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Localization of Infection in HIV Antibody Positive Patients With Fever

Comparison of the Efficacy of Ga-67 Citrate and Radiolabeled Human IgG


Patients who are human immunodeficiency virus (HIV) antibody positive are at increased risk of life threatening infection. Scintigraphic imaging with Ga-67 citrate has been used to identify the presence and site of focal infection. However, focal accumulation of Ga-67 is not specific for infection. A retrospective study was performed to compare the accuracy of Ga-67 citrate and pooled human polyclonal immunoglobulin G (HIG) labeled with Tc-99m HIG and In-111 HIG in identifying infection in HIV antibody positive patients. Twenty-five studies were performed using Ga-67 and Tc-99m HIG were compared with a second group of 25 studies using In-111 HIG in HIV antibody positive patients presenting with fever, but without localizing symptoms or signs. In-111 HIG identified 20 of 22 sites of infection and also accumulated in 5 sites without infection (accuracy = 90%). This was significantly more accurate ($X^2$, $P < 0.05$) than Ga-67 which identified 19 of 20 sites of infection, but accumulated in 18 sites without infection (accuracy = 74%) and Tc-99m HIG which identified infection in 11 of 20 sites, but accumulated in 8 sites without infection (accuracy = 77%). There was no significant difference between the accuracy of Ga-67 and Tc-99m HIG. From this preliminary study In-111 HIG would seem to be the best agent for identifying infection in HIV antibody positive patients with fever.

RAPID AND ACCURATE detection of infection is required in human immunodeficiency virus (HIV) antibody positive patients. This is relevant not only to prolong, but also to maintain quality of life. Scintigraphy using Ga-67 has proved useful in identifying infection (1–3). However, accumulation of Ga-67 occurs in tumors and the normal colon which reduce the clinical utility of this radiotracer (4,5).

It has been suggested that Tc-99m pooled human polyclonal immunoglobulin G (HIG) is a more specific agent for identifying foci of infection. Nevertheless, a study comparing it with Ga-67 revealed that Tc-99m HIG had a poor sensitivity for localizing intrathoracic sites of infection (6). This was largely because of the slow blood clearance of Tc-99m HIG which meant that there was significant intrapulmonary blood pool activity up to 24 hours after injection. The 6-hour half life of Tc-99m meant that imaging beyond 24 hours was not possible.

This problem is not encountered with Ga-67 because its longer physical half life readily permits imaging for up to 72 hours after injection. Outside the chest Tc-99m HIG was less sensitive than Ga-67 in localizing infection, but had greater specificity. Labeling HIG with a radionuclide with a longer physical half life, such as In-111, may be more successful. Indium-111 labeled HIG has been shown to localize at sites of infection in a wide variety of patients (7–9). This included patients with bone and joint disease and chest or renal infections. A preliminary study using In-111 HIG to image sites of infection in a group of HIV positive patients, presenting mainly with suspected chest infection correctly identified all sites which were subsequently found to have been infected (10).

In this study, we compared the accuracy of Ga-67,
Tc-99m HIG, and In-111 HIG scintigraphy in the identification of infection in HIV antibody positive patients presenting with fever without localizing symptoms and signs.

Materials and Methods

Study Design

In order to compare the efficacy of the radiopharmaceuticals, we retrospectively compared two groups of patients; first, a group of patients who were imaged with both Tc-99m HIG study and Ga-67, and second a group of patients imaged with In-111 HIG.

Hospital ethical committee approval was obtained for this study.

Patient Selection

All patients were known to be HIV antibody positive and had presented, with a temperature of greater or equal to 38°C continuously or intermittently for 4 or more days, without localizing symptoms or signs. At the time of the study, their diagnosis was unknown.

The patient’s demographic details are given in Table 1. Twenty-five studies were performed with each radiopharmaceutical.

Imaging

All studies were imaged using an IGE 400AC Starcam (International General Electric, Slough, UK) gamma camera computer system. For Ga-67, three photopeaks of 90, 190, and 300 keV were used. For the In-111 HIG images two photopeaks of 174 and 247 keV were used. With both these radiopharmaceuticals the camera was fitted with a medium-energy collimator.

For the Tc-99m HIG images a normal 140 keV photopeak was used and the patients imaged using a high-resolution, low-energy collimator.

In all cases, anterior and posterior images of the whole body were performed with at least 500 k counts/image.

Ga-67 images were performed 48 and 72 after intravenous administration of 111–185 MBq (3–5 mCi) of tracer. Thirty-seven MBq (1 mCi) of In-111 HIG was prepared by the Hnatowich method (11) and imaging was performed 4, 24, and 48 hours after injection. Tc-99m HIG was prepared by the standard method (12) and imaging was performed 1, 4, and 20 hours after administration of 200 MBq (5.2mCi) of tracer.

