Pharmacokinetics of ^{99m}Tc-MAA- and ^{99m}Tc-HSA-Microspheres Used in Preradioembolization Dosimetry: Influence on the Liver–Lung Shunt

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Perfusion scintigraphy using ^{99m}Tc-labeled albumin aggregates is mandatory before hepatic radioembolization with ^{90}Y-microspheres. As part of a prospective trial, the intrahepatic and intrapulmonary stability of 2 albumin compounds, ^{99m}Tc-MAA (macroaggregated serum albumin [MAA]) and ^{99m}Tc-HSA (human serum albumin [HSA]), was assessed. **Methods:** In 24 patients with metastatic colorectal cancer, biodistribution (liver, lung) and liver–lung shunt (LLS) of both tracers (12 patients each) were assessed by sequential planar scintigraphy (1, 5, and 24 h after injection). **Results:** Liver uptake of both albumin compounds decreased differently. Although initial LLSs at 1 h after injection were similar in both groups, MAA-LLS increased significantly from 1 (3.9%) to 5 h (7.7%) and 24 h (9.9%) after injection, respectively. HSA-LLS did not change significantly (1 to 5 h), indicating a steady state of pulmonary and intrahepatic degradation. **Conclusion:** Compared with ^{99m}Tc-MAA-microspheres, ^{99m}Tc-HSA-microspheres are likely more resistant to degradation over time, allowing a reliable LLS determination even at later time points.

Key Words: radioembolization; dosimetry; biokinetics; ^{99m}Tc-labeled albumin spheres; liver-lung shunt

Radioembolization with ^{90}Y-labeled microspheres is an established therapy for unresectable liver malignancies (*1*). Despite generally good tolerability, complications (e.g., gastrointestinal ulceration) due to misplaced microspheres may occur (*2*). In addition, an excessive liver–lung shunting (LLS) may cause radiation pneumonitis, potentially leading to a serious impairment of respiratory function (*3,4*). Proper estimation of the LLS is therefore a crucial component of pretherapeutic therapy simulation by perfusion scintigraphy (PS), including SPECT/CT (*5*). PS can be performed with ^{99m}Tc-macroaggregated serum albumin (^{99m}Tc-MAA) or ^{99m}Tc-human serum albumin (^{99m}Tc-HSA) (*6,7*), tracers

formally approved for lung scintigraphy (*8,9*) used off-label in therapy simulation.

Both tracers are administered into the liver arteries, and the resulting planar and SPECT/CT images are used (*1*) for the exclusion of extrahepatic tracer accumulation in organs at risk (e.g., stomach, gallbladder) (*2,10*) for the estimation of the LLS or lung doses (*5*). On the basis of the LLS determined, the activity of ^{90}Y-microspheres administered is reduced by reference to look-up tables provided by the manufacturer. In the case of a high LLS, radioembolization treatment may even be canceled to avoid an excessive pulmonary radiation exposure (*11,12*).

Because pharmacokinetic data on both MAA and HSA spheres after intravenous injection showed an in vivo pulmonary instability of the radiopharmaceutical (*13*), a timely performed PS is also recommended after intraarterial injection of ^{99m}Tc-labeled albumin compounds (*14*).

The aim of this analysis was to compare changes in the intrahepatic and intrapulmonary biodistribution and the resulting LLS determination of ^{99m}Tc-MAA- and ^{99m}Tc-HSA-microspheres over time in patients scheduled for radioembolization.

MATERIALS AND METHODS

Patients

The present subanalysis of data from both PS tracers was performed as part of a prospective phase-2 clinical trial evaluating the predictability of the accumulation of ^{90}Y-labeled resin microspheres (SIR-Spheres; Sirtex Medical Ltd.) from preceding PS.

