New Myocardial Perfusion Imaging Agents: A Review  
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ABSTRACT  
Thallium-201 ($^{201}$Tl) has been the most commonly used agent for myocardial perfusion imaging. Its uptake is proportional to myocardial blood flow. Its ability to redistribute with time is useful in differentiating between ischemia and necrosis. However, its gamma energy is suboptimal for imaging and its three day half-life presents a heavy radiation burden to the patient. Thus, new myocardial perfusion imaging agents have been developed. Two classes of perfusion imaging agents, the isonitrile complexes and BATO compounds are reviewed in this article.

Of the isonitriles, Technetium 99m($^{99m}$Tc)-sestamibi is the most promising. It exhibits a very good myocardium to background ratio which is reached at 1-1.5 hours post-injection. The radioisotope $^{99m}$Tc has an optimum gamma energy for imaging and a short half-life. $^{99m}$Tc-sestamibi does not redistribute and as such, two injections are required to distinguish between ischemia and necrosis. A same day rest-stress study can be carried out by having the two required doses in a 1:5 radioactivity ratio. The smaller dose is used for the rest study and the larger dose for the stress study.

The BATO compound currently under study is $^{99m}$Tc-teboroxime. It exhibits a very high and rapid myocardial uptake allowing images of the heart to be obtained at 1-2 minutes post-injection. Due to a very rapid clearance, a second dose of equal radioactivity can be given 1-2 hours later for the rest study. $^{99m}$Tc-teboroxime is currently not yet licensed for use in Canada.

Key Words: myocardial imaging, radiopharmaceutical, sestamibi, teboroxime

INTRODUCTION  
Thallium-201 thallous chloride ($^{201}$Tl) has been one of the most commonly used agents for cardiac perfusion imaging (Table I). This radiopharmaceutical is efficiently extracted by the myocardium from the blood. It is actively transported into the myocardium via the Na$^+$/K$^+$ ATPase pump in a similar fashion to potassium.$^1$ The myocardial uptake of $^{201}$Tl is proportional to myocardial blood flow.$^2,3$ It is easily pumped in and out of the myocardial cells. As a result, with
time, thallium exhibits a tendency to redistribute itself as changes in myocardial perfusion occur. The ability of thallium to redistribute with time is useful to differentiate transient ischemia from scar and necrotic myocardium as a result of infarction. Therefore, if $^{201}\text{Tl}$ is injected at a time of transient localized myocardial ischemia (as seen in angina or during exercise) the poorly perfused segment of the heart will show reduced uptake of the tracer. At rest, the diseased part of the heart regains its blood supply and the defect in $^{201}\text{Tl}$ uptake “fills in” with time (Figure 1). Necrotic areas following infarction would show a persistently reduced tracer uptake.

Thallium has several disadvantages as an imaging agent. It has poor imaging properties. Only a small proportion of the radiation emitted due to decay of $^{201}\text{Tl}$ is suitable for external scintigraphy. Imaging is normally performed using the mercury (Hg) X-rays which have energies of 70-80 keV. This low energy results in significant soft tissue attenuation and poor resolution. Also, $^{201}\text{Tl}$ achieves a high concentration in the kidney and has a long physical half-life of 73 hours. The combination of these factors results in a relatively high radiation dose to the patient limiting the amount of radioactivity administered to about 111 MBq (3mCi). Administration of this dose would deliver 5cGy of radiation dose to the kidneys. The redistribution of $^{201}\text{Tl}$ with time can also be a disadvantage since it necessitates the rapid initiation and completion of imaging. Several new radioactive tracers for perfusion have been developed to overcome these disadvantages.

