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Original Article

Liver enhancement in healthy dogs after gadoxetic acid administration during dynamic contrast-enhanced magnetic resonance imaging

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ABSTRACT

Dynamic contrast enhanced (DCE)-magnetic resonance imaging (MRI) consists of acquisition of native baseline images, followed by a series of acquisitions performed during and after administration of a contrast medium. DCE-MRI, in conjunction with hepatobiliary-specific contrast media, such as gadoxetic acid (GD-EOB-DTPA), allows for precise characterisation of the enhancement pattern of the hepatic parenchyma following administration of the contrast agent. The aim of the study was to assess the pattern of temporal resolution contrast enhancement of the hepatic parenchyma following administration of GD-EOB-DTPA and to determine the optimal time window for post-contrast assessment of the liver. The study was carried out on eight healthy beagle dogs. MRI was performed using a 1.5 T scanner. The imaging protocol included T1 weighted (T1-W) gradient echo (GRE), T2 weighted (T2-W) turbo spin echo (TSE) and dynamic T1-W GRE sequences. The dynamic T1-W sequence was performed using single 10 mm thick slices. Regions of interest (ROIs) were chosen and the signal intensity curves were calculated for quantitative image analysis. The mean time to peak for all dogs was 26 min. The plateau phase lasted on average 21 min. A gradual decrease in the signal intensity of the hepatic parenchyma was observed in all dogs. A DCE-MRI enhancement pattern of the hepatic parenchyma was evident in dogs following the administration of a GD-EOB-DTPA, establishing baseline data for an optimal time window between 26 and 41 min after administration of the contrast agent.

Introduction

Proliferative hepatic parenchymal lesions are common in dogs (Cullen, 2013). They can be classified into focal, multifocal or generalised, malignant or benign lesions (Lidbury and Steiner, 2013). In dogs, these lesions are diagnosed and further characterised on the basis of abdominal radiography, diagnostic ultrasound and computed tomography examination. However, since these diagnostic methods are considered to have low specificity, more sensitive and specific techniques are sought to enable minimally invasive differentiation of the type and malignancy of the lesions (Strobel et al., 2000; Kinkel et al., 2002; Forner et al., 2008). Magnetic resonance imaging (MRI) is currently considered one of the most accurate methods used to diagnose tumours of the hepatic parenchyma in human beings (Bruegel and Rummeny, 2010; Albiin, 2012).

The diagnostic potential of MRI has led to increased use of contrast agents with different biological characteristics to improve visualisation of lesions and to assess tumour vascularisation (Lin and Brown, 2007; Lohrke et al., 2016). Gadoxetic acid (Gd-EOB-DTPA) is a contrast agent used in human medicine in MRI of the hepatic parenchyma (Grazioli et al., 2012; Schalkx et al., 2014; Verloh et al. 2015). It is primarily used in focal and disseminated proliferative hepatic lesions, and combines the advantages of conventional contrast and hepatocyte-specific contrast, allowing the evaluation of specific enhancement patterns and the differentiation of proliferative lesions in human beings (Purysko et al., 2011; Campos et al., 2012; Marks et al., 2014).

After intravenous injection, gadoxetic acid initially acts as an extracellular contrast medium (dynamic phase) and remains

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within the arterial intravascular spaces (arterial phase) and venous intravascular spaces (venous phase), enabling the assessment of the vascularisation of the hepatic parenchyma. Next, there is uptake of the contrast medium by functional hepatocytes (hepatobiliary phase), which enables the assessment of the hepatic parenchyma. This distinguishes gadoxetic acid from extracellular contrast agents. Gadoxetic acid is excreted into the bile and through the kidneys (Hamm et al., 1995; Saito et al., 2005; Zech et al., 2007).

Previous studies using gadoxetic acid in dogs were carried out using low-field and high-field scanners, with repeated T1-weighted sequences at short time intervals (Yonetomi et al., 2012; Marks et al., 2014; Bratton et al., 2015). Dynamic MRI has different numbers of acquisitions compared to a standard T1-weighted (T1-W) sequence. These are usually continually repeated short acquisitions that enable constant monitoring of the magnetic resonance signal enhancement (Gribbestad et al., 2005; O'Connor et al., 2011; Taouli et al., 2013).

The aim of this study was to document changes in hepatic parenchymal contrast enhancement following intravenous GD-EOB-DTPA administration during a dynamic imaging examination lasting more than 120 min and to determine the optimal time window for post-contrast studies of the hepatic parenchyma using a chosen contrast medium.

Materials and methods

Animals

The study was approved by the Local Ethics Committee for Animal Experiments in Wroclaw (approval number 91/2015; date of approval 17th June 2015). The study was carried out on eight clinically healthy beagle dogs of both sexes (four males and four females), 3–6 years of age (mean 4.5 years; standard deviation, SD, 1.2 years), with body weights of 8–13 kg (mean 9.95 kg; SD 1.39 kg). Animals were included in the study on the basis of an unremarkable physical examination, complete blood count (CBC), plasma biochemistry and coagulation profile. The physical examination and clinical laboratory tests were repeated at 2 and 4 weeks after MRI. To evaluate the liver and extrahepatic bile ducts, an abdominal ultrasound was carried out prior to MRI in all dogs. An ultrasound guided needle core liver biopsy was also performed using a 16 G Tru-cut needle and submitted for histopathological analysis.