In a 2-armed study design, patients scheduled for ^{90}Y-radioembolization of hepatic metastases from colorectal cancer were randomized for 1 of the 2 tracers for PS: patients in arm A ($n = 12$; men-to-women ratio, 10:2; median age, 66.1 y; age range, 46.6–82.2 y) received ^{99m}Tc-MAA, and patients in arm B ($n = 12$; men-to-women ratio, 8:4; median age, 58.6 y; age range, 46.2–76.2 y) received ^{99m}Tc-HSA (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). Trial-specific inclusion criteria were the presence of metastases in both liver lobes and a life expectancy of longer than 6 mo. Trial-specific exclusion criteria were an LLS greater than 10%, concomitant chemotherapy, and variants of the arterial hepatic blood supply that would not allow bilobar evaluation by a single-tracer administration into the common hepatic artery.

This monocenter study was approved by the local ethics committee (registration number, 77/09) and supervised by responsible national regulatory agencies (ClinicalTrials.gov identifier: NCT01186263). Informed written consent was obtained from all participants enrolled.
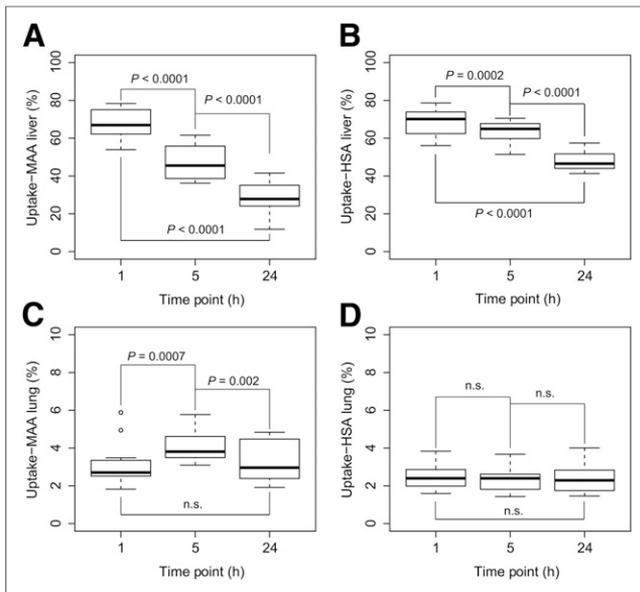
FIGURE 1. Uptake of ^{99m}Tc-MAA (A and C) and ^{99m}Tc-HSA (B and D) in liver (A and B) and lung (C and D) from PS at 1, 5, and 24 h after intraarterial injection.

Microsphere Preparation and Application

Labeling and quality control of the ^{99m}Tc-MAA (Mallinckrodt Medical B.V.) and ^{99m}Tc-HSA (ROTOP-HSA microspheres B20; ROTOP Pharmaka) were performed according to the manufacturer's recommendations (Supplemental Table 2) (8,9). ^{99m}Tc-MAA and ^{99m}Tc-HSA were injected intraarterially into the common hepatic artery during the angiographic evaluation procedure before radioembolization. To avoid nonspecific gastric uptake of free ^{99m}Tc-pertechnetate, 600 mg of sodium perchlorate were administered beforehand.

Planar Imaging and Analysis of Biodistribution

Planar imaging was performed in 6 patients (MAA/HSA = 4/2) with a dual-head SPECT γ-camera (e.cam; Siemens Medical) and in 18 patients (MAA/HSA = 8/10) with a SPECT/CT scanner (NM/CT 670; GE Medical). For both systems, planar imaging was performed with an imaging matrix of 256 × 1,024, an energy window at 140 keV ± 15%, and a scan speed of 8 cm/min. PS imaging was performed nominally at 3 time points: 1 (PS1), 5 (PS2), and 24 h (PS3) after the angiographic application of the ^{99m}Tc-labeled particles (Supplemental Table 3).

Semiquantitative analysis for LLS determination was performed with region-of-interest (ROI) analysis on planar data. ROIs for liver and lung were drawn in anterior and posterior projections. The geometric mean of the ROIs was calculated, and time–activity curves were estimated for each ROI. All data were corrected for radioactive decay to estimate the uptake of particles (percentage injected particles) within the ROIs at the different imaging time points and to estimate the in vivo pharmacokinetics of the tracers.

