ABSTRACT

A variety of different categories of liver contrast agents, and within each category, a number of individual agents, are currently available for clinical use. This review describes the use of non-specific extracellular gadolinium chelates, reticulo-endothelial system specific iron oxide particulate agents, hepatocyte-selective, and combined perfusional hepatocyte-selective agents. The greatest clinical experience is with non-specific extracellular gadolinium chelates. The relatively low cost, safety, good patient tolerance, and ability to detect and characterize a wide range of liver diseases has rendered it a very commonly employed agent. Reticulo-endothelial system agents improve lesion detection by decreasing the signal intensity of background liver on T2-weighted images rendering focal hepatic lesions with negligible reticuloendothelial cells, for example metastases, more conspicuous. Hepatocyte selective contrast agents increase the signal intensity of background liver on T1-weighted images rendering non hepatocyte containing focal lesions, for example metastases, more conspicuous. This review describes the different categories of contrast agents, techniques for their administration, sequences to be employed, and appearances of common entities on contrast enhanced studies.

INTRODUCTION

Intravenous contrast agents have been employed in clinical examinations of the liver since approximately 1988. The first category of contrast agents to be used in clinical practice were non-specific extracellular gadolinium chelates. Since that time, two other classes of contrast agents have been developed and employed for liver studies, namely reticulo-endothelial system (RES) specific contrast agents and hepatocyte-selective contrast agents. This article describes agents
in each of these three categories: non-specific extracellular, RES and hepatocyte contrast agents. Emphasis is placed on non-specific extracellular gadolinium chelates because it has been available the longest, and has the best documented safety profile and clinical applications, due to the number of publications describing its use.

In determining the role for contrast agents, understanding the information available from non-contrast sequences is important in order to appreciate what additional information is provided by contrast material.

**NON-CONTRAST SEQUENCES**

**T1-weighted sequences**

Breath hold spoiled gradient echo has achieved widespread use as an ideal T1-weighted sequence for evaluating the liver. Typical parameters include: TR = 150 msec, TE = 4 msec (at 1.5T), flip angle = 80°, slice thickness = 8 mm, slice gap = 20%, matrix 128-171 x 256 (phase encoding x frequency encoding), 14-22 seconds in a 20 second breath hold. The TR is sufficiently long to acquire enough sections to cover the entire liver in one pass, and to provide good signal to noise. The TE is the shortest in-phase TE, which provides strong T1-weighting, minimizes magnetic susceptibility effects, and permits acquisition of a sufficient number of sections to cover the entire liver. A flip angle of 80° provides good T1-weighting and less of power deposition and tissue saturation than a larger flip angle that would provide comparable T1-weighting. Matrix size and section thickness are adequate to provide good in-plane and through-plane resolution, respectively. Imaging parameters for spoiled gradient echo appear to be generalizable between MR machines produced by different manufacturers, such that the image quality of sequences performed using the above parameters would be of good diagnostic quality on all equipment that have the gradient capability to acquire them. An important feature of the multisection acquisition of spoiled gradient echo is that the central phase encoding steps (which determine the bulk signal in the image) are acquired over 6 seconds for both the entire data set and each individual section. Thereby the data acquisition is sufficiently short for the entire data set to isolate a distinct phase of gadolinium chelate enhancement (eg: hepatic arterial dominant phase) while at the same time the
data acquisition of each individual section is sufficiently long to compensate for slight variations in patient cardiac output, peak lesion enhancement and injection technique.

The immediate future of T1-weighted imaging is likely the adoption of 3D gradient echo imaging. The benefits of this technique include: increased signal-to-noise compared to 2D techniques and 3D volume acquisition, which permits high spatial resolution multiplanar display. A number of institutions already employ 3D gradient echo imaging as their T1-weighted sequence. The image quality of 3D gradient echo has not yet reached that of 2D spoiled gradient echo. Further refinements are ongoing to improve the image quality of 3D gradient echo to be more comparable to 2D spoiled gradient echo.

Magnetization prepared gradient echo sequences acquire data as a single section technique with each individual section acquired in less than 2 seconds. This sequence is relatively insensitive to artifacts from patient motion and breathing, and it has thus been termed breathing-independent. T1-weighted spin echo is generally acquired over 2-6 minutes and is therefore performed while the patient is breathing, and this sequence is termed breathing-averaged.