**Early $^{99m}\text{Tc}$-Isonitrile Complexes**

Technetium-99m ($^{99m}\text{Tc}$) is the most widely used radionuclide in nuclear medicine because it has many favourable qualities for nuclear imaging. The problem of tissue attenuation is less with the higher energy 140 keV gamma photons of $^{99m}\text{Tc}$ compared with the low energy 80 KeV Hg X-rays from $^{201}\text{Tl}$. The combination of these factors results in a relatively high radiation dose to the patient limiting the amount of radioactivity administered to about 111 MBq (3mCi). Administration of this dose would deliver 5cGy of radiation dose to the kidneys. The redistribution of $^{201}\text{Tl}$ with time can also be a disadvantage since it necessitates the rapid initiation and completion of imaging. Several new radioactive tracers for perfusion have been developed to overcome these disadvantages.

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in the lungs compared with TBI. Several studies have shown CPI to have high sensitivity and specificity for detection of coronary artery disease.

99mTc-Sestamibi

Another complex belonging to the isonitrile family is 99mTc 2-methoxy-isobutyl-isonitrile (99mTc-sestamibi, hexamibi or MIBI) (Table I). It is currently marketed in Canada by DuPont under the trade name of Cardio-lite. Its chemical structure is shown in Figure 2. Comparing TBI, CPI and sestamibi, McKusick et al have shown that sestamibi displayed the highest initial contrast due to good heart uptake and low lung and liver uptake.

Mechanisms of Uptake

99mTc-sestamibi, a lipophilic complex, enters the myocytes via passive diffusion. This results in reduced efficiency of extraction compared with 201Tl, which is transported via the active transport Na+/K+ ATPase pump. Mousa et al demonstrated that sestamibi was 40% extracted on first-pass. This compares with the 80% extraction for 201Tl. The mechanism of myocardial uptake of sestamibi can be demonstrated by the fact that its uptake is unaffected by ouabain (a Na+/K+ ATPase inhibitor), in contrast to thallium which is 50% inhibited by ouabain. Also in contrast to 201Tl, no redistribution is seen with sestamibi. This may be due to the slow rate of myocardial washout and continual renal and hepatobiliary clearance from the circulation. Some investigators have also reported that the lack of redistribution may be due to the binding of sestamibi with high affinity to a myocardial cytosolic site. This binding moiety has a small molecular weight in the range of 104 Da. Since sestamibi is unable to leave the myocardial cells and redistribute as blood flow changes (as is the case with 201Tl), this means that two injections are required. One injection must be given at rest and one during exercise in order to distinguish between transient ischemia and infarcted sites.

Pharmacokinetics

Similar to 201Tl, myocardial uptake of sestamibi is proportional to blood flow in both animals and humans. The first pass extraction fraction (40%) is lower than 201Tl (90%). Unlike 201Tl, sestamibi is cleared very slowly from the myocardium and redistribution is negligible. Sestamibi shows rapid blood clearance with low lung uptake and low peak liver activity. It is cleared quickly through the hepatobiliary pathway. Sestamibi kinetics in normal volunteers showed marked accumulation in the liver and spleen during the first 60 minutes after a resting injection. Despite this, the heart was well visualized. When given at rest, in-

Table I: Properties of Myocardial Perfusion Imaging Agents

<table>
<thead>
<tr>
<th></th>
<th>201Tl</th>
<th>99mTc-sestamibi</th>
<th>99mTc-teboroxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>gamma energy</td>
<td>70-80 KeV</td>
<td>141 KeV</td>
<td>141 KeV</td>
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<tr>
<td>physical T1/2</td>
<td>3.1 days</td>
<td>6 hours</td>
<td>6 hours</td>
</tr>
<tr>
<td>first pass extraction</td>
<td>80%</td>
<td>40%</td>
<td>80-90%</td>
</tr>
<tr>
<td>mechanism of extraction</td>
<td>Na+/K+ATPase pump</td>
<td>diffusion</td>
<td>diffusion</td>
</tr>
<tr>
<td>redistribution</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>imaging protocol</td>
<td>image after stress and repeat image 4 hours later</td>
<td>image 60 minutes after rest dose then stress dose given and repeat image 60 minutes later</td>
<td>image immediately after stress and rest dose</td>
</tr>
<tr>
<td>usual dose</td>
<td>110 MBq</td>
<td>rest = 296 MBq</td>
<td>rest = 555 MBq</td>
</tr>
<tr>
<td>stress dose</td>
<td>201Tl</td>
<td>stress = 814 MBq</td>
<td>stress = 555 MBq</td>
</tr>
<tr>
<td>dosimetry a</td>
<td>5 mGy/110 MBq</td>
<td>5 mGy/1110 MBq</td>
<td>5 mGy/1110 MBq</td>
</tr>
<tr>
<td>major route of elimination</td>
<td>renal</td>
<td>hepatobiliary</td>
<td>hepatobiliary</td>
</tr>
</tbody>
</table>

Figure 2: Structural formula of 99mTc-sestamibi.
Figure 3: A $^{99m}$Tc-Sestamibi study demonstrating transient ischemia. After administration of the stress dose, a perfusion defect is seen in the infero-lateral wall (arrow). After administration of the rest dose the previous perfusion defect has regained its blood supply.

(Reprinted with permission from: Taillefer et al, Clin Nucl Med 1989; 14:89-96)

Initially liver had accumulated more radioactivity than the heart but this decreased with time as the radiopharmaceutical was excreted into the hepatobiliary system. From 1-1.5 hours after a rest injection, the radioactivity in the heart was higher than in immediate adjacent organs. After an exercise injection, substantially less uptake in the liver was observed with excellent visualization of the heart as compared to injection at rest. When sestamibi was administered after exercise, the heart had higher concentration than the adjacent organs. Substantial excretion into the gallbladder can be noted both after exercise and at rest, reaching a maximum at approximately one hour after injection. At both rest and exercise, the gallbladder has a higher radioactivity concentration than the heart throughout the length of the study. The agent clears rapidly from the blood and is excreted through the urinary and biliary systems. Approximately 60% is excreted within the first two hours. At rest and exercise, the clearance curves are biexponential with an initial fast distribution phase and a later slow clearance phase.

Okada et al investigated the myocardial kinetics of sestamibi in 12 dogs with experimentally induced ischemia. Sestamibi myocardial clearance was minimal and not significantly different for both the normal and ischemic zones. In 15 patients with coronary heart disease, washout in normal myocardium and myocardial defects were also found to be very similar. In contrast, a study by Franceschi found different rates of myocardial washout for the normal myocardium, mild and severe myocardial defects.

Sestamibi Compared with $^{201}$Tl

When compared with $^{201}$Tl, sestamibi consistently resulted in images of improved quality. The sestamibi images were less granular and had a “crisper” quality. Clinical trials with sestamibi have reported sensitivities and specificities for detection of coronary artery disease similar to that of $^{201}$Tl. In 38 patients, comparison with $^{201}$Tl showed concordance regard-
ing either normality or abnormality in 87% of the cases. Many other investigators have also found that there is no significant difference between $^{201}$Tl and sestamibi in myocardial defect detection or in the size of the defect detected.17,18,19,20 Myocardial imaging with sestamibi has also been found to have a detection rate of coronary artery disease similar to that with coronary angiography.16,21

Radiation Dosimetry
Technetium-99m has a relatively short physical half-life of six hours. The excretion of sestamibi is mainly via the hepatobiliary route with some renal excretion. This combines to provide highly favourable radiation dosimetry. Doses as high as 1110 MBq (30mCi) per 70 kg have been routinely employed.5 According to Wackers et al.16, organs involved in the excretory pathways of sestamibi such as gallbladder, intestines, kidneys and bladder receive the highest radiation absorbed dose per unit of injected radioactivity. The critical organ appears to be the upper large intestine.5,16 It appears that 1110 MBq (30mCi) can be administered with no individual organ dose exceeding 5 cGy.16

Dosage and Administration Protocol
Since sestamibi does not redistribute, in order to distinguish transient ischemia from infarcted sites, a second injection of $^{99m}$Tc-sestamibi is needed. One injection is administered at rest and one injection during exercise.2,3,17 In order to allow for myocardial radioactivity from the first injection to decrease, the two injections have been given 24 hours apart by many investigators thereby requiring a next day visit.5,8,18,21 This is impractical in clinical practice as it is preferred to perform both studies on the same day.