Statistics

The R software package (version 3.1.3; R Foundation for Statistical Computing) was used for statistical evaluations. ANOVA was used to assess the impact of the liver volume, tumor load, and tracer on the LLS estimated at PS1. Liver volume and tumor load were subdivided into 2 groups (levels: ≤ median, and > median) each to test potential impact on LLS. Differences in tracer uptake were tested for significance by unpaired *t* tests at single time points. Change in uptake of each tracer between different time points was tested by paired *t* tests.

All tests performed were 2-sided, and statistical significance was assumed at a *P* value of less than 0.05. Biologic half-life times were estimated by regression analysis.

RESULTS

Preparation and Application of ^{99m}Tc-MAA and ^{99m}Tc-HSA

Because of constraints imposed by kit preparation, the number of injected spheres differed significantly between both radiopharmaceuticals ($P < 0.0001$, Supplemental Table 2). Furthermore, significant differences between groups were observed for free ^{99m}Tc-pertechnetate ($P = 0.002$), the residual activity in the syringe ($P = 0.03$), and the injected activity ($P = 0.014$, all Supplemental Table 2).

Tracer Uptake (Liver and Lung) over Time

Between PS1 and PS2, furthermore to PS3, a significant release of particles from the liver was observed for both pharmaceuticals ($P \leq 0.0002$, Figs. 1A and 1B). The liver and lung uptake at PS1 was not significantly different for both pharmaceuticals ($P > 0.11$, Figs. 1A and 1B). The MAA initially showed a fast and then a slower release from the liver, which is best fitted by a biexponential decay curve (Fig. 2; $T_{half-life, fast} = 7.9$ h, $T_{half-life, slow} = 22.4$ h; adjusted $R^2 = 0.77$). In contrast, HSA revealed a slow release from the liver (Fig. 2; monoexponential decay curve, $T_{half-life} = 41.7$ h; adjusted $R^2 = 0.76$).

The median MAA uptake in the lung increased significantly from PS1 to PS2 (2.7% to 3.8%, $P = 0.0007$, Fig. 1C) and decreased significantly during the following interval (PS2 to PS3), the median being 3.0% ($P = 0.002$, Fig. 1C).

The median HSA uptake in the lungs did not change significantly over time ($P \geq 0.64$, Fig. 1D).

Liver–Lung Shunt

For both tracers, ANOVA showed no significant dependency between LLS measured at PS1 and liver volume, tumor load, and tracer ($P \geq 0.26$). For MAA, the absolute LLS increased significantly from PS1 (LLS $_{PS1} = 3.9\%$) to PS2 by 3.6% ($P = 0.0005$, Fig. 3A, Supplemental Table 4). For HSA, there was no significant change in LLS over the same time period ($P = 0.74$, LLS $_{PS1} = 3.2\%$, Fig. 3B). This increase in LLS in the MAA group at PS2 was significant compared with the corresponding LLS determined in the HSA group ($P < 0.0001$, Figs. 3A and 3B).

LLS further increased from PS2 to PS3 in the MAA group (mean increase = 5.0%, $P < 0.0001$, Fig. 3A), and the corresponding
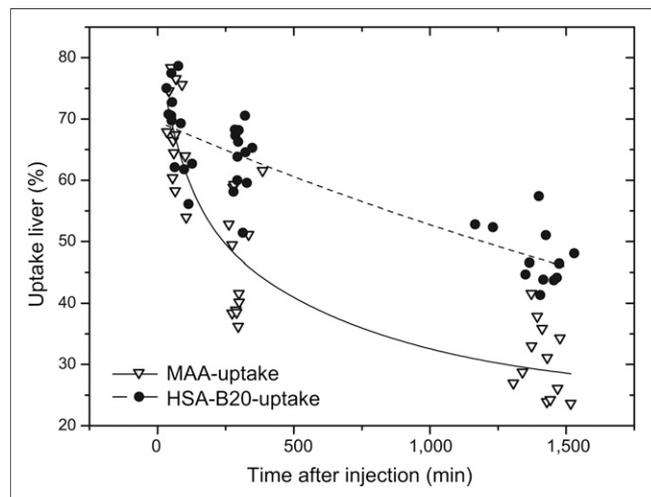