T1-weighted images demonstrate imaging features for various types of liver lesions. Lesions with a high fluid content (eg: cyst, hemangioma) are very low in signal, lesions which are hypovascular or with a high fibrous tissue content (eg: colon cancer metastases, transitional cell carcinoma metastases, antibiotic treated hepatic infective lesions, chemotherapy treated metastases that have undergone changes of fibrosis, or hepatic fibrosis) are moderately low in signal. Lesions which are hemorrhagic (eg: hemorrhagic metastases, liver hemorrhage), high protein content (eg: hepatocellular carcinoma), high fat content (eg: hepatocellular carcinoma, hepatic adenoma) or contain melanin (eg: melanoma), are high in signal. This information provided by non-contrast T1-weighted information is useful to aid in lesion detection and characterization.
T2-WEIGHTED IMAGES

Breathing-averaged T2-weighted conventional or echo train (eg: fast or turbo) spin echo, often combined with fat suppression, are the most commonly used T2-weighted sequences. In patients who breathe in a regular fashion, these sequences generate images of high diagnostic quality. Many patients however are not able to breathe regularly and the image quality of breathing-averaged sequences is inconsistent. Therefore breath-hold or breathing-independent T2-weighted images are now being employed at many centers in place of breathing-averaged T2-weighted sequences. Unlike T1-weighted spoiled gradient echo sequences, the optimized imaging parameters for T2 breath-hold or breathing-independent sequences have not been realized as yet, particularly between equipment manufacturers, and so we will not list recommended parameters.

T2-weighted images essentially provide information on fluid content (reflected by a high signal intensity) and iron content (reflected by a low signal intensity). It has been recognized that high fluid content in focal liver lesions has a strong correlation with benign disease (ie: cysts and hemangiomas), whereas lower fluid content is more typical for malignant disease. Many reports have described the value of distinguishing cysts and hemangiomas from metastases and hepatocellular carcinoma based on their appearance on T2-weighted images. Sole reliance on T2-weighted images may however not be advisable, as some liver metastases that are either cystic (eg: ovarian cancer metastases) or hypervascular (eg: gastrointestinal leiomyosarcoma metastases or islet cell tumor metastases) have a high fluid content and therefore are high in signal on T2-weighted images, while the relatively common benign liver lesions, focal nodular hyperplasia and hepatic adenoma, have a relatively low fluid content and therefore are near isointense with liver on T2-weighted images.

Sequence Modifications

Excitation-spoiling chemically selective fat suppression is effective at diminishing phase artifact from respiration and improves the dynamic range of signal intensities of abdominal tissues. Fat suppression is particularly effective at improving the visualization of contrast enhancement in regions bordered by fat (eg: subcapsular liver). Echo-train T2-weighted sequences also benefit from the
use of fat suppression, especially in the setting of fatty liver. In-phase and out-of-phase T1-weighted spoiled gradient echo sequences are routinely used in liver studies to evaluate for fatty liver.

Coil Use

Phased array or multiarray torso coils are a useful addition to MR imaging of the liver. The improvement in signal to noise permits thinner section acquisition and higher diagnostic quality of many short duration MR sequences. The benefit of their implementation is greatest with patients of lean to medium build. Substantial signal loss in the central portion of the abdomen may be very detracting in either large patients or if adequate signal normalization post processing has not been performed.

WHY CONTRAST AGENTS?

The need to more accurately characterize all different histologic types of liver lesions and to detect the full extent of malignant liver lesions have been major reasons for the use of intravenous contrast agents. The additional need to detect and characterize extrahepatic disease has developed into an equally important reason to use contrast agents. The requirement for contrast material has apparently not diminished despite the improved image quality of new non-contrast T1- and T2-weighted sequences for investigating the liver.

NON-SPECIFIC EXTRACELLULAR GADOLINIUM CHELATES

The use of these agents has been considered essential to evaluate the full complexity of abdominal disease in patients evaluated by MRI for a diverse range of indications. In order to facilitate the broad application of abdominal MRI the use of standardized imaging protocols may be advisable. Combining various sequences that are breath-hold or breathing-independent shortens total examination time, and by employing a variety of different types of sequences, different planes and the routine use of gadolinium comprehensive diagnostic information, is provided encompassing the full range of abdominal diseases.
The sequence list should be sufficiently short to avoid redundancy and excessive examination time.

Gadolinium is maximally used when it is administered as a rapid bolus, and imaging is performed with a T1-weighted spoiled gradient echo sequence that is repeated in a dynamic serial fashion. This is best achieved at high field strength (1.0 T or 1.5 T). A minimum of two post contrast sequence repetitions may be essential, and little additional information is provided if more than four sequences are acquired. Our standard is to acquire three, using the following timing of phases:

**Hepatic arterial dominant phase**

The hepatic arterial dominant phase, which is also termed the capillary phase when other organs are imaged, is the single most important data set when using a non-specific extracellular gadolinium chelate. The timing for this phase of enhancement is the only timing for post contrast sequences that is crucial. It is essential to capture the "first pass" or capillary bed enhancement of tissues during this phase. Demonstration of gadolinium in hepatic arteries and portal veins, and absence of gadolinium in hepatic veins are reliable landmarks. In general, if contrast is injected at 2-3 ml/sec by machine power injector or by hand, this phase is achieved in the majority of patients by initiating a spoiled gradient echo sequence with standard ordering of the phase-encoding table at 16-17 sec following the start of injection. Alternatively, if rapid bolus hand injection is performed injecting 0.1 mmol/kg gadolinium chelate (typically 15-20 ml dose) followed by rapid injection of a 10-ml bolus of normal saline, and initiating spoiled gradient echo following completion of the normal saline bolus, also shows consistent results. Reproducibility may be further improved using a test bolus to calculate more exact timing.

In the hepatic arterial dominant phase of enhancement, our belief is that although contrast is present in portal veins, the majority of the gadolinium present in the liver has been delivered by hepatic arteries. The absolute volume of hepatic artery delivered gadolinium is greater in this phase of enhancement than if the data is acquired when gadolinium is only present in hepatic arteries, which means that more hepatic arterial blood supply information is available. This is important since most focal lesions, especially metastases and hepatocellular carcinoma, are fed primarily by hepatic arteries. Imaging slightly earlier than this,
when only hepatic arteries are opacified (hepatic arteries-only phase) may approach the diagnostic utility of the hepatic arterial dominant phase only if the injection rate of contrast is fast and the sequence is acquired late in the hepatic arteries-only phase (within a very short time of gadolinium appearing in the portal veins). Observation of high signal of the renal cortex (approaching the signal of the aorta), pancreas, and spleen reflect adequate contrast delivery in the hepatic arteries-only phase of enhancement. It is very difficult to achieve these objectives in the hepatic arteries-only phase, and it is also difficult to judge if image acquisition is too early in this phase, at a time when the liver is essentially unenhanced. Appropriate timing, as judged by vessel enhancement, also is important for the evaluation of surrounding organs. Negligible or minimal pancreatic enhancement (ie: minimal increase in signal compared to precontrast images) is consistent with pancreatic fibrosis or chronic pancreatitis, and negligible or minimal enhancement of renal cortex may imply ischemic nephropathy or acute cortical necrosis. This can be reliably judged on hepatic arterial dominant phase images, due to the fixed landmarks of contrast in portal veins and absence in hepatic veins. In the hepatic arteries-only phase minimal enhancement of pancreas or renal cortex may reflect too early image acquisition rather than disease process. Since this immediate post gadolinium phase of enhancement is also used to diagnose adequate perfusion of these organs, it may be problematic to use enhancement of these organs as the determination of the appropriateness of the phase of image acquisition timing. Enhancement of pancreas or renal cortex provides useful ancillary information for appropriateness of timing, although it is not the major determinant, since extent of enhancement of these organs is also evaluated at this phase. In the liver, imaging too early in the hepatic arteries-only phase diminishes the ability to recognize the distinctive patterns of lesion enhancement for different lesion types, because the absolute volume of hepatic artery delivered contrast may be too small and may cause lesions to be mischaracterized based on minimal lesion enhancement.

On hepatic arterial dominant phase T1-weighted spoiled gradient echo images, various types of liver lesions have distinctive enhancement patterns: cysts show lack of enhancement, hemangiomas show peripheral nodules of enhancement in a discontinuous ring, non-hemorrhagic adenomas and focal nodular hyperplasia show intense uniform enhancement, metastases show ring enhancement, and
hepatocellular carcinomas show diffuse heterogeneous enhancement. The ability to use this information to characterize lesions as small as 1 cm may be most consistently achieved with MRI.Appearances of less common liver lesions on immediate post gadolinium images have also been reported, many of which show overlap with the above described patterns of common liver lesions. Knowledge of clinical history is often important, despite the high diagnostic accuracy of current MRI imaging protocols. In addition, many different histologic types of lesions, when they measure less than one centimeter, demonstrate virtually identical uniform enhancement eg: hemangiomas, adenomas, focal nodular hyperplasia, metastases and hepatocellular carcinoma. Ancillary information to assist in characterization of lesions is crucial, which includes: T2-weighted images that demonstrate lesion fluid content (eg: high for hemangioma and often high for hypervascular metastases, and relatively low for adenoma, focal nodular hyperplasia and hepatocellular carcinoma), appearance of other concomitant large lesions, and clinical history (eg: history of known primary tumor that can result in hypervascular metastases, such as gastrointestinal leiomyosarcoma or of underlying cirrhosis or hepatitis which would predispose to hepatocellular carcinoma). Specific appearances of various types of metastases are also appreciable on hepatic arterial dominant phase images. Colon cancer and pancreatic ductal adenocarcinoma metastases typically show ill-defined perilesional enhancement. In addition colon cancer metastases greater than 3 cm in diameter commonly have a cauliflower-type appearance.

Various enhancement patterns of liver parenchyma are also demonstrated on hepatic arterial dominant phase images. One of the most common perfusion abnormalities observed is transient increased segmental enhancement in liver segments with compromised portal venous flow due to compression or thrombosis. Other hepatic diseases that demonstrate perfusional abnormalities on immediate post gadolinium images include acute hepatocellular necrosis superimposed on chronic active hepatitis or cirrhosis, hepatic congestion, and Budd Chiari Syndrome, with different enhancement patterns for acute, subacute, and chronic forms of the disease.

Examination for liver metastases may be the most common indication for liver MR examination. Liver metastases have been classified as hypovascular (typical examples are colon cancer and transitional cell carcinoma) or hypervascular (typical examples are islet cell tumors, renal cell carcinoma and breast cancer).
A third category of vascularity has not been described well in the past and that is near-isovascular with liver. Near-isovascular refers to lesion enhancement that is very comparable to that of liver on early and late post gadolinium images. Near isovascularity is most readily appreciated when lesions are poorly seen on post gadolinium images but well seen on precontrast images. Liver metastases from primaries of colon, thyroid and endometrium may possess this type of enhancement pattern. The most common setting is post chemotherapy, although this may also be observed pre-chemotherapy. Fortunately many of these tumors are moderately low signal intensity on T1-weighted images rendering them readily apparent, and on occasion they may also be moderately high signal intensity on T2-weighted images. Although gadolinium chelate administration may appear detrimental in patient diagnosis because lesions are rendered poorly seen, near-isovascular enhancement in the presence of good lesion conspicuity on precontrast T1-weighted images is a feature of metastases, and not of other lesions, and in the appropriate setting reflects response to chemotherapy. Rarely liver metastases may also be near isointense on T1-weighted and T2-weighted images, and therefore can escape detection. The rarity of this event actually illustrates one of the great strengths of MRI over sonography and computed tomography, that the more different types of data acquired, the less likely it is for disease to escape detection. MRI simply has more acquisitions of different types of data than ultrasound or CT.

Chemotherapy-treated liver metastases deserve special mention in that chemotherapy is routinely given to many patients with liver metastases and chemotherapy alters the imaging features of metastases. Chemotherapy induces change in the signal intensity and imaging features of metastases which often results in alteration of signal intensity on T1- and T2-weighted images that approach the signal intensity of liver. Chemotherapy treated metastases may also develop an appearance that may resemble cysts, hemangiomas, or scar tissue. As mentioned above, they may also become near isovascular on post gadolinium images.

**Portal venous phase or early hepatic venous phase**

This phase is acquired at 45-60 seconds post initiation of gadolinium injection. In this phase, hepatic parenchyma is maximally enhanced so that hypovascular lesions: cysts, hypovascular metastases and scar tissue, are most clearly shown as regions of lesser enhancement. Patency or thrombosis of hepatic vessels are
also best shown in this phase. Peak hepatic parenchyma enhancement is achieved but the characteristic enhancement features of many focal liver lesions frequently divides at this phase. Peak hepatic parenchymal enhancement is of greatest importance in the setting of hypovascular lesions, and is much less important in others, particularly hypervascular lesions. Since colon cancer metastases and commonly observed in North America, and the majority are hypovascular, this explains why so much attention has been directed to this issue using non-specific extracellular contrast agents. Furthermore, since MR is more sensitive to the presence of gadolinium chelates than CT is to iodine-based contrast agents, observation of ring enhancement of the outer most visible tumor cells even in hypovascular metastases, has emphasized even more the importance of the hepatic arterial dominant phase over the portal venous phase for liver lesions detection than is the case with CT.

Hepatic venous phase or interstitial phase
This phase is acquired 90 seconds – 5 minutes following initiation of contrast injection. Late enhancement features of focal liver lesions are shown which aid in lesion characterization, such as: persistent lack of enhancement of cysts; coalescence and centripetal progression of enhancing nodules in hemangiomas; homogeneous fading of enhancement of adenomas and focal nodular hyperplasia to near isointensity with liver (these lesions should never fade to hypointensity); late enhancement of central scar in some focal nodular hyperplasias; peripheral or heterogeneous washout of contrast in liver metastases; washout to hypointensity with liver in small liver metastases and hepatocellular carcinoma; heterogeneous washout of hepatocellular carcinoma; and delayed capsule enhancement in hepatocellular carcinoma (less commonly adenoma). Enhancement of peritoneal metastases, inflammatory disease, and circumferential, superficial spreading cholangiocarcinoma are also well shown at this time frame. Concomitant use of fat suppression is essential for optimized demonstration of these findings. Fat suppression diminishes the computing high signal intensity of fat to improve conspicuity of enhancing disease tissue. Additional documentation of vascular thrombosis is provided on these images.

COMPARISON WITH CT
The preferential use of MRI over CT in the investigation of liver disease cannot be justified unless advantages of MRI are well documented. Clearly the lack of ionizing radiation of MRI and the safety of gadolinium chelates compared to iodine contrast agents are two important considerations. Regarding the safety of gadolinium, it has been shown that gadolinium chelates have negligible effects on renal function in patients in renal failure unlike iodine agents which have a deleterious effect. Gadolinium chelates are also much less likely to result in major allergic reactions than even non-ionic iodinated contrast agents. Therefore at many institutions patients with elevated serum creatinine or a history of allergies to iodinated contrast agents routinely undergo MRI to investigate for focal liver disease, and patients with these conditions are a major indication for MRI.

In addition to safety issues, virtually all reports that have compared current MR with current CT approaches since 1990 have shown that MRI is more accurate than iodine contrast enhanced CT for the detection and characterization of liver lesions. Through this time period although both modalities have evolved, MRI has remained superior. Earlier publications compared MRI with dynamic contrast enhanced CT, while later studies compared MRI with CTAP or spiral CT. The more recent comparisons have been between hepatic arterial dominant phase gadolinium enhanced MRI and hepatic phase iodine contrast enhanced CT.

EXTRAHEPATIC ABDOMEN

Although investigation of liver disease may be the most common indication for abdominal imaging, for an imaging modality to be widely utilized, it must be accurate in the investigation of other organs and tissues in addition to the liver. Few studies have evaluated the demonstration of abdominal disease outside the liver by MRI, and few have compared MRI with CT, the accepted imaging standard for extrahepatic disease, in order to demonstrate the role for MRI. A recent study by Low et al described a prospective blinded comparison between MRI and spiral CT for the evaluation of extrahepatic disease. In this study, they found that MRI using hepatic arterial dominant phase gadolinium-enhanced spoiled gradient echo and hepatic venous phase fat suppressed spoiled
gradient echo demonstrated significantly more surgically-proven sites of extrahepatic disease than spiral CT. They found that CT demonstrated 101 (65%) and MRI 140 (90%) of 155 surgically proven sites (p <0.0001).

