

# The Importance of Kinetic Enhancement

Consider the importance of kinetic enhancement of radiopharmaceuticals. In the field of nuclear medicine, essentially everything relies on the distribution or the regional kinetics of an administered radiopharmaceutical. In many cases, a picture of distribution is enough to provide the needed clinical or research information, or a quantitative measure of uptake into the tissue of interest may be needed to provide the desired information. In the most complicated cases, the desired information is obtained from analysis of the rates at which tracer accumulates or leaves one or more organs, structures, or tissues.

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Regardless of the particular method of interpretation, it is always desirable to have a large amount of radiopharmaceutical located in the regions of interest and a small amount in the nontarget regions and especially the immediate background regions. Various mechanisms, including diffusion, lipid solubility, nontarget organ interactions, and metabolism, contribute to the uptake kinetics and the observed distribution of a radiopharmaceutical. In addition, all radiopharmaceuticals are susceptible to some degree of association with the components of the blood. Most commonly, a loose and rapidly exchanging lipophilic or hydrogen-bonding interaction takes place with blood proteins or the membranes of blood cells. Serum albumin and  $\alpha_1$ -acid glycoprotein in

particular provide loose associations for many compounds. Some proteins in the blood provide strong interactions for the transport of specific target molecules. Radiopharmaceuticals can be substrates for these as well. Well-known examples include transferrin, which binds cationic iron, providing a mechanism for iron distribution, and also has a strong affinity for the gallium used in radiopharmaceuticals. Competition of transferrin for gallium must be considered when designing gallium-labeled radiopharmaceuticals (1–3). Similarly, the strong binding of sex hormone-binding globulin to estrogen- and testosterone-based radiopharmaceuticals is a significant factor (4–6) in their biologic distribution and therefore their usefulness as radiopharmaceuticals. Fortunately for the practice of nuclear medicine, most radiopharmaceuticals are susceptible to only a weak or moderate affinity to albumin and  $\alpha_1$ -acid glycoprotein, often in proportion to the lipophilicity of the radiopharmaceutical. The principle is well known anecdotally, although it has not been specifically investigated in detail.

A weak affinity to blood components has been assumed to have a small effect, if any, on ultimate radiopharmaceutical distribution. When equilibrium is rapid between bound and free tracer in the blood, most of the bound tracer should be available to a tissue even during a single capillary pass, and all of it would become available during the course of the uptake phase of a typical radioimaging procedure. In most radio-tracer kinetic modeling applications, moderate binding to serum proteins would be expected to be manifested only as a reduction of the rate constant of transport from the blood to the tissue. As the affinity of a tracer for blood components increases, the effect on the kinetics and distribution of the tracer would also be expected to

increase. There must therefore be a continuum of binding affinity of radiopharmaceuticals to blood components, the effects of which on the ultimate use of the tracer are not well understood.

In this issue of *The Journal of Nuclear Medicine* is a paper by Kuga et al. titled “Competitive Displacement of Serum Protein Binding of Radiopharmaceuticals with Amino Acid Infusion Investigated with *N*-Isopropyl-*p*-<sup>123</sup>I-Iodoamphetamine” (7). The paper represents a joint effort from 3 universities in Japan, the University of Miyazaki, Kanazawa University, and Ibaraki Prefectural University of Health Sciences, and treats the effect of radiopharmaceutical binding to serum proteins on tracer kinetics and the resulting images. As an assessment of radiopharmaceutical binding to proteins and its manipulation, the work was rigorously done. The association of the radiopharmaceutical with each of the relevant binding sites on serum proteins was assessed individually. The effect of intervention on the binding to each binding site was also measured. This work is an example to those such as me who have previously been reduced to hand waving with insufficient data when serum protein binding has been a factor in our radiopharmaceutical results. The paper focuses on serum protein binding of the popular and successful cerebral perfusion tracer, *N*-isopropyl-*p*-<sup>123</sup>I-iodoamphetamine (<sup>123</sup>I-IMP), but the methods these investigators have used are generally applicable to the study of any radiopharmaceutical. Their data demonstrate that a large fraction of <sup>123</sup>I-IMP is bound to serum proteins at all times.

The study of the protein binding of <sup>123</sup>I-IMP should be only a beginning. Data are generally lacking on the binding of radiopharmaceuticals to blood components. Kuga et al. have made an interesting observation that in

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this case the binding of the radiopharmaceutical can be manipulated. In this case it is reduced by the administration of amino acids, which compete with the protein binding of  $^{123}\text{I}$ -IMP. Most importantly, amino acids do this without competing with the target uptake of the radiopharmaceutical. The result is enhanced target uptake. A general advantage would exist to having methods that are acceptable for human use to reduce the nontarget uptake of radiopharmaceuticals and to increase uptake in target regions. Kuga et al. point out that only a limited number of discrete binding sites on serum proteins are responsible for much of the observed binding of drugs to serum proteins. The method of amino acid infusion used in this work may therefore be applicable to other radiopharmaceuticals that share this mechanism of protein binding. With this logic, the work reported here can be viewed as the first steps into a general area of investigation. One might also envision extension of the principle to radiopharmaceuticals that may bind in other ways. For the strategy to be successful, there must be an identifiable binding mechanism that interferes with distribution into the tissues. There must then be a method capable of disrupting that binding and acceptable for human use. Finally, the method of disruption of serum protein binding must not also disrupt binding of the radiopharmaceutical to its target. Continuing work to understand the dynamics of radiopharmaceutical interactions in serum and their effect on target uptake should be encouraged.