FIGURE 2. Liver uptake of MAA and HSA particles versus time. MAA uptake fitted by biexponential decay ($T_{half-life, fast} = 7.9$ h, $T_{half-life, slow} = 22.4$ h, adjusted $R^2 = 0.77$). HSA revealed monoexponential decay ($T_{half-life} = 41.7$ h, adjusted $R^2 = 0.76$).
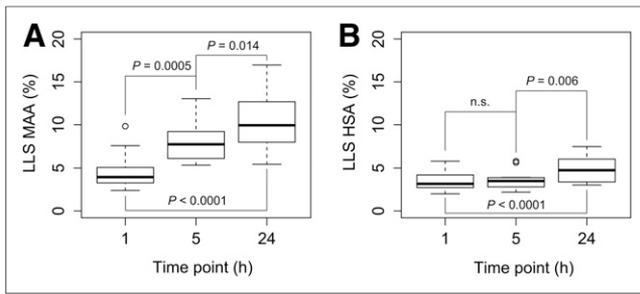
FIGURE 3. LLS over time assessed with ^{99m}Tc-MAA (A) and ^{99m}Tc-HSA (B).

LLS increases in the HSA group (mean increase = 1.3%, $P < 0.0001$) were significantly smaller ($P < 0.0001$, Figs. 3A and 3B).

DISCUSSION

The aim of the study was to compare the intrahepatic and intrapulmonary pharmacokinetics of ^{99m}Tc-MAA- and ^{99m}Tc-HSA-microspheres after intraarterial injection and their influence on estimating LLS.

Although uptake in the liver and lung did not significantly differ between the 2 radiopharmaceuticals at the first imaging time point (1 h after injection), we observed a significant, time-dependent redistribution of both tracers from the capillary bed of the liver to the capillary bed of the lung. This effect was significantly more pronounced for MAA particles, with a maximal pulmonary uptake at 5 h after injection. In contrast, the pulmonary uptake of HSA particles was almost constant for up to 24 h after injection.

Although theoretically more time points would have been desirable for the assessment of tracer biokinetics, the low number of imaging time points was chosen to guarantee patient compliance after a long and tedious angiographic procedure.

We do admit that the entire biokinetic tracer degradation and redistribution, including interactions such as compartment inflow and outflow, cannot be derived from this simplified 2-compartment model (lung, liver). Nevertheless, this model is in our opinion reliable to estimate LLS and demonstrate the effects from particle degradation.

A significant increase in the median LLS was observed for MAA particles from 3.9% (1 h after injection) to 7.7% (5 h after injection). In contrast, the LLS estimated with HSA particles was not significantly affected by the redistribution process within this clinically relevant time frame (1–5 h after injection). In light of the known pulmonary in vivo degradation of labeled albumin particles after intravenous injection, it is recommended to perform PS not later than 4 h after injection, preferably within the first 60 min after administration, to avoid an artificial overestimation of LLS (*15,16*), which could result in an unnecessary reduction of the prescribed activity or even unnecessary exclusion of patients from therapy (*12,13*). According to our data, reported 4-h tolerance intervals appear to be too long for PS with MAA.

In accordance to the longer in vivo pulmonary half-life reported for HSA (7.2 h) and in comparison with MAA (4.2 h) after intravenous injection for pulmonary scintigraphy (*9,17*), we observed a longer half-life of labeled HSA in the liver, thus suggesting a better intrapulmonary and intrahepatic stability of labeled HSA. One of the consequences of this longer half-life is a pulmonohepatic steady state when addressing the LLS estimations, remaining more or less constant even 1 d after tracer administration. However, PS is required not only for LLS determination but also for excluding extrahepatic abdominal tracer accumulation; an acquisition as early as possible is still recommended to retain optimal imaging statistics.

CONCLUSION

When ^{99m}Tc-MAA- and ^{99m}Tc-HSA-microspheres for PS before radioembolization are used, ^{99m}Tc-HSA-microspheres are likely more resistant to degradation over time, allowing a representative LLS determination even at later time points.

DISCLOSURE

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