Bitesize Physics

Negative Oral Contrast Media for MRCP

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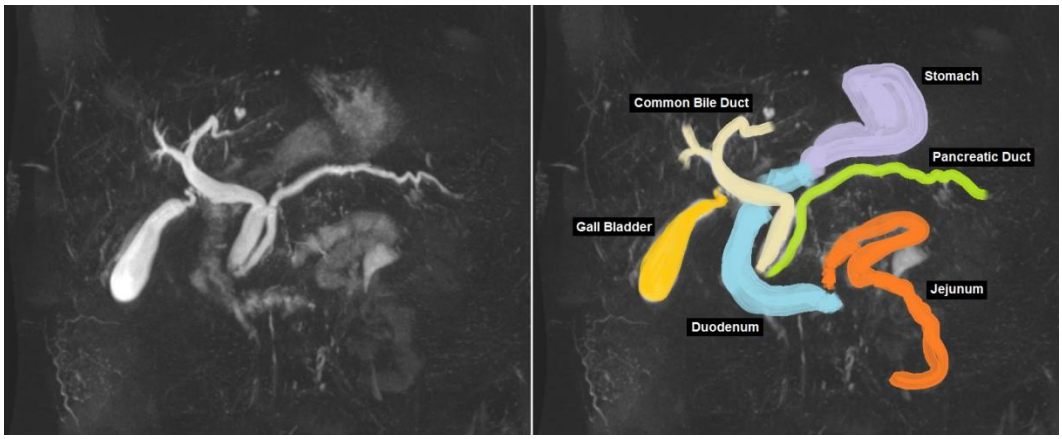
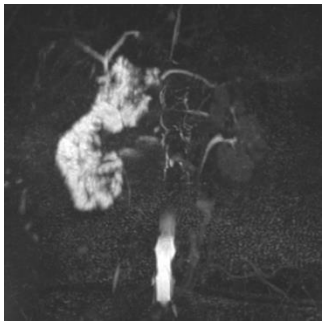
Introduction

Magnetic Resonance Cholagiopancreatography (MRCP) generally involves the acquisition of heavily T2 weighted sequences. The aim is to remove as much signal from all tissues other than those containing water-based fluid. In this way the bile filled biliary system should be well seen against a darkened background.



In reality other unhelpful fluids within the scanned volume will also return a high signal. Cerebrospinal fluid in the spinal canal, bile within the gall bladder and urine in the ureters will all appear bright. Whist in the majority of cases these can be either tolerated or removed with post processing, digested fluid in the duodenum can be unacceptably problematic due its close proximity to the area of interest.



The anatomy of the duodenum is such that it curves in a C-shape from the pyloric sphincter of the stomach, behind the common bile duct to reach the jejunum. Midway along the inner curve, the common bile duct enters the duodenum at the Sphincter of Oddi and it is at this location that stones can very often lodge. It is therefore crucial that unobstructed imaging of this area is achieved - the ideal scenario being that the duodenum is totally empty of water content and thereby returns no signal.

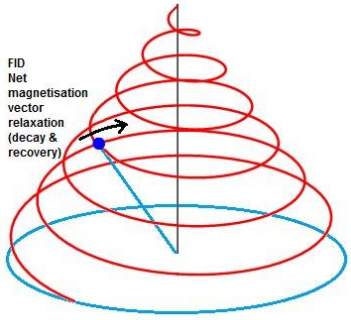
To encourage an empty duodenum it is common practice to prepare the patient by starving them for a few hours before the examination to give time for food and liquid to pass. This is not always completely successful however, so additionally in the lead up to the examination, negative oral contrast media can be used to either 'push' out, or mix with residual gastric and duodenal fluid. It is of course essential that the fluid used produces low signal on T2 weighted imaging.

RF Input and Subsequent Relaxation

When placed into an MRI scanner, the patient's hydrogen protons (and others) will move into alignment either with (parallel), or against (anti-parallel) the main magnetic field. More will go 'with', and the net result is a small magnetic vector in the direction of the main field. Whilst within the scanner, this can be considered as a state of relaxation, i.e. the protons are content to be in this alignment.

