Gallium-67/Stable Gadolinium Antagonism: MRI Contrast Agent Markedly Alters the Normal Biodistribution of Gallium-67

Robert S. Hattner and David L. White

Nuclear Medicine Section and Contrast Media Laboratory, Department of Radiology, University of California, San Francisco

An 11-yr-old patient was scanned 96 hr after the administration of gallium-67 (^{67}Ga). The scan emulated the biodistribution of a typical bone-seeking radiopharmaceutical—rather than that of ^{67}Ga. None of the factors previously identified with alteration of the biodistribution of ^{67}Ga were found. However, the patient had been injected with gadopentetate in conjunction with magnetic resonance imaging 4 hr before receiving the ^{67}Ga. Gadolinium appears to cause a strong carrier-like effect in ^{67}Ga scans.

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Factors affecting the expected biodistribution of gallium-67 (^{67}Ga) are of interest in nuclear medicine because of the frequent clinical use of ^{67}Ga for the detection of inflammation and neoplasia. Descriptions of unusual ^{67}Ga biodistributions are numerous—and usually have been attributed to abnormalities of iron metabolism—induced in the laboratory or found in the clinic (*1–7*).

A number of experimental investigations have shown that many variables can affect ^{67}Ga biodistribution in animals. These include iron loading, iron depletion using desferrioximine, and others (*1–3,6,7*). In fact, the goal of some of these studies has been to study the possibility of favorably altering the biodistribution of ^{67}Ga to enhance its diagnostic sensitivity and specificity.

It does seem clear that the biodistribution of ^{67}Ga is highly dependent on that of iron and on the availability of iron-specific binding by a number of biomolecules (*8*). These include transferrin, ferritin, lactoferrin, and bacterial siderophores.

Early in the history of the investigation of gallium isotopes for medical applications a powerful effect of either added stable ^{70}Ga or scandium was observed (*9–15*). This carrier effect was much stronger than that shown for iron in later experiments and clinical observations (*3–7*).

The result of m*M* pre- or coadministration of stable gallium or scandium was to cause carrier-free gallium isotopes to assume the distribution of pure bone seekers, like strontium (*9–11,14,15*). The now familiar soft-tissue, enteric, and bone marrow localization was lost (*16,17*). Along with this redistribution, the specificity for neoplasia and inflammation vanished (*12,13,18*).

Stable lanthanides, including gadolinium (Z = 64, M = 157.25), are chemically similar to scandium. Gadolinium (III) is paramagnetic by virtue of its seven unpaired outer shell electrons and effectively shortens proton relaxation times. The in vivo behavior of gadolinium was only recently explored as its potential as an MRI contrast agent emerged (*19*).

GdDTPA (gadopentetate) has found use as an MRI contrast agent because of its proton relaxation properties, low acute toxicity, distribution in extracellular fluid, and excretion by glomerular filtration (much like radiographic contrast agents).

Gadolinium for MRI is administered in ca. 0.1 mmol/kg doses as the stable DTPA chelate (log stability constant = 22). The limiting factor on the plasma concentration of free Gd(III), however is the very low solubility product of GdPO4 (log $K_{sp} = -22.6$) (*20*).

Thus, the free metal ion concentration under physiologic conditions ($[HPO_4^{-2} + H_2PO_4^{-1}] = 2$ m*M*) is ca. 4×10^{-15} *M*. This value is significantly lower than the calculated Ga(III) concentration (7×10^{-11} *M*) after administration of 5 mCi of carrier-free ^{67}Ga. In spite of this, we believe that the case we present shows strong evidence that GdDTPA may interfere with the normal biodistribution of ^{67}Ga.

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For reprints contact: Robert S. Hattner, MD, Nuclear Medicine Section L-340, University of California San Francisco, San Francisco, CA 94143-0252.

CASE REPORT

At the age of 9½, our patient developed otalgia and coryza. An MRI scan disclosed a nasopharyngeal mass involving the

right paranasal sinuses and orbit. A biopsy disclosed typical Burkitt's lymphoma. Comprehensive staging demonstrated bone, bone marrow, and renal involvement.

The patient's treatment featured 200 cGy to the kidneys. Systemic drugs included cyclophosphamide, vincristine, methotrexate, prednisone, and daunorubricin. Intrathecal cytosine arabinoside, methotrexate, and vincristine were administered for central nervous system prophylaxis. His marrow cleared and he appeared disease free one month later.

Four months later the patient had a seizure. A CT scan showed neoplasm involving the cavernous sinus. Cerebrospinal fluid cytology showed malignant cells. The central nervous system relapse was treated with cytosine arabinoside. A testicular relapse occurred seven months after diagnosis, and was treated with radiation therapy. Since then he has been disease free—maintained on chemotherapy.

At no time had he been anemic, had transfusions, had supplemental iron, or received erythropoietin. Since the initial bone marrow involvement cleared, his marrow has been moderately megaloblastic, otherwise normal. There is no family history of any blood disorder.

Two and one-half years after diagnosis, because of headaches, he underwent restaging. At this time he had a gadopentetate-enhanced MRI of the head (7 cc, 0.5 *M*). Four hours later he was injected with 3.3 mCi ^{67}Ga-citrate for a scan obtained 96 hr later.

Using a 40-cm diameter gamma camera with a medium-energy collimator and three single-channel analyzers—each with a 20% symmetric window centered on the 93, 184, and 296 keV energies of ^{67}Ga—a posterior thoracic image was created with 500k events. Subsequent images spanning the whole body were obtained using the time required by the first image.