For same day evaluation, two separate $^{99m}$Tc-sestamibi doses are given in a 1:5 or 1:10 ratio so that during the second examination, one can neglect the remaining radioactivity from the first injection.17 Tailfeer et al compared sestamibi images using either a short or long interval between rest and stress injections.22 For the short interval protocol, 259-370 MBq (7-10mCi) was administered at rest and the patient imaged 30 to 60 minutes later. Immediately after the resting study, 925-1110 MBq (25-30mCi) was administered at stress and the patient imaged again 30 to 60 minutes later. In the long interval protocol, the patient received a dose of 370 MBq (10 mCi) at stress two days after the initial dose of 370 MBq (10 mCi) given at rest. Qualitative and quantitative comparisons between the short and long protocol showed that both protocols had the same diagnostic accuracy in the evaluation of segmental myocardial perfusion. Both methods showed the same number of ischemic segments and fixed defects. The localization of defects was also identical. The similar results obtained in both the same day and two day imaging protocols was also confirmed by Broges-Neto et al.23 Therefore, it is feasible to administer the doses for both rest and stress studies on the same day.

To determine which study to be done first, 18 patients were enrolled in a trial comparing the rest-stress and stress-rest sequence protocols.24 Both injection sequences produced images which were similar in 15/18 patients. However, in three patients, certain myocardial segments which were normal on the rest images of the rest-stress protocol, showed persistent defects on the rest images of the stress-rest sequence. Thus, the injection of 925 MBq (25mCi) of $^{99m}$Tc-sestamibi at rest was not able to completely fill in the significant defect observed after the stress phase injection. As a result, reversible defects confirmed with a $^{201}$Tl scan were not reversible with $^{99m}$Tc-sestamibi if the stress-rest protocol was used.

Giving the resting dose first has several advantages:

1. Since the rest study usually shows relatively uniform activity distribution, it is therefore easier to visualize a defect at stress on a uniform background activity from the rest study than to demonstrate the filling in of a defect in a stress-rest protocol.

2. Although both rest and stress studies are equally important, diagnostically, it is more important to have better radioactivity counting statistics on the stress images.

3. For a given amount of injected radioactivity, the absolute myocardial uptake of sestamibi is higher at stress than at rest due to greater blood flow at exercise. This means that the myocardial uptake of the second injection in the rest-stress protocol would be higher than the uptake of the second injection of the stress-rest protocol. As a result, the difference in myocardial uptake between the rest and stress images would be greater with the rest-stress than with the stress-rest protocol.22,24

Clinical Use
In addition to myocardial perfusion imaging to detect ischemia or infarction, $^{99m}$Tc-sestamibi can also be used to assess myocardial perfusion before and after thrombolysis therapy. $^{201}$Tl cannot be readily used for this purpose since therapy would have to be delayed while a baseline perfusion image was obtained. Since $^{99m}$Tc-sestamibi does not redistribute, it can be administered prior to thrombolytic therapy and a baseline perfusion image can be obtained.
later.² ⁹⁹ᵐTc-sestamibi has been used to demonstrate the success of salvaging jeopardized myocardium following fibrinolytic therapy in patients with acute myocardial infarction (Figure 5).²⁰,²⁵,²⁶

Global and regional function of both ventricles can be assessed using the first-pass technique (images of a bolus dose of ⁹⁹ᵐTc-sestamibi on its first-pass through the heart immediately after injection). Therefore, simultaneous analysis of function and perfusion is possible.³,⁵,⁶,²²