If a frequency-matched RF pulse is introduced, some parallel protons will 'flip' dpwn resulting in the initial longitudinal magnetic field being either reduced (<90^{o} pulse) or removed (90^{o} pulse). This amount flipped is dependent on the size of the RF, but either way this reduction in magnetism is not a relaxed state. Once the RF is removed the main magnetic field will force the protons to *recover* their original magnetisation. Hydrogen protons in differing molecules will do this at differing rates which affords us the ability to exploit this as differing signal strengths from differing tissues, and ultimately image contrast. This is known as T1 *recovery* and takes a relatively long time.

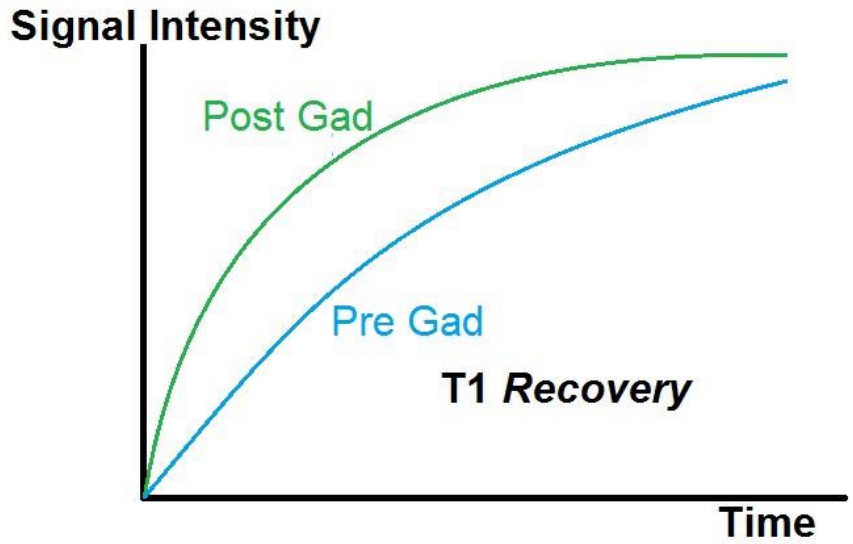
AT THE SAME TIME (and I emphasise this through a personal dislike of the graph showing the skier going up the slope and then down the mountain that some will be familiar with, which leads you to wrongly believe one happens after the other), yes at the *same time* that the longitudinal magnetisation recovers, transverse magnetisation will *decay*. This is known as Free Induction Decay (FID).



Transverse magnetisation never existed before the RF pulse as all precessing protons were in random positions and cancelled each other out. The RF pulse has a secondary effect of aligning them in their phase of spin, i.e. they will point in the same direction and hence create a transverse magnetisation. Once the RF is removed the protons will experience an energy transfer between each other and rapidly lose their phase coherence. As a result transverse magnetisation will *decay*. This is known as T2 (or T2*) *decay* and happens relatively quickly. This energy transfer is more efficient in some tissues than others. Those tissues where this magnetism loss is rapid i.e. have a short T2 time, produce less signal that those where the loss takes longer. As before an alternative contrast between differing tissues can therefore be obtained and imaged.

