Primovist enhanced MRI for the detection and evaluation of focal liver lesions

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To make an efficacy evaluation of Gadolineum Ethoxybenzyl (Gd-EOB) DTPA-enhanced MR-imaging (Gadoxetic acid, Primovist, Bayer Schering Pharma, Berlin) and Respiratory Triggered Diffusion Weighted Imaging (DWI) for the detection and characterization...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON36761

Source
ToetsingOnline

Brief title
PRIDE-study

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
focal liver lesion, focal liver tumor

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: een grant van Bayer Schering Pharma opdat de uitvoering van het onderzoek gefinancierd kan worden (aanstelling van de onderzoeker). Daarnaast betaald de divisie RRN van het UMC Utrecht de kosten voor de additionele MRI's. ,Bayer

Intervention

Keyword: Characterization, Detection, Focal liver lesions, Primovist MRI

Outcome measures

Primary outcome

Primary parameters:

Negative predictive value and positive predictive value for the detection and

characterization of focal liver lesions on a per patient basis.

Secondary outcome

Secondary parameters:

Accuracy and agreement between MR-Gadovist and MR-Primovist for lesion

detection and characterization on a per lesion basis.

Change in surgical strategy

Study description

Background summary

In patients with liver cancer or other liver lesions, liver imaging is crucial to establish the extent and nature of the tumour(s). These two factors are essential to define the therapeutic strategy or intervention.
MR imaging has gone through major developments the last decade with an increase in contrast agents and new MR sequences.
Contrast enhanced MRI has shown to be a very high-quality detection tool for focal liver lesions, with even higher sensitivities for the detection of focal liver lesions than CT[5-8]. Recently, new MR contrast agents have been developed to increase the sensitivity for the detection and characterization of focal liver lesion. Primovist (Gd-EOB-DTPA, Gadoxetic acid, Bayer Schering Pharma, Berlin) is one of these new, highly specific hepatocyte-specific MRI contrast agent for the imaging, detection and characterization of liver pathology, including liver tumours, cysts, as well as other malignant and benign lesions. Primovist has a water-soluble compound which is taken up by the hepatocytes selectively (approximately 30%) and is equally excreted through the renal and biliary systems in humans*.

Primovist enhances the signal of T1 weighted MR images immediately after administration. The first phases after Primovist enhancement are similar to other non-hepatocyte specific agents like Gadovist (Gadobutrol, Bayer Schering Pharma, Berlin) and include an arterial, portal and late phase. However, there is an additional effect due to the selective uptake of the contrast agent by the hepatocytes. Due to the contrast-uptake by the hepatocytes, the signal intensity of the normal liver parenchyma will increase during the so-called hepatobiliairy phase 10 and 20 minutes after contrast injection. This results in specific lesion patterns during the specific phases. E.g. malignant tumours like metastases or HCC show improved lesion-to-liver contrast (lesions presenting dark against bright parenchyma) because they do not contain either hepatocytes or their functioning is hampered*. Furthermore, as this agent is specific for hepatocytes, it is postulated that lesions such as Focal Nodular Hyperplasia (FNH) can be better distinguished form lesions such as adenoma. After administration of Primovist a dynamic phase scan can be performed in arterial phase, portal-venous phase and equilibrium phase.
In recent years several articles have been published showing the use of Primovist for the detection and characterization of focal liver lesions. Two articles from Bluemke et al. and Huppertz et al. used Primovist enhanced MRI for the detection and characterization of liver metastases. In both articles MR-Primovist was compared with a plain MR, showing a higher sensitivity and specificity for both detection and characterization with the MR-Primovist. Nevertheless, these results are not very useful, since it has been clear that contrast-enhanced MR-imaging shows improved detection and characterization than MR-imaging without any contrast. Hammerstingl et al. and Halavaara et al. reported similar detection and characterization rates for Primovist enhanced MR and they compared the results with contrast-enhanced CT. As expected, Primovist enhanced MR showed higher detection and characterization rates than the contrast-enhanced CT, which is similar to other MR contrast agents. No articles have been published comparing the current gold standard, Gadovist-enhanced MR, with the Primovist-enhanced MR. Furthermore, to determine the actual diagnostic value of MR-Primovist it is most important to define if MR-Primovist improves patient outcome by determining the correct treatment. Therefore it is important to demonstrate that if MR-Primovist leads to higher sensitivities for detection and characterization of focal lesions than other MR-agents, this actually does result in a higher correct treatment management. Until now, MR-Primovist was only evaluated for the diagnostic value of specific patient groups like HCC or CRLM, and the articles only assessed the change in surgical resection strategy due to adding the Primovist sequences to plain sequences. Therefore this study proposal is innovative and necessary and of special interest to the clinical practice.
Apart from the new contrast agents, there are also major advances in MR sequences, including Diffusion Weighted Imaging (DWI). Diffusion Weighted Imaging originates from the T2 weighted images and uses the motion of protons in the extra-cellular space by using large bipolar gradients. Bipolar gradients suppress the area with large movement of water molecules (diffusion). This signal is converted to high or low signal intensity on the MR-images. For

