Intra-Individual Comparison of 3(R)-BMIPP and 3(S)-BMIPP Isomers in Humans

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The racemic 15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid (BMIPP) is currently used at several centers for myocardial metabolic imaging with SPECT. Recently, the 3(R)-BMIPP isomer showed a 20%–25% higher myocardial uptake and lower liver uptake than 3(S)-BMIPP in fasted rats. The aim of this study was to determine if these differences in myocardial and liver uptake also occur in humans. **Methods:** Iodine-123-labeled 3(R)-BMIPP and 3(S)-BMIPP isomers were injected at rest, on two separate days, in six patients with stable coronary artery disease. Dual-head, whole-body scintigraphy was performed 20 min and 3 hr after injection. SPECT cardiac imaging was performed 60 min after injection. **Results:** Myocardial activity averaged (% injected dose ± s.d.) 3.15 ± 0.49 versus 3.01 ± 0.44 at 20 min (p = ns) and 2.64 ± 0.38 versus 2.55 ± 0.41 at 3 hr postinjection (p = ns) for the 3(R)-BMIPP and 3(S)-BMIPP isomers, respectively. Liver activity averaged 9.50 ± 1.18 versus 9.44 ± 0.66 at 20 min and 5.33 ± 0.64 versus 5.43 ± 0.66 at 3 hr, respectively (p = ns). SPECT showed no difference in the distribution of the two isomers between normal and infarcted myocardium. **Conclusion:** There is no significant difference in myocardial and liver distribution of the 3(R)-BMIPP and 3(S)-BMIPP isomers in humans.

Key Words: 15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid; fatty acids; biodistribution study

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15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid (BMIPP) is a methyl-branched long-chain fatty acid analog that is of widespread interest for evaluating myocardial metabolism with SPECT (*1,2*). A methyl group was introduced at the beta-carbon to achieve prolonged retention of the tracer in the myocardium. Thus far, the racemic 3(R,S)-methyl mixture of BMIPP has been used. Because single enantiomers in a racemic mixture may show differences in their biological activity, transport or metabolism as a result of stereoselective and/or stereospecific interactions, it might be possible that more specific myocardial uptake is seen for either the 3(R)-BMIPP or 3(S)-BMIPP isomer.

Recently, 3(R)-BMIPP and 3(S)-BMIPP have been resolved and characterized (*3*). In fasted rats, 3(R)-BMIPP showed 20%–25% higher myocardial uptake than 3(S)-BMIPP, whereas blood levels and uptake and clearance from liver, lungs and kidneys were nearly identical for both isomers (*4*). No differences in metabolism and lipid-pool distribution were found, suggesting that higher myocardial uptake of 3(R)-BMIPP in rats may result from differences in transport into myocytes (*5*).

The purpose of this study was to determine if differences in myocardial uptake and biodistribution of 3(R)-BMIPP and 3(S)-BMIPP also occur in humans.

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MATERIALS AND METHODS

3(R)-BMIPP and 3(S)-BMIPP

3(R)-BMIPP and 3(S)-BMIPP isomers were synthesized as described earlier by Lin et al. (*3*) and labeled with ^{123}I using the Cu(I)-assisted isotopic exchange reaction developed by Mertens et al. (*6*).

Patient Population

Six men (age range 43–70 yr; mean age 62.3 yr) with chronic stable coronary artery disease participated in the study after giving informed consent. All patients had a history of previous acute myocardial infarction 2–16 yr before the study. All patients had severe multivessel disease for which they underwent either coronary bypass surgery (five patients) or angioplasty (one patient). All patients were asymptomatic and in stable hemodynamic condition during the last 6 mo before the study. The usual drug regimen was not modified during the study period.

Study Design

Each patient was studied on two separate days, in a random sequence. On the first day, 148–185 MBq of one ^{123}I-labeled BMIPP isomer was intravenously injected at rest; the other ^{123}I isomer was investigated under the same conditions 2 days later. The patients were studied at rest after an overnight fast. They received oral Lugol's solution 10 min before the injection to block thyroid uptake of free iodine. Dual-head, whole-body scintigraphy was performed 20 min and 3 hr postinjection. SPECT cardiac imaging was performed 60 min postinjection. The study protocol was approved by the Commission of Medical Ethics of the Free University Brussels.