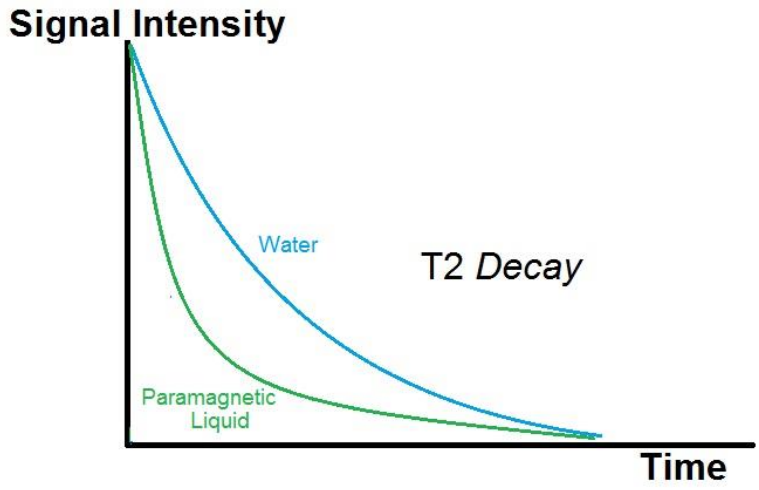
T1 Contrast Enhancement

We are very familiar with the concept of gadolinium-based contrast media increasing T1 signal, but why is this? Well, it is due to paramagnetism causing T1 shortening. Gadolinium is a paramagnetic element i.e. it has incompletely filled atomic orbitals which result in it gaining magnetization in the presence of an external magnetic field. Tissues that absorb gadolinium will therefore *recover* their T1 signal more quickly, and so produce a stronger signal in a T1-weighted image. So, by imaging with T1 weighting we can use gadolinium enhancement to cause differential enhancement between normal tissue and pathology and thereby aid diagnosis. (fig 4)



T2 Contrast Darkening

In contrast to T1 relaxation being a *recovery*, T2 relaxation is a *decay*. Immediately after the RF excitation there is maximal T2 magnetisation, but this will disappear as a result of energy transfer between spins. This energy transfer is more efficient in some tissues than others. Those tissues where this magnetism loss is rapid i.e. have a short T2 time, produce less signal that those where the loss takes longer. Paramagnetic substances lose their spin coherence very rapidly and so tissues that have absorbed paramagnetic contrast media will darken quickly on T2 weighted imaging. So in this way an oral paramagnetic liquid can be used remove unwanted high signal from duodenum during an MRCP[1]



Branded Oral Contrast Media

Feromoxsil is a large siloxane coated superparamagnetic iron oxide in a viscous solution. The 10nm particles contain ferric and ferrous iron and as such produce a large amount of T1, T2 and T2* shortening [2]. The result with the T2 imaging used with an MRCP study is a significant darkening of any residual fluid that it replaces or mixes with in the duodenum. Though no longer available, GastroMark and Lumirem were both contrast agents once available in the UK for this use.

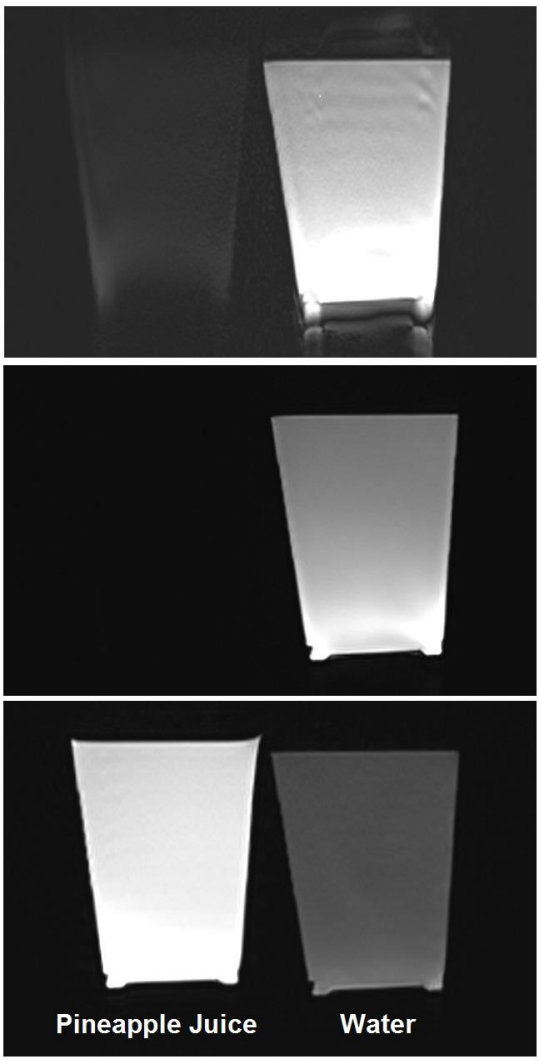
Manganese

Manganese is one of the most abundant metals on earth and is a component of more than 100 minerals. Besides being an essential trace element in the metabolic processes in the body, it is also a paramagnetic metal that possesses similar characteristics to gadolinium[3]. Intravenous manganese was in fact one of the earliest reported examples of MRI contrast media and was for example available for many years in the form of Teslascan, a very successful liver contrast agent[4,5]. It might yet still have a part to play in the future for newly developing IV contrast media, but in the meantime its existence in naturally occurring juices means that it's paramagnetic properties can assist us in a very cost effective way[6].

