Tc-99m glucoheptonate is poor man’s fluorodeoxyglucose

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ABSTRACT

While fluoro-deoxy-glucose (FDG) has emerged as an important radiotracer for imaging tumors, myocardial viability and infection, the role of other glucose analogues should also be explored. Tc-99m Glucoheptonate (GHA) has been used for imaging brain tumors and lung tumors. The uptake mechanism may be linked to GLUT-1 (Glucose transporter) and GLUT-4 expression similar to FDG. GHA is easily available and cheap. With the availability of single photon emission computed tomography/computed tomography (SPECT/CT), GHA imaging should be re-explored as a tumor agent and also for imaging myocardial viability.

Keywords: Tc-99m Glucoheptonate, fluoro-deoxy-glucose, SPECT-CT, PET-CT

INTRODUCTION

A recent editorial in the European Journal of Nuclear Medicine and Molecular Imaging—“PET and SPECT: Synergy rather than competition” by Giulino Mariani and William Strauss has triggered this article. For over a decade, I have been proposing that Tc-99m glucoheptonate (GH) is the poor man’s fluorodeoxyglucose (FDG). This has been stated in the preface of my book “Principles and Practice of Nuclear Medicine and Correlative Medical Imaging, with a foreword by Dr. Henry Wagner.

Tc-99m GH was introduced in the 1970’s in Dr. Henry Wagner’s Nuclear Medicine Department at John’s Hopkins, Baltimore USA, Rossman, Siegel, and Friedman in 1974; Rossman, Strauss, Siegel, and Pitt in 1975 studied the utility of Tc-GH to image myocardial infarction. In mouse and canine models after ligation of a coronary artery, the greatest concentration of the tracer was noted in areas distal to the occlusion that had 20-40% of normal perfusion, which showed persistent ventricular akinesia, indicating severe persistent ischemia that would subsequently lead to infarction [Figure 1]. In their pre-occupation with myocardial infarct imaging, where they commented that Tc-GH is not an ideal agent for that purpose, they overlooked the utility of Tc-GH as an ischemia imaging agent; although the authors emphasized that concentration of GH in the myocardium depended on sufficient residual or collateral flow, and an alteration in the myocardial cell allowed the tracer to be actively transported across the membrane. In 1975, there was no knowledge of what alteration in the myocardial cell allowed GH to be actively transported across the ischemic muscle cell membrane. Today, we know these alterations (vide infra).

Arnold, et al., showed the utility of Tc-GH as a renal imaging agent.

GH for tumor imaging

In as early as 1975, Tanasescu, et al., showed the utility of Tc-GH as a brain scanning agent. Léveillé, et al., described Tc-GH as an important advance in brain tumor detection. They noted progressive tracer concentration over time as shown by comparison of late (5-6 h) with early (1 h) images. They suggested that Tc-GH is taken up like a glucose analog by an active transport mechanism to be used as a substrate for energy by the metabolically active tumor tissue [Figure 2].

Sty, et al., showed the utility of Tc-GH in brain tumors and metastases. Delayed images were useful to detect low-grade gliomas and other slowly growing avascular tumors in pediatric population. Sodee and Ballistrea showed that Tc-GH Single-photon emission computed tomography (SPECT) is better than computed tomography (CT) with contrast and contrast...
equally useful compared to magnetic resonance imaging (MRI). They observed that Tc-GH accumulated in viable components of the tumor and not in necrotic parts. In 1987, Kaplan, et al.,[10] compared Ti-201 2 mCi (30 min), Tc-GH 20 mCi (4 h), and Ga-67, 7 mCi (48 h) images and CT brain scan in 29 patients with malignant gliomas with pathological correlation in 7 autopsies. In all tumors, GH accumulation was more than Ti and Ga-67. While Ti-201 showed tumor only, GH showed tumor as well as surrounding edema not defined by CT. Steroid therapy did not interfere with tumor uptake of Ti and GH, unlike Ga-67 uptake, which was reduced [Figure 3].

Vorne, et al.,[11] showed accumulation of Tc-GH in 23 of 26 patients with primary lung cancer. The visualization of malignant tumors was much better in late (5 h) than in early (1 h).
images. A total of 23 patients without lung disease gave negative Tc-GH results. Tc-GH accumulated in the viable parts of 2 lung tumors, but not in necrotic tissue. Uptake in benign lesions was not gradually progressive. The authors commented “Perhaps Tc-GH is taken up like a glucose analog by an active transport mechanism to be used as a substrate for energy by the metabolically active tumor tissue” [Figure 4].

Passmonte, et al., [12] and Sauerland et al., [13] also showed the utility of Tc-GH imaging in lung cancer and cervical lymph node metastases. Crane, et al., [14] showed that Tc-GH imaging was comparable to the CT for brain metastases from small cell lung cancer. In 1981, Wim de Kieviet [15] studied the chemical structure [Figure 5] and tissue distribution of Tc-GH in stomach, intestines, liver, spleen, kidneys, bone, and bone marrow, thyroid, and blood in Wistar rats. At that time, there was no knowledge about glucose transporters to compare the behavior of GH with glucose or FDG.

**Glucose transporter (GLUT) expression in health and disease**

Oxidation of glucose is a major source of metabolic energy for mammalian cells. Two classes of glucose carriers have been described in mammalian cells: Na⁺ glucose cotransporters and facilitative glucose transporters. Intestinal transport of glucose was shown by Crene in 1960 to be by flux-coupling via sodium-glucose co-transporters. Facilitative glucose transporters have distinct tissue distribution as shown in Table 1. Molecular biology of mammalian glucose transporters was reviewed by Bell, et al., [17] Flier, et al., [18] showed elevated levels of GLUT 1 transporter mRNA induced by RAS or SRE oncogenes.

GLUT-1 is over-expressed on cell surface of many cancers. GLUT-1 is also increased in hypoxic areas of tumors near necrotic regions. All malignant cells exhibit increased GLUT-1, leading to increased FDG uptake (recognized by GLUT-1 as glucose). Phosphorylated FDG-6P is trapped within the cell without further metabolism, enabling FDG-PET imaging for visualization, staging, monitoring progress, and response to therapy. FDG uptake in breast cancer cells is positively correlated to GLUT-1. Effective therapy reduces FDG uptake substantially and often completely.

The availability of metabolic tracers (FDG for glucose and palmitate for fatty acids) clarified the metabolic behavior of the normal heart. Aerobically, perfused myocardium prefers free fatty acids (FFAs) as major energy source. In the postprandial state, glucose and insulin levels in the blood increase and FFA levels decrease and glucose uptake by the heart increases. Lactate may be the main substrate after exercise.

During myocardial ischemia, when blood flow and oxygen level are decreased, FFA utilization is decreased. Impaired fatty acid uptake persists much longer than the duration of ischemia. This is demonstrated by I-123 BMIPP SPECT imaging (cold spot due to decreased uptake). If cyclotron-produced I-123 becomes
readily available SPECT/CT has great future for myocardial ischemia imaging. Hypoxia-induced factor $\alpha$ stimulates GLUT-1 expression and glucose uptake, glucose utilization is upregulated.$^{[27]}$

Ischemia and hypoxia increase glucose uptake by the myocardium. During and following acute ischemia, glucose is the main energy source for anaerobic glycolysis for several hours.$^{[28,29]}$ This is achieved by translocation of GLUT-1.$^{[20,24]}$ Clinically, sudden coronary occlusion with acute ischemia rapidly increases regional FDG uptake.$^{[44]}$

GLUT-1 may act as a “stress-induced protein” stimulated by hypoxia inducible transcriptional factor, hypoxia inducible factor (HIF1$\alpha$).$^{[32]}$ There is 50% increase in glucose uptake in ischemic myocardial regions.$^{[33]}$ HIF1$\alpha$, in response to hypoxia, stimulates expression of GLUT-1 and GLUT-3 in articular chondrocytes and promotes anaerobic glycolysis.$^{[34]}$

Stunning of the myocardium following transient periods of ischemia was first described by Heyndrickx in 1975. Clinically, stunning has been observed after exercise induced ischemia, unstable angina, and after hypothermic ischemic arrest for cardiac surgery.$^{[35,36]}$ Ischemia-induced accumulation of free intracellular calcium causes a decreased myofilament responsiveness in calcium-dependent proteases.$^{[37]}$ Cardiac function completely recovers in time. Increase in FDG uptake is utilized for anaerobic glycolysis and is not utilized for restoration of the glycogen pool.$^{[38]}$ GLUT-1, 2, 3, 4, and 8 are expressed in myocytes. The contribution of GLUT-3 and GLUT-8 to glucose transport appears to be less important than that of GLUT-4 and GLUT-1 in the myocardium.$^{[39]}$ Chronic ischemia is a result of intermittent reductions of coronary flow. Several distinct strategies are used by the heart to adapt to the repeated under perfusion.

Hibernating myocardium$^{[40]}$ is characterized by uncoupling of cardiac contractile function and blood flow. Myocytes show a perinuclear loss of contractile protein, alteration of all structural proteins and abnormally shaped and sized nuclei that demonstrate heterogenous distribution of chromatin.$^{[41]}$ Hibernating myocardium takes up FDG via increased GLUT-1 expression.$^{[42]}$ Human myocardial biopsies of hibernating myocardium showed intense GLUT-1 expression compared to normal heart regions. Most strikingly hibernating myocytes are filled with glycogen deposits.$^{[42,43]}$ Doenst, et al.$^{[44]}$ showed that the FDG uptake by these myocytes is converted to glycogen. Accumulation of glycogen is a characteristic of the fetal heart.$^{[45]}$

GLUT-4 translocation in the myocardium can occur following ischemia and reperfusion mediated by p38 MAPkinase$^{[46,47]}$ SB 202190, an inhibitor of p38 MAPkinase attenuates the increased FDG6P accumulation in preconditioned hearts.