Magnetic resonance imaging

The dogs were fasted for 12 h prior to general anaesthesia and premedicated with 0.005 mg/kg medetomidine (Narcostart, Le Vet BV) intramuscularly and 0.005 mg/kg butorphanol (Torbugesic, Pfizer) intramuscularly. Anaesthesia was induced with 1 mg/kg IV propofol (Scanofol, ScanVet) and maintained with isoflurane (Forane, AbbVie). Respiratory rate, heart rate, oxygen saturation, carbon dioxide concentration in respired gases, and the inspiratory and expiratory concentration of the anaesthetic gas, were monitored over the course of the MRI examination.

MRI was performed using a 1.5 T scanner (Philips Ingenia) and a 32-channel torso phased array coil. All the dogs were positioned in dorsal recumbency. The imaging protocol consisted of a navigator echo respiratory-triggered T1-weighted (T1-W) turbo field echo (TFE) sequence, a T2-weighted (T2-W) turbo spin echo (TSE) sequence and dynamic T1-W TFE sequences performed in the transverse plane (Table 1). The dynamic T1-W sequence was obtained using single 10 mm thick slices (Fig. 1) at the level of the gall bladder. Gadoxetic acid (Primovist, Bayer Pharma) was administered intravenously during the eighth acquisition of the dynamic sequence at a dose of 0.1 mL/kg (0.025 mmol/kg), followed by 15 mL of a 0.9% saline solution flush. A manual hydraulic pump was used to administer the contrast medium and the saline flush. Following administration of the contrast agent, the study was continued for at least 120 min.

Image analysis

A nonstandard dynamic T1-W gradient echo (GRE) sequence using a radial acquisition scheme with respiratory triggering based on navigator echoes was created to minimise any movement artefacts during the entire study. The acquisition was triggered by a pause in respiratory movement of the diaphragm. Hence, the intervals between scans varied from 0 to 8 s, where 0 s corresponded to two dynamics acquired one after another without delay. This methodology provided excellent images, which compensated for movement artefacts and did not require further post processing. However, due to variable intervals between the acquired scans, the study could not be analysed with the current commercial software, which works only on fixed intervals. Therefore, in-house C++ software was developed to analyse the images more precisely; this used real acquisition times written in a dicom header to create a data table consisting of acquisition times and ROIs with the % relative signal intensity. The relative % signal intensity was calculated in relation to the ROI signal intensity before bolus administration of the contrast agent.

Table 1
Magnetic resonance (MR) sequences and imaging parameters used to assess the hepatic parenchyma prior to administration of the contrast agent (T1-W TFE and T2-W MV HR), as well as dynamic contrast enhancement, in eight healthy beagle dogs.

	T1-W TFE[a]	T2-W MV HR[b]	Dynamic T1-W[c]
Echo time (ms)	4.6	100	4.6
Repetition time (ms)	10	3745	10
Flip angle (degree °)	25	90	15
Bandwidth (Hz)	141.7	531.9	125.3
FOV (mm)	220 × 192	250 × 250	175 × 175
Matrix	220 × 192	500 × 500	88 × 88
Slice thickness (mm)	3	5	10
GAP (mm)	0	0.5	0
Number of slices	100	50	1

[a] T1-weighted turbo field echo.
[b] T2-weighted MultiVane high-resolution turbo spin echo.
[c] Dynamic T1-weighted turbo field echo.

Enhancement of the hepatic parenchyma was assessed in the dynamic T1-W sequence using three square ROIs. The ROIs were placed in the right medial lobe (ROI 1), the left medial lobe (ROI 2) and the quadrate lobe (ROI 3), avoiding large blood vessels and organ boundaries. An additional ROI was placed in the aorta (ROI 4). The first, second and third ROIs each measured 1 cm^2, while the fourth ROI measured 0.36 cm^2 (Fig. 2). The signal intensity was presented in the form of a time intensity curve, created on the basis of the enhancement values obtained for each ROI. Contrast enhancement was assessed visually based on the obtained curves (Fig. 3).

Sets of data, including values of relative enhancement for each ROI during consecutive acquisitions, were obtained for each dog. The relative enhancement was calculated automatically by the software and represented the ratio of pre- and post-contrast signal intensity × 100. The maximum relative enhancement was defined as the ratio of maximal post-contrast enhancement:pre-contrast signal intensity × 100. The mean maximum relative enhancement for each dog was calculated as the arithmetic mean of the maximum relative enhancement for ROI 1, ROI 2 and ROI 3.

Statistical analysis

Student's *t* test for independent samples was used to compare values of mean enhancement in the hepatic parenchyma at 10 and 20 min of the examination, similar to the methodology described by van Kessel et al. (2012). In that analysis, the relative enhancement from the three ROIs located in the hepatic parenchyma in each acquisition in each dog was used. Next, the series of relative enhancement values obtained in all the acquisitions at 10 and 20 min were compared. The analyses were repeated for each dog separately and for all the dogs together. The significance level was set at $P < 0.05$ and data were analysed using Statistica 12 software (StatSoft). The 95% confidence interval (CI) based on the mean and standard deviation (SD) of the samples was used to assess the mean start and end time of the plateau phase. The time of data acquisition is presented in minutes.

Results

A complete dynamic MRI was carried out in seven dogs. The number of acquisitions obtained during the dynamic phase of the study ranged from 267 to 1400 (mean 1019, SD 486) due to breath triggering. In one dog, the examination was terminated after 80 min due to anaesthetic concerns and 564 acquisitions were performed.

MRI prior to administration of the contrast agent revealed a normal structure and signal intensity of the hepatic parenchyma. In all dogs, the signal intensity of the hepatic parenchyma was uniformly hypointense on T2-W images compared to the splenic parenchyma. The hepatic parenchyma was homogenous and moderately hyperintense on T1-W images compared to the splenic parenchyma. The wall of the gall bladder and the bile ducts were not visible in either of the sequences. The gall bladder content was