Abstract: The objective of this study was to determine the diagnostic efficacy and safety of Gd-EOB-DTPA (Eovist®) at 4 doses (3.0; 6.0; 12.5 and 25.0 µmol Gd-EOB-DTPA/kg BW [body weight]) as compared to placebo (0.9% saline) in patients with known focal liver lesion(s). A total of 171 received contrast medium injection or placebo (0.9% saline). Thirty five patients received placebo, 33 patients received 3, 32 received 6, 34 patients received 12.5 and 35 patients received 25 µmol Gd-EOB-DTPA/kg BW in randomized manner.

Conclusions: Gd-EOB-DTPA is a safe contrast medium. The optimum dose is 25 µmol/kg BW.

Common noninvasive techniques to evaluate liver are ultrasound, CT and MRI. Among these noninvasive modalities, MRI has shown (1) to possess the highest sensitivity and specificity, which still can be improved by the application of various contrast media. Examples of liver specific agents include Feridex® and Teslascan®. Gd-EOB-DTPA is a new liver specific contrast agent being developed by Schering AG, Berlin/Germany. The bolus applicable Gd-EOB-DTPA, a hepatobiliary contrast agent is an ethoxybenzyl (lipophilic) derivative of Gd-DTPA. Gd-EOB-DTPA has about 10 % protein binding and through the active carrier mediated transportation is taken up by hepatocytes. This leads to a distribution both into the extracellular space (similar to extracellular contrast agents) and uptake by hepatocytes. This unique property is utilized for liver MRI by performing dynamic imaging during perfusion phase and hepatocyte phase imaging thereafter. The hepatocyte uptake increases the signal intensity of normal hepatic parenchyma thereby increasing lesion-to-liver-contrast that is the basis of improving lesion detection. As hepatocyte uptake of Gd-EOB-DTPA is dependent on presence/absence of functional hepatocytes, hepatocyte phase imaging also provides functional information within the tumors that aids in tissue characterization. Gd-EOB-DTPA is completely eliminated from body by excretion through biliary and renal route (about 50% biliary and about 50% renally) (2). Ti relaxivity is nearly double than that of conventional “extracellular” gadolinium chelates.

Study objectives: The objective of this study was to determine the diagnostic efficacy and safety of Gd-EOB-DTPA at 4 doses (3.0; 6.0; 12.5 and 25 µmol Gd-EOB-DTPA/kg BW [body weight]) as compared to placebo (0.9% saline) in patients with known focal liver lesion(s).

Material and Methods: This multicenter, double blind, randomized, placebo-controlled dose-ranging study was conducted in 7 centers in Europe from June 1996 to January 1997. After precontrast MRI (T1 and T2-weighted sequences), patients were injected either Gd-EOB-DTPA either 3, 6, 12.5, 25 µmol Gd-EOB-DTPA/kg BW or saline in blinded fashion according to predetermined randomization. Postcontrast imaging included T1-weighted dynamic imaging up to 8 minutes post injection (PI). Accumulation phase (hepatocyte phase) imaging was performed at 20 and 45 minutes PI using T1-weighted GRE sequence.

The efficacy assessment included lesion detection, classification and characterization, SNR, CNR and % enhancement, visual evaluation of lesion(s), and patient management (therapy and investigation) and diagnostic confidence. The efficacy variables were analyzed with the many-to-one Dunnett test and the exact Fisher test. The dose response curve for the primary variable was estimated using the logistic regression equation. The final diagnosis was established by using all clinical data (patient history, other imaging procedures, histopathology lab parameters) and by consultation with the clinician within 2 wks after MRI.

Safety variables included evaluation of vital signs, physical examination, clinical laboratory tests, and adverse events. A total of 171 received contrast medium injection or placebo (0.9% saline). Of these 171 Patients, 169 patients were evaluated for efficacy. There were 87 males and 84 females. The age ranged from 26-82 yrs. The median age was 59 years for males and 57 years for females. The diagnosis of patients in each dose group is listed in table 1.

Results: The change in diagnostic confidence (primary variable) revealed a statistically significant difference versus placebo (p < 0.001) for dose groups 12.5 and 25.0 µmol/kg BW considering good or excellent improvement (41.2%; 67.7% of patients respectively). Good or excellent improvement in visual evaluations (lesion visualization, lesion delineation and contrast) were recorded only for dose groups 6.0, 12.5, and 25.0 µmol/kg BW (10-13%, 34-42%, 53-58% of patients respectively). This good or excellent improvement in visual evaluation, was a statistically significant (p < 0.05) for dose groups 12.5 and 25.0 µmol/kg BW versus placebo.

The number of patients with more lesions being visualized on post than on pre-contrast scans increased with increasing dose up to 12.5 µmol (at 20-minute post MRI: 12.1% [3.0 µmol]; 15.6% [6.0 µmol]; 30.3% [12.5 µmol]; 31.4% of patients [25.0 µmol]); at 45-minute post-MRI same trend was observed. The enhancement of hepatic vessels and liver parenchyma during dynamic imaging increased with increasing dose.

A dose dependent increase in SNR, CNR, and % enhancement was seen. The % enhancement was most pronounced at 25 µmol/kg BW. There was no significant improvement in quantitative or qualitative efficacy parameters at 45 minutes PI compared to 20 minutes PI.

No serious adverse events were reported in any of the patients. In 6 patients 8 adverse events were seen. There was no dose dependency seen in the occurrence of AEs. Of these 4 adverse events (4%) were considered as possibly or probably drug related. All adverse events were mild except one (anxiety). No significant changes in vital signs or lab parameters were observed.

Conclusions: Gd-EOB-DTPA is a safe contrast medium. The optimum dose is 25 µmol/kg BW. Dynamic imaging can start immediately after bolus injection. Accumulation phase imaging can be performed at 20 minutes PI.

References: