TEACHING EDITORIAL

Development of Nonionic Gamma-Emitting Radiopharmaceuticals for Myocardial Imaging

The establishment over the past four years of thallium-201 myocardial scanning as a clinically accepted procedure has been an important advance in nuclear imaging. In concert with the development of gated-blood pool and infarct-avid imaging, nuclear techniques are now available for studying both morphologic and functional aspects of a wide range of heart diseases, the leading cause of death in the United States. In spite of its pivotal role in making myocardial imaging a clinical reality, Tl-201 has significant shortcomings related to its high cost and suboptimal imaging properties. These deficiencies have naturally stimulated a continued interest in the development of alternative myocardial agents. In view of the accepted clinical utility of Tl-201 myocardial imaging, it would seem that radiopharmaceutical development programs should not be philosophically restricted only to replacing Tl-201, but should also be directed at providing agents with alternative photon energies for combined studies (e.g., injections at rest and stress during a single clinic visit) and alternative mechanisms of localization to allow measurement of myocardial parameters other than perfusion.

The area that holds perhaps the greatest promise in the development of nonionic myocardial tracers is labeled fatty acids, where modest clinical experience is already available. Evans and coworkers, in the mid- and late 1960's, successfully iodinated oleic acid across the double bond, and demonstrated that it could be used to visualize the myocardium and detect myocardial infarction (*1,2*). These initial efforts were limited by low specific activities, the relatively poor imaging properties of I-131, and limitations in administered activity dictated by radiation dosimetry. Oleic acid and other fatty acids radioiodine-labeled across the double bond are biologically distinguishable from their respective parent compounds and demonstrate reduced myocardial extraction.

In the 10 years following Evans' original report (*1*), a number of investigators proposed other fatty acid labels, including fluorine-18, carbon-11, iodine-123, and technetium-99m (*3–5*). Of the proposed agents in this frame, carbon-11 palmitic acid has been successfully used for clinical myocardial imaging in conjunction with positron tomography systems. Although C-11 palmitic acid will never become generally available, the pharmacokinetics of this and other C-11-labeled products have become standards of comparison for gamma-emitter labeled agents.

In 1975 Robinson and Lee made a discovery of major importance: radioiodine can be introduced in the terminal (ω) position of a fatty acid without significantly altering its predilection for the heart (*6*). Terminally labeled 16-iodo-9-hexadecenoic acid has been shown by Poe and coworkers to have an initial myocardial distribution proportional to blood flow (*7*). Its specific myocardial extraction and blood clearance half time of 1.7 min closely resembles potassium-43 distribution. The labeling process is compatible with the use of I-123, allowing relatively large doses to be administered (*6*). Poe and coworkers were able to obtain satisfactory high count density myocardial images in as little as 2–3 min per view in a small pilot study using I-123 hexadecenoic acid (*8*).

The major disadvantages of the terminally iodinated fatty acids are their rapid myocardial metabolism and the resulting high levels of blood background radioactivity. Machulla and coworkers confirmed many of the pharmacokinetic observations of Poe and Robinson using 17-iodo-heptadecanoic acid and showed that essentially all the blood radioactivity is due to free iodide (*9*). The source of the free iodide is probably not due to deiodination of the intact parent compound, but rather a result of rapid metabolism leading to unstable metabolites such as iodoacetate, which then deiodinate (*7*).

With several agents now demonstrating excellent initial pharmacokinetics and carrying I-123 with its superior imaging properties, slowing of the metabolic turnover rate may be the key to the successful application of fatty acids for myocardial imaging. An obvious method of slowing the metabolism is to synthesize substituted branch-chained fatty acids that will resist β-oxidation. Another possibility is the attachment of radioiodine to an ω-phenyl-substituted fatty acid. This latter approach will not necessarily slow the metabolism, but will result in metabolites that are more stable towards deiodination. We are currently pursuing both of these methodologies in our laboratory.