**Reticulo-endothelial System Contrast Agents**

Iron oxide particulate agents are selectively taken up by reticulo-endothelial cells in the liver, spleen and bone marrow and result in T2 signal loss due to the susceptibility effects of iron. This class of contrast agents was formerly termed superparamagnetic iron oxide (SPI0) and currently is termed ferumoxides. The first of these agents licensed for use in the United States has the trade name of feridex. Lesions which contain negligible or few reticulo-endothelial cells remain largely unenhanced while the normal liver enhances (ie: becomes low signal on T2-weighted images) with the result that contrast-to-noise between enhanced (low signal) liver and unenhanced (persistently high signal) liver lesions is improved on ferumoxide-enhanced T2-weighted sequences compared to non-contrast T2-weighted sequences. This affords both increased lesion conspicuity and increased lesion detection compared to non-contrast images. The lesion histology in which improved detection with this contrast agent may be most clinically useful is liver metastases. Studies have shown that ferumoxide-enhanced T2-weighted images perform comparably to CT arterial portography for the demonstration of liver metastases (38), suggesting that the role for this agent may be as a replacement to CT arterial portography as a modality to improve detection of liver metastases in patients already know to have liver metastases. The patient group in which this role for ferumoxide may be the most applicable is patients with colon cancer liver metastases who are considered surgical candidates for hepatic resection based on the suspicion of limited involvement of the liver with metastatic disease.

Although serious adverse events are rare, approximately 3% of patients will experience severe back pain while the contrast agent is being administered. This back pain appears to be a side effect of particulate agents in general, and not specific to ferumoxides, and is limited to the injection period and slightly beyond. It develops in patients in whom the contrast agent is administered too rapidly (ie: faster that the recommended slow intravenous drip infusion over .5 hours), and is more likely to occur in patients with liver dysfunction such as cirrhosis. Slowing the injection rate, or terminating the injection, allowing the
back pain to resolve, and restarting the administration at a slower rate, are generally sufficient measures, without loss of diagnostic quality of the images. It is important to realize that it is not necessary to terminate the examination. The long infusion period (30 minutes) is an inconvenient aspect of this agent, which no doubt has decreased enthusiasm for its utilization. Attractive features of the agent include: the long imaging window (1 hour to 4 hours), precise dynamic image acquisition related to contrast administration is unnecessary (unlike the case with the non-specific extracellular gadolinium chelates), and that image quality is acceptable on various field strength machines, with no requirement that the patient breath hold or that the MR machine be able to perform breath hold sequences. These latter two requirements are necessary with non-specific extracellular gadolinium chelates (5-7). Many centers employ breathing-averaged T2-weighted fat suppressed sequences in conjunction with this agent. Image quality however is more reproducible with breath-hold or breathing-independent T2-weighted sequences. Breath-hold echo train spin echo, breath-hold STIR, breath-hold gradient echo, and breathing-independent echo train spin echo are all effective with this agent. Unlike the case with T1-weighted breath-hold spoiled gradient echo, used for gadolinium-enhanced studies, the imaging parameters that are optimal for use with this agent have not been established. Empirically, one sequence that is effective is a gradient echo sequence with TR=150 msec, TE=9 msec and flip angle=45° at 1.5 T; the parameters so chosen in order to utilize the T2* effects of the contrast agent. A cautionary note is that the dosage of feridex that is licensed for use in North America is approximately one third less than that used in Europe. The importance of this understanding is that sequences effective with one dose may not be effective with the other. For example, a T1-weighted spoiled gradient echo sequence, which is essentially the same sequence that we employ with non-specific extracellular gadolinium chelates, has been reported as an ideal sequence for use with ferumoxide in a European study, whereas using the same sequence employing the dose of contrast used in North America will generally result in obscuring the lesions. The explanation for this is that the dosage of feridex in North America is not enough to produce sufficient T2* effects to lower the signal of liver below that of liver lesions, such as metastases, in a consistent, reproducible fashion.
The increased uptake of ferumoxide agents by focal nodular hyperplasia, because of their high content of reticulo-endothelial cells, has also been investigated as a possible clinical role for ferumoxides. There may however be too much of an overlap of the concentration of reticulo-endothelial cells in focal nodular hyperplasia, adenoma and hepatocellular carcinoma for this clinical application to be sufficiently accurate for routine use.