Fruit Juice

Manganese occurs in high concentrations in some pure fruit juices including pineapple, blueberry and cranberry. Pure juice can therefore be used as an effective oral negative T2 contrast media for MRCP. Studies have shown pineapple juice for example to give similar effect to branded contrast media in reducing T2 signal, yet with an improved taste!

I produced the following image by scanning a cup of water next to a cup of pineapple juice.



You can see that on both the T2 weighted sequences water gives a high signal, but that the pure pineapple juice gives a low signal. This is due to the fact that whilst water protons have retained T2 phase coherence at the TE time used, the paramagnetic nature of the manganese in the juice has caused a much more rapid decay of transverse magnetism. In fact, by using a very long TE, as is common with MRCP imaging, the pineapple juice can be made to become just about without signal. The transverse magnetisation has had enough time to become completely lost (*decayed*).

On the T1 sequence, the T1 shortening properties of the manganese in the pineapple juice resulted rapid T1 *recovery* compared with water, and so produces a high signal. The pineapple juice used was a simple, cheap branded carton.

Manganese-containing fruit juices therefore offer a safe, simple and well tolerated method of improving the quality of MRCP T2 weighted imaging. It should be noted that manganese concentration is variable in commercially available brands. Therefore one with high manganese concentration should be selected.[7] Never fall into the trap of using a cordial, i.e. mixing concentrate with water, as this is mainly water and therefore will not work!

References

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Manganese-based oral contrast agent for liver magnetic resonance imaging: evaluation of the time course and dose response of liver signal intensity enhancement
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2 Leung Kam

Ferumoxsil: Large SPIO

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3 Jørgensen JT[1], Rief M, Brismar TB, Wagner M and Albiin N

A new manganese-based oral contrast agent (CMC-001) for liver MRI: pharmacological and pharmaceutical aspects
Acta Radiol. 2012 Sep 1;53(7):707-13. doi: 10.1258/ar.2012.120034. Epub 2012 Jul 20

4 Dipanjan Pan, Anne H. Schmieder, Samuel A. Wickline and Gregory M. Lanza

Manganese-based MRI contrast agents: past, present and future
Tetrahedron. 2011 Nov 4; 67(44): 8431–8444

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7 Arrivé L[1], Coudray C, Azizi L, Lewin M, Hoeffel C, Monnier-Cholley L, Lacombe C, Vautier S, Poupon J and Tubiana JM.

Pineapple juice as a negative oral contrast agent in magnetic resonance cholangiopancreatography
J Radiol. 2007 Nov;88(11 Pt 1):1689-94

Primovist and Multihance took over

********** HERE **********

Manganese offers great advantages as a T1 weighted MR contrast agent due to its favourable electronic configuration and enriched biochemical features. However, manganese in its free form is toxic and needs to be “masked” before administration. Manganese chelates, e.g. Mn-DPDP (Teslascan™), prevent the premature release of the metal and enhance the T1 signal. Teslascan™ has been successfully used in the clinic for the detection of liver lesions.

The T2 time determines how quickly an MR signal fades after excitation. Let us take an example of fat and CSF again. The T2 decay occurs as a result of energy transfer between spins. The energy exchange in the hydrogen atoms in fat is more efficient than in water. As a result, hydrogen in the fat loses transverse magnetization more rapidly than in CSF. The T2 time of fat(80ms) is shorter than the CSF(200ms). Therefore, the transverse magnetisation of fat decays faster. The magnitude of transverse magnetisation in CSF is large. It therefore appears very bright as compare to fat in T2 contrast image.

Low T2 signal

The patient is asked to drink this Contrary to water-based fluid, these needs to offer low signal on T2 weighted imaging. For this there are a few options.