At this point it is interesting to offer two speculations regarding the potential for unique new diagnostic approaches with labeled fatty acids. With the ionic tracers, the primary interest has been in the uptake patterns based primarily on perfusion. As Poe and coworkers have already indicated in their initial clinical experience, fatty acid release patterns, reflecting regional myocardial metabolism, may be of equal or greater interest (*8*). If agents with suitable metabolic behavior can be developed, it should be possible to detect areas of stress-induced ischemia by injecting the tracer at rest and determining which areas differentially retain radioactivity when the heart is subjected to stress. This approach would provide a "hot-spot" technique for demonstrating ischemia. Secondly, the recent work of Bilheimer and coworkers demonstrates increased fatty acid accumulation around the border zone of acute myocardial infarcts as early as 6 hr post insult (*10*). It may be possible to utilize non-metabolizable radioiodinated fatty acids to evaluate the effects of pharmacologic interventions on the extent of recovery of myocardial cells making up the peripheral area surrounding the infarct.

A newer area that has not received the attention accorded the radiolabeled fatty acids is the development of agents that bind to specific cardiac receptor sites. This approach is exemplified by the work of Jiang and coworkers presented in this issue of *The Journal of Nuclear Medicine* (*11*). Their goal was to develop radioiodinated derivatives of cardioselective β-adrenoreceptor blocking agents. Previous experience in our laboratory in developing agents for other purposes using this rationale suggests that the problems facing development in this area are even greater than for the fatty acids.

In 1974, Aurbach and coworkers demonstrated with a radioiodinated β-blocking agent that β receptors show high affinity but are few in number, compared with catechol receptor sites, and are also highly stereospecific (*12*). In imaging studies, β-receptor sites in the heart will be readily saturated (with the "overflow" activity distributed as background to nontarget organs) if high specific activity radiotracers are not used. The same problem has been encountered when trying to localize radiolabeled estrogens and androgens in their respective target tissues and will undoubtedly pertain to the whole field of imaging via hormone-receptor binding.

In addition to the specific activity problem, all of the blockers studied by Jiang and coworkers are small molecules. Labeling such small molecules with radioiodine or radioactive metallic ions may cause steric hindrance or otherwise alter the native functional groups, thus modifying the usual biologic behavior. This problem has also been encountered repeatedly in radiopharmaceutical development and has indeed been a major problem in our own efforts at developing radiolabeled enzyme inhibitors for cardiac and adrenal applications. The introduction of a radionuclide carrying group, such as the (3-iodo-4-hydroxy)-phenethyl moiety in Jiang's work, is a potential solution to this problem. In view of the work by Aurbach and colleagues, who showed that hydroxybenzylpindolol is a potent cardioselective β-blocker, the present authors would have perhaps obtained better results had they used β,β-dimethyltyramine as their radionuclide carrying group. Nonetheless, the heart:blood and heart:lung ratios of the practolol derivative are indeed promising.

It should be noted, however, that a radionuclide-carrying group itself can interfere with functional groups. In our laboratory, when a radionuclide-carrying group is used, the intermediate compound (small molecule + radionuclide-carrying group) is routinely evaluated through tritium or C-14 distribution studies. If these distribution studies do not demonstrate specificity of uptake, it is highly unlikely that further insult to the molecule through gamma labeling will produce a useful radiopharmaceutical. There are pitfalls in our approach that

must also be kept in mind: carbon-14 labeled products generally have low specific activities that can lead to spuriously poor results, and it is possible for tritium to exchange with hydrogen in soft tissues.

Undoubtedly, the general area of receptor site binding will see further investigations. The effort will require refining and extending structure-distribution studies in a manner similar to the structure-activity studies of medicinal chemistry, and the development of techniques to obtain the highest possible specific activities. B. R. Baker's classic monograph *"Design of Active Site Directed Irreversible Enzyme Inhibitors"* (*13*) presents a modus operandi for introducing alkylating groups into bulk tolerance regions of enzyme inhibitors. This type of analysis could also be useful to radiopharmaceutical chemists for determining where to best incorporate a radiolabel into a bioactive compound. The need for increasingly sophisticated methods of assessing chemical and radiochemical purity is also clearly apparent, and the reader should note that Jiang and coworkers used at least two chromatographic systems to evaluate each product.

Although several new radiopharmaceuticals offer promise for myocardial imaging, a closing word of caution is necessary. The clinical efficacy of each new agent must be independently determined by systematic clinical trial. Theoretical mechanisms of localization and apparent similarity to previous agents cannot be used alone to determine the clinical significance of observed imaging patterns. The utility of thallium-201 was established through correlation with other procedures both scintigraphic and nonscintigraphic. The same type of correlative work will be required with any new myocardial agent.

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