The paper opens new questions for investigation. An interplay seems to be present between tracer binding and the various binding sites in serum. The binding percentage to individual serum components did not fit a simple relationship to binding in whole serum. This finding may indicate a dy-

namic system and may be amenable to further analysis. However, the brain uptake seems to indicate a system that is more static. The relative increase in plasma free fraction of  $^{123}\text{I}$ -IMP was nearly the same as the relative increase in brain uptake. This result would be expected of a perfusion tracer when uptake is driven only by the free plasma concentration. If rapid equilibration existed between bound and free  $^{123}\text{I}$ -IMP, effectively providing access to the tissue for bound  $^{123}\text{I}$ -IMP, one would expect a proportionately lesser effect on brain uptake caused by a change in the plasma free fraction. Is equilibration simply slow relative to capillary transit time? Again, target organ uptake may be able to be modeled mathematically from the binding characteristics of a tracer and of its inhibitors to carrier proteins in the serum to allow a fuller understanding and optimization of this approach. Binding of  $^{123}\text{I}$ -IMP to serum proteins was about 80% using standard procedures. The normal free fraction of  $^{123}\text{I}$ -IMP in plasma is therefore just over 20%. The reported intervention with Proteamin 12X Injection (Tanabe Seiyaku Co., Ltd.) succeeded in raising the available fraction of tracer in plasma to nearly 30%, which still left fully 70% bound to serum proteins. Would it be possible to increase the effectiveness of the intervention to tap this much larger reservoir of radiopharmaceutical?

The improvement in  $^{123}\text{I}$ -IMP target uptake reported in this paper was significant though moderate. It represents an interesting scientific observation and may lead to further work of increasing significance. In this instance, deposition in the brain due to the intervention increased by about 30%, compared with standard procedures. Increases in liver and bladder uptake were also observed. The enhanced uptake may allow for a concomitant reduction in the injected

dose or an improvement in image quality for a clinical study. The enhancement comes at the minor cost of an added intervention in the form of administration of relatively large doses of the amino acids that reduce the serum binding of  $^{123}\text{I}$ -IMP. Similar interventions are commonplace; still, the clinician must make the decision of whether the marginal extra effort is worthwhile to obtain the marginal improvement in image quality or reduction in radiopharmaceutical dose. As this approach is refined and expanded, we may hope for substantial gains in the effectiveness of this and other radiopharmaceuticals, possibly allowing useful results to be obtained from radiopharmaceuticals that might otherwise be ineffective.

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## REFERENCES

1. Hnatowich DJ. A review of radiopharmaceutical development with short-lived generator-produced radionuclides other than  $^{99\text{m}}\text{Tc}$ . *Int J Appl Radiat Isot.* 1977;28:169-181.
2. Moerlein SM, Welch MJ. The chemistry of gallium and indium as related to radiopharmaceutical production. *Int J Nucl Med Biol.* 1981;8:277-287.
3. Thakur ML. Gallium-67 and indium-111 radiopharmaceuticals. *Int J Appl Radiat Isot.* 1977;28:183-201.
4. Parent EE, Dence CS, Sharp TL, Welch MJ, Katzenellenbogen JA. 7 $\alpha$ - $^{18}\text{F}$ -fluoromethyl-dihydrotestosterone and 7 $\alpha$ - $^{18}\text{F}$ -fluoromethyl-nortestosterone: ligands to determine the role of sex hormone-binding globulin for steroidal radiopharmaceuticals. *J Nucl Med.* 2008;49:987-994.
5. Tewson TJ, Mankoff DA, Peterson LM, Woo I, Petra P. Interactions of 16 $\alpha$ - $^{18}\text{F}$ -fluoroestradiol (FES) with sex steroid binding protein (SBP). *Nucl Med Biol.* 1999;26:905-913.
6. Bonasera TA, O'Neil JP, Xu M, et al. Preclinical evaluation of fluorine-18-labeled androgen receptor ligands in baboons. *J Nucl Med.* 1996;37:1009-1015.
7. Kuga N, Shikano N, Takamura N, et al. Competitive displacement of serum protein binding of radiopharmaceuticals with amino acid infusion investigated with *N*-isopropyl- $p$ - $^{123}\text{I}$ -iodoamphetamine. *J Nucl Med.* 2009;50:1378-1383.