example, normal liver parenchyma has a certain motion which correlates to a large diffusion and therefore low signal on MRI (white), while tumour tissue a much smaller diffusion and therefore gives a high signal on MRI (dark). The motion of the extra-cellular protons is called the apparent diffusion coefficient (ADC). With malignancy, the extra-cellular space is decreased resulting in a decrease in ADC value. Benign lesions like cysts normally show an increase in extra-cellular space which results in an increase in ADC value. The value of the ADC may therefore be used to distinguish between normal liver parenchyma and focal liver lesions. DWI is an excellent MR tool for the detection of pathological lesions, and is increasingly applied for tumour evaluation in the abdomen and pelvis. There are different DWI sequences, with b=50 s/mm2 and b=500 s/mm2 regularly used. b=50 will provide improved anatomical information and has a high sensitivity for the detection of lesions. b=500 improves the specificity for lesion characterization, meaning that malignant lesions emphasize on this image, while benign lesions do not. There have been major improvements in the use of MR-DWI for liver imaging and the current literature shows there is an important role for DWI in the oncological imaging of the liver.
In conclusion, many articles have been published concerning the application of Primovist for detection and characterization of focal lesions, the optimal scanning protocol [18] and the application of Primovist for the detection and staging of HCC. However, no significant studies have been published comparing MR-Primovist to extracellular MR contrast agents for lesion detection and characterization and the actual outcome on treatment management have not been assessed yet. Furthermore, the 4 major articles about Primovist and the detection and characterization of focal liver lesions lack the use of a good reference standard.
In this study we will determine the diagnostic value of MR-Primovist for the detection and characterization of focal liver lesions on a per-patient and a per-lesion basis. Furthermore we will determine the accuracy of MR with Respiratory Triggered DWI (RT-DWI) for the detection and characterization of focal liver lesions. We will calculate ADC values for the different tumour types.

Study objective

To make an efficacy evaluation of Gadolineum Ethoxybenzyl (Gd-EOB) DTPA-enhanced MR-imaging (Gadoxetic acid, Primovist, Bayer Schering Pharma, Berlin) and Respiratory Triggered Diffusion Weighted Imaging (DWI) for the detection and characterization of focal liver lesions

Study design

This is a prospective cohort study.

Study burden and risks

After inclusion, each patient will receive two liver MRI*s: one MRI with Gadovist enhancement, one MRI with Primovist enhancement. Since all these patients were referred to the Radiology Department for a Gadovist enhanced MRI of the liver, only the Primovist enhanced MRI is associated with an extra burden. The Diffusion Weighted Imaging images do not increase any risk or burden. Apart from the MRI investigations, each patient will be called by the study coordinator one week and one month after the Primovist enhanced MRI, to determine if any (S)AE occurred during the study period.
Primovist is a registered contrast agent with no more side effects than Gadovist, therefore no more (serious) adverse effects or (serious) adverse reactions are expected to occur compared to the standard liver MRI with Gadovist. Bayer Schering Pharma has extensively tested Primovist for its safety within phase 1,2 and 3 studies1-4.
In 10.3% of patients receiving Primovist AE*s are expected1,2. The most frequent AE*s that occur are headache and nausea with an incidence of 1.1%, which is comparable to other Gadolineum contrast agents*. No other AE*s show any incidence higher than 1.1%*. No deaths are reported in phase 2 and 3 studies due to the administration of Primovist2,*. SAE*s were classified according to the ICH-GCP definition and included any event resulting in death, were life-threatening, required inpatient hospitalization/prolonged existing hospitalization or resulted in persistent significant disability/incapacity or a congenital birth defect. SAE*s were seen in 3.3% of patients with AE*s and in 0.3% (6/1755) of total population*.
No other investigations, time-consuming events, questionnaires or visits to the hospital are necessary when participating in this study. Participation in this study will result in a close and thorough investigation of the patients* liver disease, although patients do not necessarily benefit from participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Suspicion of focal liver lesions, both benign and malignant
2) Age > 18 years

Exclusion criteria

- clinical query on liver MRI chart directed to other liver disease than focal liver lesions like cirrhosis, hepatitis or liver abces
- previous liver surgery
- a pacemaker
- administration of a liver specific contrast agent within 2 weeks prior to the first MRI with Primovist
- claustrophobia
- hypersensitivity to active substance or any of the recipients of Gd-EOB-DTPA contrast
- caution should be exercised in patients with clinically severe cardiovascular disease. myocardial infarction, uncontrolled hypertensia, instable angina pectoris, congestive hert failure, uncontrolled arhythmia's requiring medication
- severe kidney failure (creatinin clearance <30ml/min)
- pregnancy or lactating women
- high plasma concentration of rifampicin (inhbitor of Gd-EOB-DTPA uptake)

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2010
Enrollment:	230
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Primovist
Generic name:	Paramagnetic contrast agent (Primovist)

Ethics review

Approved WMO Date:	08-03-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-03-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-012115-18-NL
CCMO	NL27862.041.09