Iron oxide particles have also been formulated as smaller particulate agents, which have been termed ultra small particulate iron oxide (USPIO). These agents have a more prolonged intravascular half life than the larger particle agents, and in a dilute intravascular phase they possess T1-effects that emulate the vascular phase effects of T1-agents. Therefore they can provide additional characterization information such as the demonstration of peripheral nodular enhancement in hemangiomas. These agents also can provide bright vessel enhancement in the vascular phase that can be used for MR angiography. Another major advantage of the ultra small particle agents (eg: Resovist) over the small particle agents (eg: Feridex) is that they can be administered as a rapid intravenous bolus in a very small volume. They are much more convenient to use and also, because of the small volume, should not result in back pain as an adverse effect.

HEPATOCELLULAR CARCINOMA

Hepatocyte-selective contrast agents undergo uptake by hepatocytes and elimination through the biliary system. This category of contrast agents are T1-agents and result in increased signal intensity on T1-weighted images of tissues which show contrast uptake. Normal liver and focal hepatic lesions which contain hepatocytes take up these agents and lesions which do not contain hepatocytes do not.

Currently the only hepatocyte-selective contrast agent which is licensed for use in the United States is Manganese-DPDP. This agent is administered as a slow, one minute, intravenous infusion and the maximal imaging window is between 15 minutes and 4 hours. Dynamic images are not acquired with this agent, but virtually all T1-weighted sequences can be used. Unlike the circumstance with the non-specific extracellular gadolinium chelates, adequate imaging with
Manganese does not require that the MR machine be high field or that breath hold sequences be performed, nor does it require that the patient be able to breath-hold. At this early stage of clinical use, this agent appears to be safe and well tolerated, despite the fact that free Manganese may be the active contrast agent.

At the present time, the best clinical role for Manganese-DPDP appears to be as an agent to improve detection of the number and extent of focal liver lesions, particularly colon cancer liver metastases, in patients in whom hepatic resection is being contemplated. As with ferumoxides, the tissue selective aspects of Manganese-DPDP are under investigation. Focal liver lesions such focal nodular hyperplasia, adenoma, and well differentiated hepatocellular carcinoma all take up the agent, whereas hemangiomas and metastases do not. It is not clear how often the distinction between hepatocyte-containing and non-hepatocyte-containing lesions is of clinical importance, since benign versus malignant lesions is often the more important clinical question.

A feature of hepatocyte-selective contrast agents is that they are eliminated in part through the biliary system. They permit therefore evaluation of hepatocyte functions and appearance and integrity of the biliary tree.

**CONTRAST AGENTS WITH COMBINED PERFUSIONAL AND HEPATOCYTE-SELECTIVE PROPERTIES**

These contrast agents exhibit elimination by both renal and hepatic excretion pathways and thereby possess both early perfusional information (renal elimination pathway) and later hepatocyte-selective information (hepatic excretion pathway). These agents therefore combine the liver lesion detection and characterization information provided by non-specific extracellular gadolinium chelates with the liver lesion detection and characterization (hepatocyte vs. non-hepatocyte) information provided by hepatocyte-selective contrast agents. Gadolinium-BOPTA and gadolinium-EOB-DTPA are examples of this category of contrast agent.
COMPARISON BETWEEN CONTRAST AGENTS

Several studies have shown that MRI enhanced with various individual contrast agents is superior to various forms of state-of-the-art CT. On the basis of these studies it would appear reasonable to believe that contrast enhanced MRI is superior to CT for the detection of focal liver lesions. There is however a paucity of studies that have attempted to compare MR agents among themselves. Since non-specific extracellular gadolinium chelates are not only relatively inexpensive but also provide comprehensive information on a wide range of abdominal diseases, definite advantages of newer agents or specific roles for new agents must be devised.

SUMMARY

Various categories of contrast agents are available for clinical use, all of which have been shown to be able to demonstrate more liver lesions than non-contrast MR images, and current state-of-the-art CT techniques. Non-specific extracellular gadolinium chelates are safe, relatively inexpensive, provide information on detection and characterization of a wide range of focal liver lesions and other liver diseases, and on the extrahepatic abdomen. The clinical application of new contrast agents must evolve into an integrated diagnostic scheme to supplement information provided by non-specific extracellular gadolinium chelates (eg: the detection of additional metastases in patients with known metastases who are considered for surgical resection), or in patient groups in whom non-specific extracellular gadolinium chelates may not show lesions well (eg: post chemotherapy) or when they provide novel information (eg: demonstration of biliary elimination by hepatocyte selective agents).
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