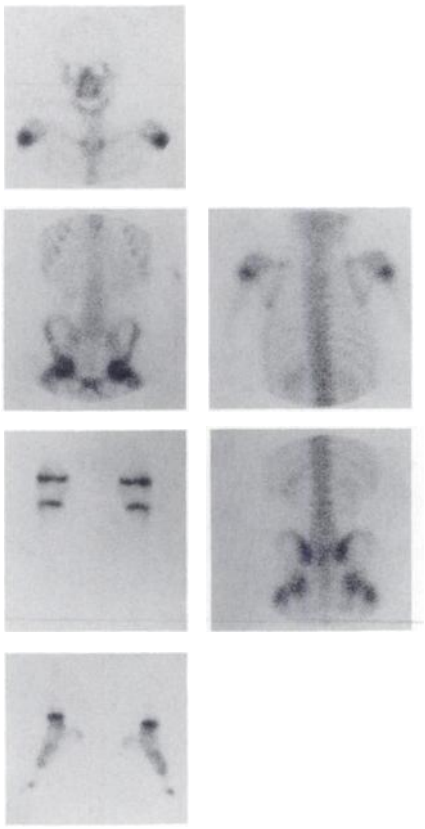

FIGURE 1
Gallium-67 scintigrams obtained 96 hr after 3.3 mCi dose. Left column, anterior scans (top-to-bottom): Head and thorax; thorax, abdomen, and pelvis; knees and feet. Right column, posterior scans (top-to-bottom): thorax, abdomen and pelvis. Note absence of usual ^{67}Ga scan features and remarkable emulation of skeletal perfusion, especially epiphyseal plate avidity.

RESULTS

The ^{67}Ga scan of our patient is illustrated in Figure 1. We noted that liver and bowel activity are barely perceptable. Unexpected renal activity is evident. The skeletal distribution does not emulate that of erythropoietic bone marrow, but that of bone perfusion. Note especially the marked epyphyseal plate activity.

DISCUSSION

Hayes et al. originally investigated ^{67}Ga as a potential bone scanning agent because of the post-war reports of ^{72}Ga being a bone seeker (*18,21*). What they found was much different (*9–13*). They attributed this to the fact that the ^{72}Ga used in those early experiments was mostly ^{70}Ga, stable gallium.

Thus, a strong carrier effect was inferred from the dramatically different biodistribution of carrier-free ^{67}Ga. Further experiments testing the effect of graded amounts of added carrier ^{70}Ga or scandium to ^{67}Ga confirmed this (*9–12,14,15*). With carrier gallium or scandium ^{67}Ga became a bone seeker, like ^{72}Ga and just like that shown by our patient.

In addition to these surprising findings, they observed carrier-free ^{67}Ga localization in both inflammatory and neoplastic lesions, and heralded the inception of ^{67}Ga into modern nuclear medicine (*12*). On the other hand, they noted that this specificity for neoplasia and inflammation was lost when carrier gallium or scandium was added (*11,12,14,15*).

As calculated above, the free gadolinium concentration should be many logs less than that of carrier-free ^{67}Ga if injected simultaneously. Why would a carrier effect occur? First, Hayes et al. showed that the greater the interval from administration of tracer and carrier, the less carrier was required to cause the effect.

Second, the whole-body retention of GdDTPA is 10% at 24 hr. If no translocation from the DTPA was occurring, this retention would be far less than 1%. Ten percent of the gadolinium corresponds to three logs more than the ^{67}Ga, sufficient to explain a carrier effect in spite of the strong chelation.

Zak and Aisen reported a value of 8.90 for the log effective stability constant of Gd-transferrin at physiologic bicarbonate concentration and determined that only one gadolinium was bound sufficiently strongly to measure (*22*). Harris and Peccarro determined log sta-

bility constants of 20.3 and 19.3 for binding of Ga(III) to transferrin (*23*).

Consideration of the Ga(III) and Gd(III) concentrations and transferrin stability constants indicates that Ga-transferrin formation is thermodynamically highly favored: [Ga-Tf]/[Gd-Tf] = 10^{+16}. Thus if gadolinium administration affects the distribution of gallium, and is mediated by transferrin, it requires that Gd-Tf be kinetically inert. This would seem to indicate that the altered ^{67}Ga biodistribution might require administration of the gadolinium a number of hours before the ^{67}Ga is given, and scanning carried out days later, as both were in this case.

Our patient seems to demonstrate a carrier effect of GdDTPA. Should this change our expectations of the results of ^{67}Ga scanning in patients who have received GdDTPA? We think so. Carrier gallium and scandium, a lanthanide chemically similar to gadolinium, adversely affect the diagnostic quality of ^{67}Ga scans (*10–12,18*). A seemingly similar phenomenon after Gd-DTPA administration with MRI is worrisome, if not likely.

Finally, the implications of this observation transcend the potential interference of GdDTPA with ^{67}Ga scanning. Could GdDTPA be used to enhance the diagnostic quality of ^{67}Ga scans? This intriguing possibility deserves a look.

CONCLUSION

In conclusion, nuclear physicians should be aware of the possibility of substantial interference of GdDTPA with ^{67}Ga. We are currently studying other patients who had ^{67}Ga scans around the time that they received GdDTPA. This observation needs confirmation, and the pharmacokinetics of the potential interference need characterization.

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