Plasma Activity and Urinary Excretion

Blood samples were drawn into heparine syringes at 15 min, 90 min and 3 hr after tracer administration. Plasma was separated by centrifugation, and the activity was measured on samples of 1 ml in a well counter (Cobra II Inspector 5003; Canberra-Packard, Downers Grove, IL). Total plasma volume was estimated from patient's body weight and length and the hematocrit. By comparison to a standard, plasma activity was expressed as a percentage of the injected dose (ID). Urinary excretion was calculated on urine samples collected at 3 hr postinjection.

Whole-Body Scintigraphy

Whole-body scintigraphy was performed 20 min postinjection and 3 hr postinjection using a dual-head gamma camera (Bodyscan; Siemens, Inc., Hoffman Estates, IL) equipped with low-energy, high-resolution collimators. The photopeak was set at 159 keV with a 15% window. The scanning speed was 10 cm/min. The anterior and posterior images were used to create a whole-body geometric mean image to correct for the relative depth of the organs in the body. Irregular regions of interest (ROIs) were drawn around the heart and liver on the 3(R)-BMIPP and 3(S)-BMIPP geometric mean images displayed side-by-side. Organ activities were expressed as a percentage of the total counts in the whole body at 20 min postinjection that correspond to the injected dose.

TABLE 1
Plasma Activity and Urinary Excretion

	3(R)-BMIPP	3(S)-BMIPP	p value
Total plasma activity			
15 min pi	16.4 ± 2.9	13.2 ± 1.6	ns
90 min pi	20.2 ± 2.9	18.8 ± 3.5	ns
3 hr pi	21.2 ± 3.5	19.1 ± 2.31	ns
Urinary excretion			
3 hr pi	7.29 ± 3.25	6.77 ± 2.86	ns

Results are in percentage of the injected dose.
pi = postinjection; ns = not significant.

Activities measured at 3 hr postinjection were corrected for isotopic decay.

Heart-to-Liver and Heart-to-Lung Ratios

The anterior projection of SPECT cardiac imaging obtained 60 min postinjection (vide infra) was analyzed separately with ROIs drawn around the left myocardium, liver and right lung. The heart-to-liver and heart-to-lung ratios were calculated. Activities are given in counts/pixel/mCi.

SPECT Cardiac Imaging

SPECT cardiac imaging was started 60 min postinjection using a triple-head gamma camera (MultiSPECT 3, Siemens, Inc.) equipped with medium-energy collimators (*7*). The photopeak was set at 159 keV with a 15% window. Ninety-six projections (60 sec/stop, 32 stops, 64 × 64 format, zoom 1.23) were recorded over 360°. Tomographic images were reconstructed (Butterworth filter, cutoff frequency at 0.5 cycle/pixel, order = 5) using the projections corresponding to a 180° acquisition, symmetrical to the long axis of the left ventricle. Myocardial activity was measured on representative two-pixel-thick apical, midventricular and basal short-axis slices using 3 × 3 pixel ROIs drawn over the anterior, lateral, inferior and septal myocardium. The minimum count in the left ventricular cavity was also determined on the basal representative slice. Activities are given in counts/voxel/mCi.

Abnormalities in the uptake of 3(R)-BMIPP and 3(S)-BMIPP were identified and quantified on distance-weighted polar maps using the values obtained in 10 healthy volunteers with 3(R,S)-BMIPP as a reference. A severity index was calculated as the product between the extent of abnormal uptake (in percent of the left ventricular surface below 2 s.d. of the mean normal values) and the average intensity of the defect (in percent of the mean normal values). The severity index is expressed in 1/10,000.

Statistical Analysis

Results are given as mean ± s.d. The differences in activities between the isomers were compared with Wilcoxon's signed rank test. Probability values < 0.05 were considered statistically significant.

RESULTS

Plasma Activity and Urinary Excretion

There was no significant difference in plasma activities at 15 min, 90 min and 3 hr postinjection between the 3(R)-BMIPP and 3(S)-BMIPP isomers (Table 1). Urine excretion at 3 hr postinjection averaged 7.29% ID (s.d. = 3.25) for 3(R)-BMIPP and 6.77% ID (s.d. = 2.86) for 3(S)-BMIPP (p = ns).