In the many clinical trials of sestamibi, reactions from its administration have not been noted. Serious complications such as severe arrhythmia, worsening of angina or myocardial infarction have not occurred during or after stress testing. A transient metallic or bitter taste was experienced however by many patients within one minute of stress or rest sestamibi injection. This minor side effect lasted less than 15 seconds.²¹,²²,²⁴

**Bato Compounds**

BATO compounds are boronic acid adducts of technetium oxime complexes.²⁷ They are neutral seven coordinate technetium vicinal dioxime complexes which have a boron group at one end.³,²⁷ One promising BATO compound, not yet available in Canada, is ⁹⁹ᵐTc-SQ30217, also known as teboroxime (Figure 6 and Table I).

**Uptake Mechanism**

Teboroxime, a lipophilic compound, diffuses rapidly across the cell membrane.²⁸ In dogs, where the tracer was injected directly into the proximal left anterior descending coronary artery, the myocardial first-pass extraction fraction averaged 80-90%. There was no relationship between extraction fraction and myocardial blood flow over a wide range of flows (from 0.3 - 7.7 mL/min/g myocardium).²⁸,²⁹ This favourable characteristic means that the percentage of the dose extracted on the first-pass will be the same over a wide range of blood flow. Other tracers such as ²⁰¹Tl and ⁹⁹ᵐTc-sestamibi demonstrate different extraction fractions with varying blood flow.

![Figure 5: Assessing the efficacy of thrombolytic therapy by myocardial perfusion imaging using ⁹⁹ᵐTc-sestamibi. ⁹⁹ᵐTc-sestamibi was administered following acute myocardial infarction immediately prior to initiating thrombolytic therapy. Image obtained 4 hours after injection of ⁹⁹ᵐTc-sestamibi revealed a septal perfusion defect. A follow up study with ⁹⁹ᵐTc-sestamibi 5 days later demonstrated improved perfusion of the septal area. (Reprinted with permission from: Kayden et al, J Nucl Med 1988; 29:1865-7)](image)

![Figure 6: Structural formula of ⁹⁹ᵐTc-teboroxime.](image)
Pharmacokinetics

Studies in dogs and human volunteers showed rapid clearance of 99mTc-teboroxime from the myocardium. Lung uptake was low. The hepatobiliary pathway was the major route of excretion for 99mTc-teboroxime. In animal testing, during the 24 hours after administration, approximately 68% of the dose was excreted in the feces and approximately 13% in the urine. Initially, the hepatic radioactivity was low, but rapidly increased relative to the heart so that the hepatic radioactivity peaked five to ten minutes after injection. 99mTc-teboroxime exhibited a biphasic washout pattern from the heart. Up to two thirds was cleared with a half-life of two to four minutes in the initial rapid phase. The remainder was cleared slowly with a half-life ranging from 40 to 78 minutes. Narra et al also demonstrated in rats that clearance from the blood was rapid. At one minute postinjection, less than 4% of the injected dose was present in the blood. In one clinical trial, 15 minutes after injection only 9.5% remained in the circulation.

Comparison with 201T1

Several investigators have found close agreement between 99mTc-teboroxime and thallium test results. In a multicentre trial, 444-1480 (12-40mCi) of 99mTc-teboroxime was administered to 19 patients. Investigators rated the quality of the teboroxime myocardial images as fair or good in 92% of the studies. Sensitivity and specificity were 83.2% and 92.1% respectively. Imaging with 99mTc-teboroxime showed agreement with 201T1 in 90.4% of the cases. In another study, diagnostic information obtained from 30 patients who recently underwent 201T1 imaging and/or cardiac catheterization was compared to images obtained with 99mTc-teboroxime. Correlation of diagnostic information was noted in 90% of cases. Location of ischemia and infarction was correlated exactly in 21 of 28 patients. There appears to be no significant difference between the ability of 99mTc-teboroxime and 201T1 to detect myocardial perfusion defects and coronary artery disease. In one study by Seldin et al, it was noted that due to the high liver activity observed with 99mTc-teboroxime, inferolateral segments of the heart were obscured in 15 of 21 patients studied. However, this did not affect the identification of perfusion abnormalities and resulted in no significant difference between 201T1 and 99mTc-teboroxime in detection efficacy.

Radiation Dosimetry

Since 99mTc-teboroxime is mainly excreted via the hepatobiliary route and to a lesser extent in the urine, the small and large intestines are the critical organs. Based on animal data, the small and large intestines will each receive 2.55 and 2.40 cGy/555 MBq (170 and 160 mrad/mCi) respectively. The liver, kidneys, and ovaries will each receive approximately 0.75 cGy/MBq (50 mrad/mCi). Thus a dose of up to 1100 MBq (30 mCi) per clinical study either in single or divided dose may be given with acceptable radiation dosimetry.

Dosage Administration and Imaging Protocol

Myocardial images of good quality can be obtained as early as one to two minutes after injection (Figure 7). From the pharmacokinetic studies which demonstrated a very rapid myocardial clearance and peak hepatic uptake at five to ten minutes post injection (PI), it is suggested that imaging be started within two minutes PI and completed by ten minutes PI. Image completion within ten minutes can be accomplished by decreasing the acquisition time per projection for single photon emission computerized tomography (SPECT) imaging or using planar imaging techniques.

The rapid myocardial clearance kinetics allows administration of a second dose within one to two hours. After one to two hours, most of the myocardial radioactivity has cleared. There is no need to inject a second dose containing higher radioactivity as is the case with 99mTc-sestamibi. Several investigators have used two equal 555 MBq (15 mCi) doses for both the rest and stress studies with a two to three hour interval between studies.

Summary

Due to the imaging and radiation dosimetry limitation of 201T1, a number of 99mTc labelled myocardial perfusion imaging agents have been developed. These include 99mTc isonitriles and the BA TO compounds.

Of all the isonitrile complexes, 99mTc-sestamibi seems to be the most promising, exhibiting the best target: background ratio. 99mTc-sestamibi is a useful agent for assessing myocardial perfusion. It is taken up into the myocardium in proportion to myocardial blood flow. Clinically, its ability to detect a perfusion abnormality is similar to that of 201T1, the current perfusion imaging agent of choice. However, better quality images were consistently reported for 99mTc-sestamibi due to the more optimum gamma energy of 99mTc.
for imaging. It is cleared rapidly from the blood mainly via the hepatobiliary pathway. The short half-life of $^{99m}$Tc (six hours) and the rapid clearance of sestamibi combine to give favourable dosimetry. A dose of 1110 MBq (30 mCi) can be given without any organ exceeding 5 cGy. The administered dose is ten times higher than that permitted with $^{201}$T1. The lack of redistribution seen with sestamibi necessitates two separate injections to differentiate between ischemia and infarct. Studies have shown that the best protocol is to split the two doses in a 1:5 ratio. The small dose is administered first for the resting phase and the large dose is administered second for the stress phase of the study.

$^{99m}$Tc-Teboroxime or SQ30217 is of the BATO family. Its first-pass myocardial extraction is very high (approximately 90%). It is cleared quickly from the blood and the myocardium. Five minutes after injection, approximately 70% of the activity has cleared from the myocardium. The rapid washout means that imaging should be started within two minutes PI and completed by ten minutes PI. Its rapid clearance also allows for same day evaluation of rest and stress perfusion and the rest dose and stress dose can be of equal radioactivity. Based on animal data, it is thought that 1110 MBq (30mCi) can be safely administered to humans. This means that 555 MBq (15mCi) can be injected for the rest study and two to three hours later another dose of 555 MBq (15mCi) can be administered for the stress study. The clinical trials to date have shown $^{99m}$Tc-teboroxime to be comparable to $^{201}$T1 in evaluating myocardial perfusion defects.

**REFERENCES**
