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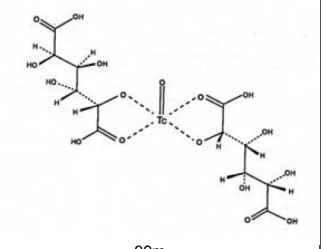
AMISCAN

Overview

AMISCAN (^{99m}Tc-glucarate) has been in development as a radiopharmaceutical diagnostic imaging agent for the diagnosis of acute myocardial infarct (AMI) for more than a decade. Previously the agent was thought to be specific for necrotic myocardium or MI. However, more recent preclinical studies suggested that ^{99m}Tc-glucarate uptake is increased in the setting of ischemia, even in the absence of necrosis. This expanded specificity has led to the hypothesis that this imaging agent could be used to accurately assess the presence of ACS in the chest-pain patient with equivocal diagnosis. A multisite clinical study is being planned to extend the evaluation of ^{99m}Tc-glucarate imaging by studying its ability to detect ACS in chest pain patients with no signs of AMI but with previous cardiovascular disease (CAD), in the setting of the emergency department (ED).



Structure of ^{99m}Tc-glucarate

Introduction

Coronary artery disease is the leading cause of death in the US. Acute coronary syndrome (ACS) is an umbrella term used to cover any group of clinical symptoms compatible with acute myocardial ischemia. ACS thus covers a spectrum of clinical conditions ranging from unstable angina (UA) to non-Q-wave MI and Q-wave MI. These are life-threatening disorders, which are a major cause of emergency medical care and hospitalization in the US. Differentiating ACS from noncardiac chest pain is the primary diagnostic challenge for the ED physician. The majority of chest pain patients are admitted to the hospital or observation unit because the initial clinical evaluation and diagnostic tests were unable to eliminate the possibility of AMI or UA. Nonetheless, most of these patients prove not to have acute ischemia. Furthermore, among chest-pain patients discharged from the ED, a small percentage actually have acute ischemia, leading to unfavorable outcomes.

Differentiating acute coronary syndrome (ACS) from noncardiac chest pain is the primary diagnostic challenge for clinicians in the emergency department. Studies of myocardial perfusion imaging have demonstrated important information for risk-stratifying stable post-ACS patients. However, this method is of limited value in patients with prior history of CAD, since these patients will often have abnormal resting perfusion patterns precluding the ability to differentiate old infarcts from new ischemic events. ^{99m}Tc-glucarate does not detect old heart attacks, and thus, should provide an advantage in the specificity for imaging suspected ACS patients with previous CAD.

Development Status

Our glucarate product is supplied as a lyophilized formulation in a 10 mL vial. It is labeled with ^{99m}Tc by sterilely adding ^{99m}Tc-pertechnetate, obtained from readily available generators in

nuclear medicine labs. After 10 minutes at room temperature a rapid quality control test is done to confirm complete binding of the ^{99m}Tc and the agent is ready to be administered to the patient.

To date, six studies of ^{99m}Tc-glucarate in approximately 300 patients have been carried out. No early or delayed adverse reactions of any type were reported in any of the studies. Studies evaluating dosimetry of ^{99m}Tc-glucarate showed all radiation dose estimates were at acceptable levels. Seminal clinical data were reported by Dr. Guiliano Mariani in the November 1999 issue of the *Journal of Nuclear Medicine.* Results suggested that ^{99m}Tc-glucarate localized in zones of acute myocardial necrosis when injected within nine hours of onset of chest pain.

Latest Phase II Clinical Trial

The company has completed a phase II study funded by NHLBI to assess the ability of ^{99m}Tc-glucarate to detect cardiac ischemia in chest pain patients. This study was an open-label, non-randomized, single arm trial of ^{99m}Tc-glucarate in 100 chest pain patients suspected of ACS with no obvious sign of MI and prior history of CAD. Patients were imaged with ^{201}thallium, which provided landmark images. Since ^{99m}Tc-glucarate is a “hot spot” imaging agent, no outline of the myocardium is seen in ^{99m}Tc-glucarate images and hot spots of apparent uptake cannot be localized without a myocardial landmark. ^{201}Thallium was chosen over technetium-99m perfusion agents to avoid logistical difficulties due to radionuclide interference with the ^{99m}Tc-glucarate.

Patient 212 is an example of positive ^{99m}Tc-glucarate myocardial uptake. **Fig 1** shows fused ^{201}thallium and ^{99m}Tc-glucarate images with clear ^{99m}Tc uptake in the apical region of myocardium. Patient 212 had a discharge diagnosis of angina so this positive ^{99m}Tc-glucarate scan must be preliminarily classified as a false positive pending adjudication of the discharge diagnosis.