Reporting

All studies were formatted onto x-ray film and were reported by two observers blind to the patient’s clinical condition and any results of diagnostic tests.
TABLE 2. Number of Infective Sites Identified per Zone Identified With Each Imaging Agent

<table>
<thead>
<tr>
<th>Type and Zone of Infection</th>
<th>Ga-67</th>
<th>Tc-99m HIG</th>
<th>In-111 HIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterial</td>
<td>6/6</td>
<td>0/6</td>
<td>6/6</td>
</tr>
<tr>
<td>Pneumocystis carinii</td>
<td>3/3</td>
<td>1/3</td>
<td>3/4</td>
</tr>
<tr>
<td>Other</td>
<td>9/9</td>
<td>4/9</td>
<td>3/3</td>
</tr>
<tr>
<td>Total</td>
<td>14/14</td>
<td>7/14</td>
<td>12/13</td>
</tr>
<tr>
<td>Abdominal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>1/2</td>
<td>1/2</td>
<td>0/0</td>
</tr>
<tr>
<td>Colitis/proctitis</td>
<td>1/1</td>
<td>1/1</td>
<td>4/5</td>
</tr>
<tr>
<td>Ischiorectal abscess</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
</tr>
<tr>
<td>Total</td>
<td>2/3</td>
<td>2/3</td>
<td>5/6</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>2/2</td>
<td>1/2</td>
<td>0/0</td>
</tr>
<tr>
<td>Soft tissue infection</td>
<td>1/1</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0/0</td>
<td>0/0</td>
<td>1/1</td>
</tr>
<tr>
<td>Total</td>
<td>3/3</td>
<td>2/3</td>
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</table>

Because patients with HIV infection tend to have multiple infections, the body was split into three zones: 1) the lungs; 2) the abdomen and pelvis; and 3) elsewhere.

A zone in any study was scored positive if there was any focal activity greater than surrounding soft tissue seen in any part of the zone which was seen on at least two occasions. The lungs were also scored positive if there was diffuse increased uptake. All colonic activity of Tc-99m HIG or In-111 HIG was scored positive. Ga-67 activity in the colon was scored positive if it the activity was greater than the liver and persisted at the same site for 24 hours.

Clinical Correlation

In each case, the results of the scintigraphic studies were compared with the final clinical diagnosis established by microbiological and histological investigation involving cultures of blood, urine, feces, sputum, bronchoalveolar lavage, or biopsy of liver, lymph node, or colon.

Statistical Analysis

The accuracy of each agent was compared with the accuracy of each of the other two agents using the 2 x 2 contingency table X² test (1 degree of freedom) described by Yates (13).

Results

In the group of patients imaged with both Ga-67 and Tc-99m HIG, a total of 20 zones in 18 patients with infection were clinically identified. Ga-67 identified 19 of these zones giving a sensitivity for the localization of infection of 95% (Fig. 1, Table 2). However, only 11 of these sites were identified by Tc-99m HIG, a sensitivity of only 55%.

Fig. 2. A patient with lymphoma in the chest and abdomen. There was also a left sided axillary lymph node infection due to Staphylococcus aureus. Only the infected lymph node has positive accumulation of In-111 HIG.
HIC, 22 zones in 20 patients were found to contain pathologic activity. In the group of 25 studies performed with In-111 HIC, one case of Pneumocystis carinii pneumonia was also reported. One patient had spinal osteomyelitis and another patient had negative In-111 HIC study, although seven were in the chest negative In-99m HMPH study. Of the nine zones with confirmed infection, but a

**Figure 3.** A 25-year-old man with Inhaled penicillins and non-HIV-1 infected patient had spinal osteomyelitis and another patient had negative In-111 HIC study, seven were in the chest negative In-99m HMPH study. Of the nine zones with confirmed infection, but a
A significant difference was detected between the number of patients with colorectal cancer in the presence of colorectal cancer was higher.

The number of patients with colorectal cancer was higher in the absence of colorectal cancer than in the presence of colorectal cancer.

A significant difference was observed between the number of patients with colorectal cancer and the number of patients with colorectal cancer in the presence of colorectal cancer. This difference was not statistically significant.

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with Ga-67 than expected from a previous study in which colonic uptake was only associated with colonic infection (17). As has been previously reported, the presence of bowel excretion of radiolabeled immunoglobulin can occur in patients with pathology elsewhere in the body, except in the absence of bowel infection (6). Both of our patients with colonic activity of In-111 HIG in the absence of colonic infection had B cell lymphoma (this did not involve the colon). The explanation remains unclear, but may be related to excretion of proteins into the bowel lumen.

Uptake of In-111 HIG into a noninfected hematoma is usually associated with an inflammatory response. This may then be visualized by any radiolabeled agent used to localize infection and inflammation.

It is unclear why the patient with acute renal failure should have diffuse intrapulmonary and intra-abdominal accumulation of In-111 HIG. Despite these cases, the specificity of In-111 HIG remains higher than Tc-99m HIG or Ga-67. The combination of high sensitivity and specificity of In-111 HIG means that it is significantly more accurate than either Ga-67 or Tc-99m HIG.

It was not possible to perform imaging using all three radiopharmaceuticals in the same patient for two reasons. First, it represents a significant radiation burden to patients who already face extensive radiological investigations. Second, because all three imaging studies would be performed sequentially, it would take approximately 2 weeks to perform the studies by which time the patient's clinical condition may have been modified by specific antimicrobial therapy or the natural history of the infection.

In conclusion In-111 HIG more accurately localizes in a wider range of infections in HIV antibody positive patients than either Ga-67 or Tc-99m HIG. This study suggests that In-111 HIG should be the scintigraphic method of choice in imaging infection in HIV antibody positive patients presenting with fever of unknown cause.

Acknowledgments

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References