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EDITORIAL

Are Animal Scanners Really Necessary for PET?

For nuclear medicine not only to survive, but also to prosper, it must constantly seek out new radiopharmaceuticals that yield more information about tissue physiology than can be obtained by any other imaging modality. This process of radiopharmaceutical development is difficult, time-consuming and hindered by the lack of suitable instrumentation to facilitate evaluation of tracer pharmacokinetics (*1,2*).

Novel pharmaceuticals are routinely being developed at considerable cost. Human tumor lines have been successfully replicated in animals. Both these initiatives benefit from imaging procedures that can determine the interaction of drugs on regional metabolism, blood flow, and receptor occupancy and the extent of therapeutic intervention (*3*). Hence, radiopharmaceutical imaging is poised to play an even greater role in diagnosis, characterization and management of disease and dysfunction.

Two steps are entailed in the development of new radiopharmaceuticals that foster this approach: (1) synthesis and purification of a radiopharmaceutical, followed by (2) biodistribution and imaging studies to determine regional localization of the tracer. The easiest developmental path for new agents is by PET, since these agents are directly compatible with natural and man-made biomolecules. Incorporation of nuclides such as ^{13}N, ^{11}C and ^{18}F, is usually more straightforward than developing complex chelates from classical nuclear medicine nuclides such as ^{99m}Tc and ^{111}In. The short half-life of PET nuclides can be helpful when utilized for human studies (a lower patient dose is required and repeatability of imaging procedures is good), but they can also hinder successful tracer development (specific activity is reduced over time, rapid synthesis and quality assurance procedures are required, long incorporation times are not possible, and biodistribution studies are very difficult). But radiochemists have the ability to develop many more PET radiopharmaceuticals than can be thoroughly tested. Why? Quite simply, it takes too long to realistically evaluate whether a new radiopharmaceutical can be used to successfully visualize the desired physiological or biochemical parameter for which it was designed. Animal biodistribution studies must be performed for each new agent prior to undertaking human imaging (*4–6*). Numerous animals are required to gather limited amounts of kinetic data. The early uptake phase of a rapidly cleared tracer is difficult to measure by these techniques. Interanimal variability further increases the number of animals that must be killed. The cost and more importantly, the effort to collect biodistribution data for a few time points along this uptake process are significant, and become even more difficult when short half-life PET nuclides are used. Furthermore, conventional biodistribution methods of dissection provide no regional tissue uptake information.

In this issue of the *Journal* Marriott and coworkers present information about measuring biodistribution and regional uptake of PET radiopharmaceuticals in small animals (*7*). This builds upon their previous work (*8*) and employs avalanche photodiode detectors coupled to conventional BGO scintillator material. This work embodies two important issues, namely use of a dedicated small PET scanner for animal imaging and the development of new PET detector technology. The unique feature of their tomograph design is the application of the avalanche photodiode as the main

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detector element. The avalanche photodiode is a small, solid-state amplifier which performs well at high photon counting rates and replaces the conventional photomultiplier tube. Discrete detectors are utilized rather than a block design in order to achieve higher count rates and better resolution (*9,10*). The avalanche photodiode may indeed provide a necessary breakthrough for reducing costs of commercial PET scanners.

The concept of constructing smaller versions of PET ring tomographs for animal work using conventional technology is not new (*2,3,11,12*). Previously, it was just too costly to build a device for such a small market. The complexity and lack of recognition of need have stymied acceptance of specialized animal PET scanners. The approximate resolution of PET scanners used for human imaging is currently 4–5 mm FWHM in all dimensions. This is not good enough to clearly visualize animal tissues in the submillimeter range. Dedicated animal scanners for PET imaging must be capable of at least 1–2 mm FWHM resolution to be truly useful in biodistribution studies and in measuring regional kinetic information. Imaging of animals with conventional gamma cameras and collimators, while possible, is far from optimal since the thin NaI(Tl) crystal provides only minimal sensitivity to the high energy 511 keV annihilation photons. Lastly, epidemiologic issues severely restrict the use of human facilities for animal imaging.

The need to accelerate the process of testing and selecting promising radiopharmaceuticals from a long list of potential candidates has come of age. The ability to quantitatively conduct biodistribution studies without animal sacrifice (or at best minimize it) in order to obtain complete kinetic data of tracer uptake and washout is intriguing. Marriott et al. point out limitations in their work: (1) incomplete ring geometry, (2) choice of radiopharmaceutical, and (3) the necessity of killing the animal. These specific issues do not, however, detract from the general notion that animal PET scanners are realistic and necessary tools to carry out significant radiopharmaceutical development.

In summary, more experimentation is needed to test the avalanche photodiode system for stability, linearity and count rate performance. PET scanners that employ these devices will push the conventional limits of resolution, sensitivity and cost. But if the challenges are met, the benefits are significant. It is important to develop dedicated, high-resolution instrumentation that combines new detector technology with more rapid biodistribution analyses. The future of PET and nuclear medicine depends on new radiopharmaceuticals entering the imaging arena more rapidly and at an economical cost.

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