Percentage of Total-Body Uptake

Whole-body images obtained in a Patient 20 min postinjection are shown in Figure 1. Early and late images show similar distribution with 3(R)-BMIPP and with 3(S)-BMIPP. The percentage of total-body uptake in the heart and in the liver are given in Table 2.

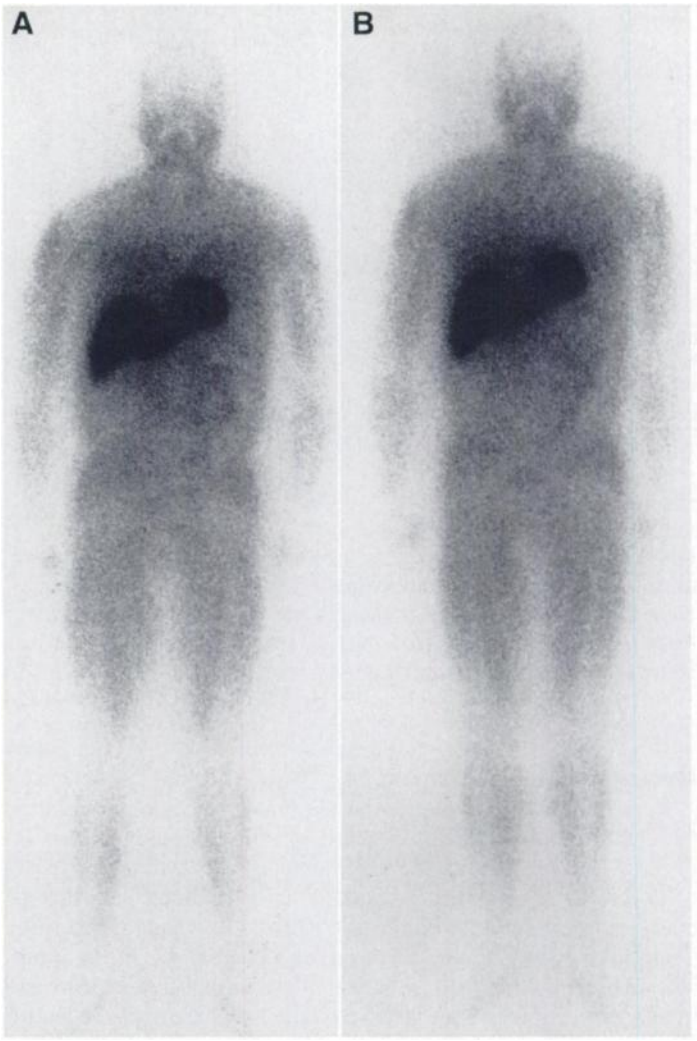

FIGURE 1. Whole-body images (anterior view) obtained with ^{123}I-3(R)-BMIPP (A) and 2 days later with ^{123}I-3(S)-BMIPP (B). Images were acquired 20 min postinjection.

On early whole-body scintigraphy (20 min postinjection), cardiac activity averaged 3.15% (s.d. = 0.49; range 2.58–3.75) of the total-body uptake with 3(R)-BMIPP and 3.01% (s.d. = 0.44; range 2.46–3.52) with 3(S)-BMIPP (p = ns). Liver activity averaged 9.50% (s.d. = 1.18; range 8.53–11.39) with 3(R)-BMIPP and 9.44% (s.d. = 0.66; range 8.77–10.28) with 3(S)-BMIPP (p = ns).

Washout rates from the heart between 20 min and 3 hr postinjection averaged 18.7% (s.d. = 4.5) with 3(R)-BMIPP and 18.3% (s.d. = 7.6) with 3(S)-BMIPP (p = ns). Changes in liver activity were 28.5% (s.d. = 4.8) and 27.0% (s.d. = 8.3) for 3(R)-BMIPP and 3(S)-BMIPP, respectively (p = ns).