Contrast Media – Manganese

Ferumoxsil is composed of iron particles of about 10 nm and the hydrodynamic diameter is about 300 nm. The iron particles are coated with a non-biodegradable and insoluble matrix (siloxane) and suspended in viscosity-increasing agents such as starch and cellulose [2]. They are used in oral large SPIO preparations. Ferumoxsil has been tested in clinical trials as negative contrast agent that decreases signal on T2 images. Ferumoxsil is used in bowel MR imaging.

Brand names – Lumirem or GastroMARK

Most liquids we come into contact with contain a large proportion of water. Water is bright on T2, so we can be forgiven for thinking all liquids behave in this way, but it is not the case. High manganese = low contrast. Where is manganese – tea! But this wont work because of the majority of the liquid

being water. Be careful of trying to use pineapple or cranberry squash (cordial). This is mainly water too – it must be juice!

Manganese offers great advantages as a T1 weighted MR contrast agent due to its favorable electronic configuration and enriched biochemical features. However, manganese in its free form is toxic and needs to be “masked” before administration. Manganese chelates, e.g. Mn-DPDP (Teslascan™), prevent the premature release of the metal and enhance the T1 signal. Teslascan™ has been successfully used in the clinic for the detection of liver lesions.

IV Manganese was one of the earliest reported examples of paramagnetic contrast material for MRI because of its efficient positive contrast enhancement

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PMCID: PMC3203535

NIHMSID: NIHMS319362

Manganese-based MRI contrast agents: past, present and future

Dipanjan Pan,* Anne H. Schmieder, Samuel A. Wickline, and Gregory M. Lanza

To date the only manganese-based contrast agent ever approved for worldwide sales and clinical use was mangafodipir trisodium (Mn-DPDP), marketed in the 1990's under the tradename Teslascan®. Due to low sales, poor clinical performance, and concerns over toxicity, Teslascan® was withdrawn from the US market in 2003 and from the EU in 2010.

Acta Radiol. 2012 Sep 1;53(7):707-13. doi: 10.1258/ar.2012.120034. Epub 2012 Jul 20.

A new manganese-based oral contrast agent (CMC-001) for liver MRI: pharmacological and pharmaceutical aspects.

Jørgensen JT[1], Rief M, Brismar TB, Wagner M, Albiin N.

Author information

Abstract

Manganese is one of the most abundant metals on earth and is found as a component of more than 100 different minerals. Besides being an essential trace element in relation to the metabolic processes in the body, manganese is also a paramagnetic metal that possesses similar characteristics to gadolinium with regards to T1-weighted (T1-w) magnetic resonance imaging (MRI). Manganese, in the form of manganese (II) chloride tetrahydrate, is the active substance in a new targeted oral contrast agent, currently known as CMC-001, indicated for hepatobiliary MRI. Under physiological circumstances manganese is poorly absorbed from the intestine after oral intake, but by the use of specific absorption promoters, L-alanine and vitamin D(3), it is possible to obtain a sufficiently high concentration in the liver in order to achieve a significant signal enhancing effect. In the liver manganese is exposed to a very high first-pass effect, up to 98%, which prevents the metal from reaching the systemic circulation, thereby reducing the number of systemic side-effects. Manganese is one of the least toxic trace elements, and due to its

favorable safety profile it may be an attractive alternative to gadolinium-based contrast agents for patients undergoing an MRI evaluation for liver metastases in the future. In this review the basic pharmacological and pharmaceutical aspects of this new targeted oral hepatobiliary specific contrast agent will be discussed.

Oral-based +ve contrast use!

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http://mriquestions.com/uploads/3/4/5/7/34572113/mr_cholangiopancreatography_before_and_after_oral.pdf

MR Cholangiopancreatography Before and After Oral Blueberry Juice Administration Papanikolaou, Nikolaos; Karantanas, Apostolos; Maris, Thomas; Gourtsoyiannis, Nickolas Journal of Computer Assisted Tomography . 24(2):229-234, March/April 2000.

