinically in the US.

If we are not careful, we may see the end of the commercial development of radiodiagnosticstics within our professional lifetimes. The expense of bringing these products to market may soon exceed the revenues they generate. Radiodiagnosticstics are not as profitable as pharmaceuticals since they are used only once or twice in a patient's lifetime. The obvious big winners—technetium-99m-labeled myocardial and brain perfusion agents, tumor agents, and perhaps one or two others—are being developed today. The vast number of radiodiagnosticstics that are being synthesized and tested throughout the research community—as exciting as these tracers are—have increasingly limited appeal to industry because commercial development costs are too great and large-scale application is too problematic.

The Society of Nuclear Medicine (SNM), along with its sister organizations, has championed increased efficiencies within the FDA and more rapid turn-around times for...

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ity Hospital in Basel and Solco Basle Ltd., Switzerland, concluded that bone marrow scintigraphy with technetium-99m nanocolloid is as effective as indium-111 leukocyte imaging for detecting osteomyelitis, and that the bone marrow procedure offers some advantages over the leukocyte scan (p.99). This group calls bone marrow scintigraphy "the poor man's inflammation scan." Is nanocolloid better than leukocytes?

Three groups reported on NMR investigation of the bone marrow system. Drs. H. Stettmeier, R. Bauer, and colleagues at the Technical University of Munich, concluded that NMR can show bone involvement in metastatic cancer sooner than scintigraphic studies of bone or bone marrow, which do not detect small cold lesions (p.62). Is NMR better than bone marrow scintigraphy?

Drs. A. Widding and Prof. Dr. med. Harald Schicha et al., of the University of Cologne, FRG, showed that, in patients with malignant lymphoma or plasmocytoma, NMR signals do not always correspond to tumorous involvement of the bone marrow (Fig. 3); in some cases, these pathologic NMR signals may be caused by compensatory hematopoietic proliferation (p.62).

There is no best diagnostic method for bone/joint diseases. Specific clinical demands require different approaches and, in some cases, complementary imaging procedures provide the best answers.

Therapy

Ethiodol is retained in hepatocellular carcinoma longer than in normal liver tissue. Dr. Matthew L. Thakur, PhD, and colleagues at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania, US, proposed treating liver tumors with 10–25 mCi (370–930 MBq) of iodine-131 ethiodol, and reported that the tumor receives about 8,000-rad (80-Gy) dose (p.15). This group demonstrated that the cold spot on a conventional colloid scan is filled in after iodine-131 ethiodol injection; 90
drug approvals. The Inter-Society Commission on Radiopharmaceuticals, under the chairmanship of Alex Gottschalk, MD, has made a great deal of progress toward formulating recommendations to improve the FDA's response to the nuclear medicine community. The FDA has expressed its willingness to implement as many of these recommendations as it can; since our meeting last year with the FDA commissioner, there have been indications of some progress (see Newsline, Jan. 1987, pp. 1–11). The SNM and its sister organizations must continue to work with the FDA to ensure that technology transfer to clinical practice occurs as rapidly as possible within the limits of FDA regulations and without compromising patient safety.

The fact remains that rapid turn-around of radiodiagnostic new drug applications (NDAs) does little good if no NDAs are being filed—a tragic outcome given the plethora of radiotracers that are being investigated in the field today. The basic problem we face, of course, is that our radiodiagnostics are treated under a set of regulations that have been formulated to test safety in pharmaceuticals with pharmacologic effects and toxicities that may be orders of magnitude greater than our radiotracers. We need less stringent regulations so that we can sift through the vast numbers of radiodiagnostics available to us and narrow our search to the most promising. By narrowing the field and obtaining at least preliminary data on utility, we could far more efficiently determine the radiodiagnostics most suitable for commercialization.

We must streamline the process by simplifying the testing of radiodiagnostics once one compound in a class has undergone the scrutiny of existing FDA regulations. Once one compound in the isonitrile family, for example, has undergone the extensive toxicology, dosimetry, and safety studies required for a Phase I investigational new drug (IND) study, subsequent isonitriles no longer need testing in two animal species and toxicology requirements could be substantially reduced. Furthermore, the supervision of the subsequent studies should be in the hands of the institutional radioactive drug research committees (RDRCs). These hospital-based review committees operate as arms of the FDA, and are fully qualified to evaluate the adequacy of the INDs for subsequent radiodiagnostics after the first compound has passed muster following the traditional pathway. The FDA would be saved reams of paperwork, and researchers in the field could more effectively search out the most promising analogues within a class of radiodiagnostics.

If we are to successfully argue for a streamlined screening procedure for radiodiagnostics, we must be able to carefully document the changes in FDA regulations that would accomplish our goals. These changes must stand the scrutiny of the academic as well as the regulatory community. It seems likely that we will have to press for changes in the regulatory process in the legislative, rather than the regulatory, arena. Ultimately, the US Congress will decide whether the radiodiagnostics and radiotracers that excite all of us at our scientific meetings will ever see the light of day in routine clinical use.

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hours later, the agent is cleared from the normal liver but not from the hepatoma.

Prof. Dr. med. Helmut Röser and associates at the University of Berne, Switzerland, presented data showing that hyperthyroidism in autonomously functioning thyroid nodules is nonlinearly dependent on size (p.64).

This last paper that I will mention is truly one of the highlights of this congress. The therapeutic effects of an iodine-131 monoclonal antibody, which has a tumor uptake of 50% and a tumor half-life of five days, was evaluated for the treatment of human mammary carcinoma xenografts in nude mice by Dr. Reingard Senekowitsch et al. of the Technical University of Munich, FRG (p.52). A 15-MBq (0.4-mCi) dose of this labeled antibody, delivering an estimated 50-Gy (5,000-rad) dose to the tumor, resulted in a “dramatic” reduction in tumor size; mice treated with the same amount of unlabeled antibody, with the same amount of radioactivity from an iodine-131-labeled unspecific antibody, and with saline did not show a comparable reduction in tumor size (Fig. 4).

In histologic sections of tumor tissue obtained seven to 42 days after treatment, marked areas of necrosis were seen; by day 42, most of the tissue was identified as mouse connective tissue. No signs of damage to the bone marrow were observed. These exciting results indicate the possibility that therapy with a specific iodine-131-labeled monoclonal antibody could destroy human tumors without any side effects.

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