TABLE 2
Percentage of Total-Body Uptake in Heart and Liver

		3(R)-BMIPP	3(S)-BMIPP	p value
20 min pi	Heart	3.15 ± 0.49	3.01 ± 0.44	ns
	Liver	9.50 ± 1.18	9.44 ± 0.66	ns
3 hr pi	Heart	2.64 ± 0.38	2.55 ± 0.41	ns
	Liver	6.60 ± 0.36	6.79 ± 0.54	ns

Results are in percentage of the geometric mean counts of the whole body 20 min pi.
pi = postinjection; ns = not significant.

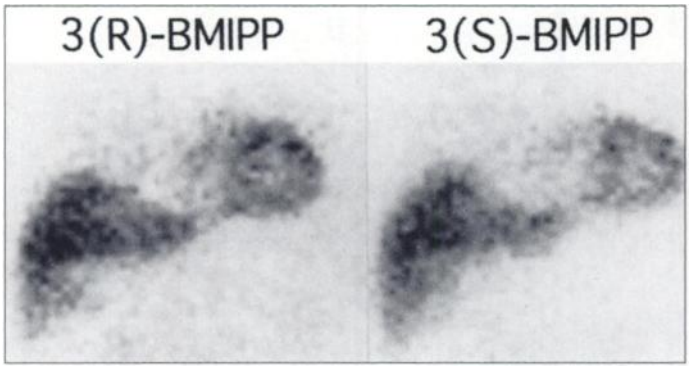

FIGURE 2. Planar images (anterior view) obtained with ^{123}I-3(R)-BMIPP (left panel) and 2 days later with ^{123}I-3(S)-BMIPP (right panel). Images were acquired 60 min postinjection.

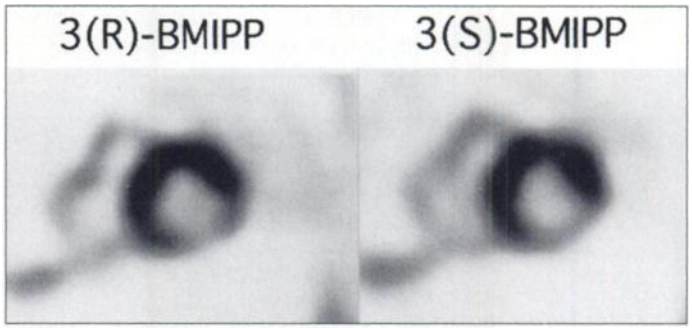

FIGURE 3. Midventricular short-axis slices obtained with ^{123}I-3(R)-BMIPP (left panel) and 2 days later with ^{123}I-3(S)-BMIPP (right panel) in a patient with inferior myocardial infarction. Images were acquired 60 min postinjection.

Heart-to-Liver and Heart-to-Lung Ratios

Planar images obtained 60 min postinjection with 3(R)-BMIPP and 3(S)-BMIPP are shown in Figure 2. Quantitative measurements are given in Table 3. No significant differences were found between 3(R)-BMIPP and 3(S)-BMIPP for heart, liver or lung activities. However, a small improvement in the heart-to-liver ratio was calculated with 3(R)-BMIPP 1.06 (s.d. = 0.15) versus 0.94 (s.d. = 0.19) with 3(S)-BMIPP ($p = 0.028$).

Myocardial SPECT Imaging

Representative midventricular short-axis slices obtained in a patient with an inferior myocardial infarction are shown in Figure 3. High-quality SPECT images were obtained with 3(R)-BMIPP and with 3(S)-BMIPP in all patients. No differences were found between the two isomers on visual inspection. Quantitative measurements are given in Table 4. On the polar maps, the location and severity of abnormalities in BMIPP uptake were similar with the two isomers. The severity index of BMIPP defects averaged 372 (range 54–873) with 3(R)-BMIPP and 336 (range 16–985) with 3(S)-BMIPP (p = ns).

DISCUSSION

The availability of the 3(R)-BMIPP and 3(S)-BMIPP isomers has provided us with the unique opportunity to evaluate the relative tissue uptake properties of the ^{123}I-labeled isomers in an initial group of six patients.