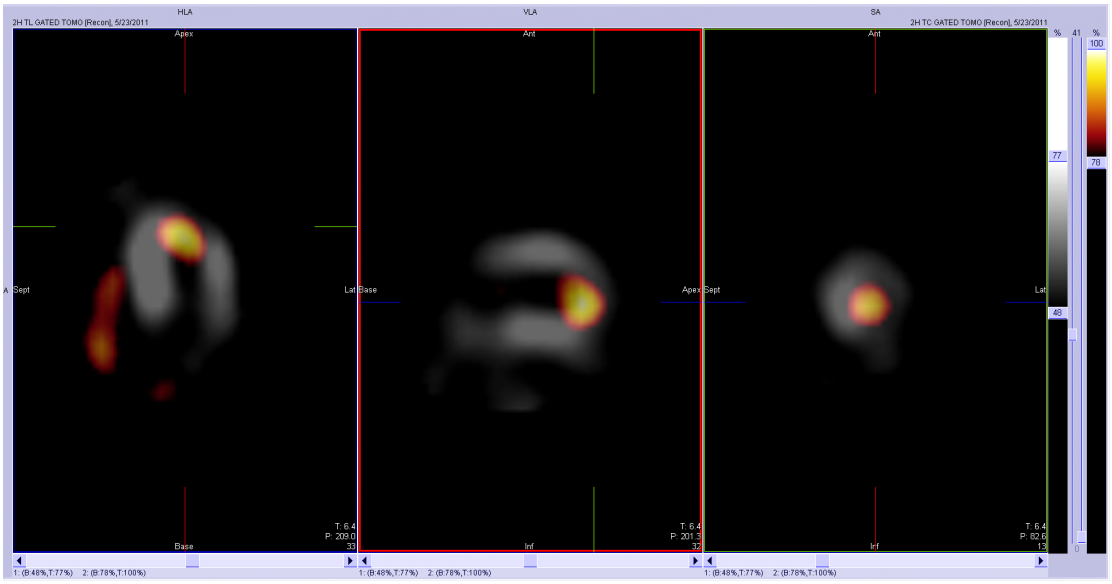


Fig 1. Patient 212 **-** fused images. ^{201}thallium (white) and ^{99m}Tc-glucarate (colored). HLA left panel, VLA middle panel, SA right panel. ^{99m}Tc-glucarate activity is clearly seen in the apical region of myocardium.

As another example image of positive ^{99m}Tc-glucarate myocardial uptake, **Fig 2.** shows the fused ^{201}thallium and ^{99m}Tc-glucarate images from patient 329. This patient had a discharge diagnosis of Non-ST elevation MI with a significant peak in cardiac enzymes. The fused images show an intense infero-lateral myocardial wall uptake.

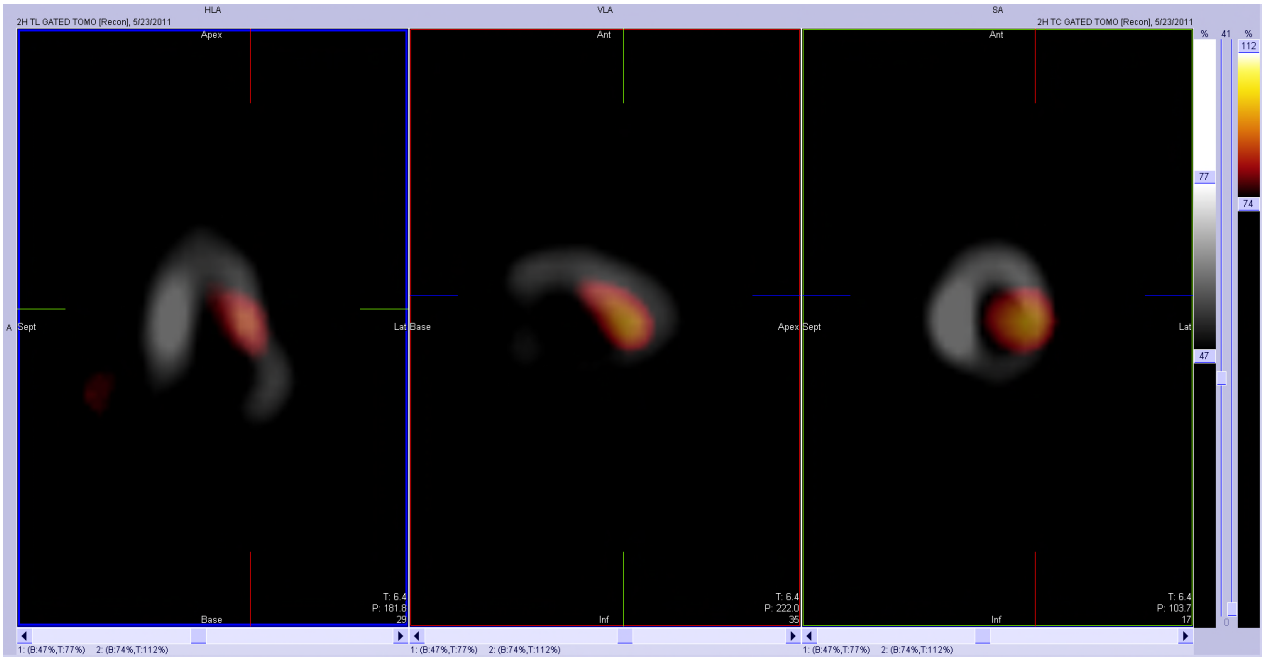


Fig 2. Patient 329 fused images. ^{201}thallium (white) and ^{99m}Tc-glucarate (colored). HLA left panel, VLA middle panel, SA right panel. ^{99m}Tc-glucarate activity is clearly seen in the infero-lateral region of myocardium.

The data from the phase II trial continue to be analyzed. Statistical analysis must await adjudication of discharge diagnoses and the blinded reads. One conclusion of the trial is that the interpretation of a hot spot imaging agent such as ^{99m}Tc-glucarate cannot be interpreted without a myocardial landmark image such as thallium or possibly CT.