Gd-EOB-DTPA: When is transitional period between distribution phase and hepatobiliary phase?

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BACKGROUND AND PURPOSE

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA [EOB]) is a liver-specific MR imaging contrast agent whose use makes it possible to simultaneously evaluate hepatic perfusion and hepatocyte-selective properties [1-3]. The distribution of EOB in the liver is divided into two phases [4]. During the first-, the distribution phase, which occurs between 0 and approximately 70 seconds after EOB injection, the temporal course of EOB enhancement is similar to that of extracellular gadolinium-based agents such as gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA). During the second-, the hepatobiliary phase, the compound is taken up by hepatocytes [5, 6]. This phase starts just after EOB injection and hepatic enhancement due to the uptake of EOB by hepatocytes gradually increases and reaches its maximum about 20 min after the start of EOB injection.

In general, extracellular contrast agents have an equilibrium phase that occurs about 180 - 300 sec after the start of contrast injection. At hepatic dynamic MRI or dynamic CT with an extracellular contrast agent, the equilibrium phase is important for the characterization and differentiation of hepatic tumors [7-9]. However, the equilibrium phase is superimposed on the start of the hepatobiliary phase, and the "pure" equilibrium phase does not exist on hepatic dynamic MRI using EOB. Therefore, we defined the transitional period between the distribution- and the hepatobiliary phase as the late phase. Although there are many reports regarding the hepatobiliary phase on hepatic dynamic MRI scans acquired with EOB, the late phase has not been addressed well and optimal scan timing for the late phase remains to be determined.

The purpose of this study was to determine the appropriate timing for the late phase.
Methods and Materials

MATERIALS AND METHODS

Patient Population

Between May 2009 and August 2009, 80 patients (40 women, 40 men; mean age 63.1 years, range 35 - 82 years) were enrolled for this prospective study. Our inclusion criteria were: suspected space-occupying hepatic lesions based on an earlier CT or sonographic examination (43 patients), type B-, C-, or alcoholic hepatitis associated with elevated levels of tumor markers (#-fetoprotein or protein induced by vitamin K absence, or antagonist-II) (21 patients), and known liver tumors (16 patients).

MRI Technique

The patients were asked to fast for a minimum of 4 hrs before their examination. MRI was on a 1.5-T scanner using a torso Synergy Body coil. Dynamic images using fat suppressed T1-weighted gradient-echo images with 3D acquisition sequences were obtained before (pre-contrast) and 30-, 70-, 120-, 180-, 240-, and 300 sec after the intravenous (iv) administration of EOB. The agent was delivered as a bolus at a rate of 2 ml/s; flushing was with 20 ml saline using a power injector. Images were acquired in the transverse plane, the section thickness was 4 mm with a 50% slice overlap. The other parameters were: repetition time (TR, ms)/echo time (TE, ms), 4.2/2.0; flip angle (FA), 10; field of view, 395 x the rectangular FOV (RFOV) 65% cm; matrix, 256 x 192; parallel imaging factor, 4; number of signals acquired (NSA), 2; acquisition time, 19 s.

Quantitative Analysis

The signal intensity (SI) of the liver parenchyma was measured at 0-, 30-, 70-, 120-, 180-, 240-, and 300 sec after the administration of EOB on T1-weighted images with fat suppression. It was calculated by setting a circular region of interest (ROI) that did not include vascular structures and liver space-occupying lesions (SOL). ROI were placed at 2 locations in the right lobe (anterior and posterior segment) and one location in left lobe on images obtained at the level of the main portal vein. The ROI was set as the entire lesion in all series. Relative enhancement (RE) of the liver was calculated using the equation

\[
RE(\%) = \frac{(SI_{postcontrast} - SI_{precontrast})}{SI_{precontrast}} \times 100
\]

Mean RE was calculated in each patient as the mean of the ROIs of 3 regions.

Statistical Analysis
We used two-way ANOVA to investigate differences among REs at each time point. When the overall differences were statistically significant, we performed posthoc analysis using the Tukey-Kramer test for multiple comparisons among REs at each time point. P values of less than 0.05 were considered to indicate statistically significant differences.
Results

RESULTS

RE of the liver after EOB injection

RE increased steeply until 70 sec and gradually between 70- and 120 sec. There was a statistically significant difference between RE before- and 30 sec post-injection, and between RE at 30- and 70 sec. There was no statistically significant difference in RE at 70- and 120 sec. RE steeply decreased between 120- and 180 sec. There was a statistically significant difference between RE at 120- and 180 sec. After 180 sec, RE gradually increased again until 300 sec. (Fig. 1 on page 6, Fig. 2 on page 6)
**Fig. 0**: Fig.1 Relative enhancement (RE) of the liver after the injection of EOB. RE increased significantly until 2 min and was decreased significantly at 3 min. This may reflect the uptake of contrast medium by hepatocytes indicating that images acquired at 3 min post-contrast injection are affected not only by the contrast distribution but also by the uptake of contrast medium by these cells.