Single enantiomers in a racemic mixture may show differences in their biological activity as a result of stereoselective and/or stereospecific interactions within a chiral biological environment. In the racemic 3(R,S)-BMIPP mixture that is currently used for clinical studies, the 3(R)-BMIPP and 3(S)-BMIPP isomers may show different extraction and/or pharmacokinetic properties in transport, activation and metabolism. Increased specificity of one single enantiomer for the myocardium would improve the quality of cardiac imaging and reduce the radiation exposure to patients and costs.

The 3(R)-BMIPP and 3(S)-BMIPP isomers have been recently resolved and synthesized (*3*). In dual-label experiments conducted in fasted rats, the 3(R)-BMIPP isomer exhibited 20%–25% higher myocardial uptake and lower liver uptake than the 3(S)-BMIPP isomer (*3,4*). The results of the studies summarized here clearly demonstrate that the global uptake and washout kinetics of ^{123}I-labeled 3(R)-BMIPP and 3(S)-BMIPP are essentially the same in humans after fasting and under the usual resting conditions. Differences in relative myocardial activity were much less pronounced in humans (5%–7%) than observed in the initial animal studies conducted in rats (20%–25%). No differences were observed in the distribution of the two isomers between normal and infarcted myocardium.

Medium-energy collimators were used to calculate the heart-to-liver and the heart-to-lung ratios and to determine the severity of myocardial defects on SPECT. The ^{123}I spectrum contains high-energy photons, exceeding 400 keV, with a 2.5% abundance. The relative influence of these photons in the 159 keV photopeak window is amplified, up to 30%, when low-energy collimators are used for cardiac imaging because of septal penetration from sources out of the direct field of view, such as the liver. Phantom studies have indicated a systematic underestimation of defect contrast when low-energy collimators were used but not with medium-energy collimators (*7*).

Although slight differences in the relative myocardial uptake of the 3(R)-BMIPP and 3(S)-BMIPP isomers were detected in fasted rats, a careful analysis of the incorporation of the two isomers into lipids of the myocardium and other rat tissues did not show any differences (*4,5*). These results may indicate that there are species differences in some aspect of the carrier protein-mediated uptake of fatty acids into the myocytes.

Recent studies have reported that myocardial uptake and washout of BMIPP could be changed after glucose or exercise loading compared with fasting and resting states (*8,9*). However, nearly all BMIPP studies extensively reported in the literature have been and are conducted at rest, rather than exercise, and in fasting condition, rather than after glucose

TABLE 3
Heart, Liver and Lung Activity on Anterior Planar Imaging 60 Minutes Postinjection

	3(R)-BMIPP	3(S)-BMIPP	p value
Heart	18.63 ± 3.47	16.88 ± 3.57	ns
Liver	17.66 ± 3.17	18.10 ± 2.30	ns
Lung	9.58 ± 1.39	8.74 ± 2.39	ns
Heart-to-liver ratio	1.06 ± 0.15	0.94 ± 0.19	0.028
Heart-to-lung ratio	1.94 ± 0.20	1.97 ± 0.22	ns

Activities are in counts/pixel/mCi.
ns = not significant.

TABLE 4
Myocardial Counts on SPECT Imaging 60 Minutes Postinjection

	3(R)-BMIPP	3(S)-BMIPP	p value
Myocardium	47.50 ± 10.0	44.21 ± 12.29	ns
Cavity	19.27 ± 6.58	18.64 ± 8.74	ns
Myocardium-to-cavity ratio	2.56 ± 0.38	2.62 ± 0.88	ns
Severity index	372 ± 367	337 ± 409	ns

Activities are in counts/voxel/mCi. Severity index is in 1/10,000.

loading (*10–17*). For these reasons, the comparative studies with 3(R)-BMIPP and 3(S)-BMIPP were conducted exactly in the same type of protocol that is widely used. The detection of any major differences in myocardial uptake and washout kinetics in humans would complicate the extensive data that have been presented in the literature over the last several years.

CONCLUSION

No differences were observed in the distribution of the 3(R)-BMIPP and 3(S)-BMIPP isomers in humans. The results of our studies demonstrate that the use of the racemic ^{123}I-3-(R,S)-BMIPP does not provide any anomalies with respect to possible different behavior of the two isomers of BMIPP.

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