A and $\beta$ adrenergic stimulation contributes to ischemia-induced GLUT-4 and GLUT-1 in isolated perfused rat hearts.$^{[48]}$ In canine heart model in vivo, moderate regional ischemia results in a 2-3 fold increase in glucose uptake mediated by a 2-fold increase in GLUT-4 and 40% increase in GLUT-1.$^{[49]}$ This translocation of GLUT-1 and GLUT-4 persists several hours longer than the duration of ischemia. Ischemia-induced increased myocardial FDG uptake is 10-fold or more higher than the regional variability of glucose uptake at rest in the non-ischemic myocardium. Qualitative analysis is presently quite useful until quantitative programs are developed.

**GH and FDG as analog of glucose?**

FDG is similar but not identical with glucose. While glucose is nearly totally reabsorbed from renal tubules in normal individuals, FDG is substantially excreted in the urine unchanged.

GH is filtered by the renal glomerulus and protein bound fraction is secreted by the renal tubules and some of it is actively secreted in the bile and intestines. About 12% activity remains in the renal cortex for up to 6 h, while most of the injected activity appears in the urine. Kidneys show GLUT-1, 2, 5, 9, and SGLT-1 and SGLT-2 expression.

There is sufficient persuasive evidence that GH behaves as a glucose analog, actively transported as a source of energy. The obvious unanswered question is—does GH utilize GLUTs similar to glucose or FDG? The most persuasive evidence came recently from an in vivo evaluation of apoptosis with Te-99m GH.$^{[50]}$ A549 lung cancer cell lines showed uptake of Te-99m GH, whereas chemotherapeutically induced apoptosis in A549 cells led to decrease in Te-GH uptake depending on the level of apoptosis.

**Hypoxia imaging**

Hypoxia imaging with radiolabeled nitroimidazole (e.g., F18 fluoromisonidazole PET), while suitable for tumor hypoxia, which is a persistent phenomenon; the relatively slow extraction and gradual accumulation requiring prolonged circulation time, make it unsuitable for imaging exercise-induced transient hypoxia. It is useful for imaging chronic persistent hypoxia in chronically ischemic and viable hibernating myocardium.$^{[51]}$ Since hypoxia stimulates GLUT1 over-expression, Te-GH may severe as a surrogate marker of hypoxia in these situations.

**Tc 99m-GH for myocardial ischemic imaging?**

Recently, stress FDG PET has been successfully utilized to demonstrate myocardial ischemia.$^{[52,53]}$ Can Te-GH be used for the same purpose? Since the best images with GH are obtained at 4 h, it is presumed that the “ischemic memory” may persist for 4 h after the GH is injected during exercise stress. Prospective studies are undergoing at Jaslok Hospital and Research Centre and Lilavati Hospital and Research Centre, Mumbai to determine the utility of Te-GH for myocardial ischemia imaging similar to stress FDG PET. The economic advantage of Te-GH SPECT over FDG PET is obvious; hence, the importance of the study.

Tc-99m GH SPECT for tumor imaging can be seriously considered as an alternative to FDG PET/CT. Effective chemo/
radiotherapy reduced FDG uptake substantially and often completely.\textsuperscript{19,28} It is worth exploring if delayed 5 h images with Tc-GH SPECT/CT can take the place of FDG PET/CT for the purpose of metabolic monitoring.

Since macrophages and neutrophils accumulate FDG more than normal cells, FDG PET/CT is extensively used for imaging infection/inflammation apart from malignancy.\textsuperscript{[54]}

GLUT-1 and GLUT-3 expression in white blood cells (WBCs) in inflammatory tissues was studied with C-14 FDG and immunohistochemistry, and compared to tumor tissue, GLUT-1 was significantly higher in tumor than in WBCs, while GLUT-3 was only slightly higher in WBCs than in tumor. Strauss (1996)\textsuperscript{[55]} had recognized the “false positive” FDG as a major problem in oncology. Hamacher and Coenen (2002) proposed fluoroethyl tyrosine (FET) PET as the preferred imaging modality for tumor imaging since it has no uptake in inflammatory cells. I-123 iodomethyl tyrosine SPECT/CT will be a better option than FET PET/CT.

Whether Tc-GH is accumulated in infection/inflammation need to be studied separately. Whether it will be able to differentiate infection from malignancy (current dilemma with FDG PET) can be addressed by multi-centric prospective studies in India.

Back-to-back studies on the same patient to compare Tc-GH SPECT/CT and FDG PET/CT will clinch the issue that has great financial implications especially in the third-world countries, since Tc-GH SPECT/CT will be more widely available and more affordable at one-tenth the cost of FDG PET/CT.

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