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### P values in the pairwise comparisons of REs in each time point after injection of the EOB

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</table>

**Fig. 0:** P values in the pairwise comparisons of REs in each time point after injection of the EOB.

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Conclusion

DISCUSSION AND CONCLUSION

We found that RE increased until 70 sec after contrast injection and that there was a significant difference in RE before and 30 sec after injection and at 30- and 70 sec post-injection. There was no significant difference at 70 sec and 120 sec after contrast delivery. RE steeply decreased between 120- and 180 sec and RE after 180 sec was not significantly different. Based on these results we posit that the window between 120 and 180 sec may be optimal for the late phase because both enhancement by portal venous flow and EOB uptake by hepatocytes is minimal during that period. It remains to be determined which exact time point between 120- and 180 sec is optimal for the late phase.

The equilibrium phase of hepatic dynamic MRI or CT is a somewhat ambiguous concept because the pharmacokinetic equilibrium phase corresponds to the portal venous phase in which hepatic enhancement reaches its maximum [9]. Foley defined the equilibrium phase as a portion of the time-enhancement curves where hepatic and aortic enhancement decline in parallel after hepatic peak enhancement [7, 8]. Although this definition was not rigorously based on pharmacokinetics, the equilibrium phase is important for the detection and characterization of hepatic tumors especially hepatocellular carcinomas and hepatic hemangiomas [10, 11]. On hepatic dynamic MRI using EOB, the late phase may correspond to Foley’s equilibrium phase, however, there is an overlap due to enhancement attributable to the uptake of EOB by hepatocytes.

The diagnostic value of the late phase may be especially high with respect to the diagnosis of hepatic hemangiomas. These neoplasms are often demonstrated as a low intensity area in the hepatobiliary phase on hepatic dynamic MRI using EOB. As it is often difficult to identify "fill-in", i.e. enhancement in the periphery of the hepatic tumor, during the arterial phase in relatively small hepatic hemangiomas, analysis of enhancement during the portal venous or late phase is indispensable. Doo KW [12] reported that high-flow hemangioma might show relatively low signal intensity (‘pseudo washout’) because of EOB contrast uptake in the surrounding normal liver parenchyma during the late phase (3min delay) phase and these enhancement patterns did not permit a confident diagnosis of hepatic hemangioma and mimicked HCC (Fig. 1 on page 10, Fig. 2 on page 10). From this reason, it is very important to take late phase on the timing when the effect of hepatobiliary uptake of Gd-EOB-DTPA is as small as possible and evaluate vascularity of liver tumor on the appropriate late phase.

In the current study we only investigated the optimal scan timing for the late phase based on the time course of RE of the liver on hepatic dynamic MRI scans using EOB. We did not explore the ability to detect and characterize liver tumors. Studies are underway to compare the diagnostic ability during the late- and hepatobiliary phases.
In conclusion, the optimal scan timing for the late phase is between 120- and 180 sec after the administration of EOB because images acquired at 3 min post-contrast injection are affected by enhancement attributable to contrast uptake by hepatocytes. Radiologists charged with diagnosing hepatic tumors must be aware that late phase images include both equilibrium- and hepatobiliary phase components.
Fig. 0: 59-year-old man with chronic hepatitis B and histologically proven HCC in segment VII. On EOB-enhanced T1-weighted images, lesion in segment VII shows dominant enhancement during arterial phase (30sec), relatively hypointense signal during late phase (70sec, 120sec, 180sec, 240sec and 300sec) and definite low intensity during hepatobiliary phase (15min). Note slightly hyperintense on T2-weighted image.
**Fig. 0:** 46-year-old man and hepatic hemangioma in segment VI confirmed by follow up US. On EOB-enhanced T1-weighted images, lesion in segment VI shows dominant enhancement during arterial phase (30sec), relatively hypointense signal during late phase (180sec) and definite low intensity during hepatobiliary phase (15min). Note bright signal intensity of lesion on T2-weighted image.

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References