The manganese in blueberry juice exists as a divalent ion (20). The T2 relaxation enhancement effects of blueberry juice are due to manganese (17) and iron ions. Blueberry juice reduces the intraluminal signal of the gastrointestinal tract on T2-weighted images due to the paramagnetic properties of manganese and the superparamagnetic properties of iron ions found in it. Both ions result in T2 shortening, which is responsible for signal elimination.

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http://www.diva-portal.se/smash/get/diva2:938888/FULLTEXT01.pdf

Oral instead of IV again...

Invest Radiol. 2010 Sep;45(9):565-71. doi: 10.1097/RLI.0b013e3181e9e120.

Manganese-based oral contrast agent for liver magnetic resonance imaging: evaluation of the time course and dose response of liver signal intensity enhancement.

Rief M[1], Huppertz A, Asbach P, Franiel T, Schwenke C, Hamm B, Taupitz M, Wagner M.

Abstract

OBJECTIVES:

Recently, an oral contrast agent (CMC-001, CMC Contrast, Lund, Sweden) containing manganese chloride tetrahydrate ($MnCl_2$) as active substance has been introduced for liver magnetic resonance imaging (MRI). The aim of this study was to evaluate the time course and

dose response of liver signal intensity (SI) enhancement and liver-lesion contrast (LLC) after administration of 2 doses of CMC-001 corresponding to 0.8 g MnCl2 and 1.6 g MnCl2.

MATERIALS AND METHODS:

A total of 20 patients with liver metastases diagnosed by computed tomography were included in this prospective study. Patients were randomly assigned to receive either 0.8 g MnCl2 (n = 11) or 1.6 g MnCl2 (n = 9). MRI was performed precontrast (0 hour) and at 1, 2, 3, and 6 hours after contrast agent administration using a breath-hold T1-weighted gradient echo sequence (GRE). For quantitative analysis, SI was measured in regions of interest in the liver and in representative liver metastases. Liver SI enhancement and LLC were calculated. Area under the curve analysis was performed for liver SI enhancement and LLC in both dose groups. The dose groups were compared with a Wilcoxon rank-sum test for independent samples. Tests for pairwise differences between the time points were performed with paired Wilcoxon signed-rank tests.

RESULTS:

Area under the curve analysis revealed no statistical significant differences for liver SI enhancement and LLC between the 0.8 and 1.6 g MnCl2 dose group (P = 1.00 and P = 0.94, respectively). Liver parenchyma showed significant SI enhancement until 3 hours after contrast agent administration (median of pooled data from both dose groups: 1 hour, 24.7%; 2 hours, 37.2%; 3 hours, 54.9%; 6 hours, 47.3%). LLC significantly increased until 2 hours after contrast agent administration (median of pooled data from both dose groups: 0 hour, 0.19; 1 hour, 0.29; 2 hours, 0.36; 3 hours, 0.37; 6 hours, 0.36). Liver SI enhancement and LLC showed no significant differences between 3 hours and 6 hours after contrast agent administration (P = 0.75 and P = 0.25, respectively). Mild adverse events occurred in 6 patients (30%) after contrast agent administration.

CONCLUSIONS:

CMC-001 at doses corresponding to 0.8 and 1.6 g MnCl2 offers robust liver SI enhancement with a diagnostic time window for liver MRI between 2 and 6 hours after oral administration.

J Radiol. 2007 Nov;88(11 Pt 1):1689-94.

[Pineapple juice as a negative oral contrast agent in magnetic resonance cholangiopancreatography].

[Article in French]

Arrivé L[1], Coudray C, Azizi L, Lewin M, Hoeffel C, Monnier-Cholley L, Lacombe C, Vautier S, Poupon J, Tubiana JM.

Author information

Abstract

PURPOSE:

The quality of magnetic resonance cholangiopancreatography (MRCP) images is frequently degraded by high signal from the gastrointestinal tract on heavily T2W images. The purpose of this study is to evaluate pineapple juice (PJ) as an oral negative contrast agent in MRCP.

MATERIALS AND METHODS:

Results from MRCP in 50 patients with PJ and 50 patients with paramagnetic contrast (ferumoxsil-Lumirem) were compared. Reviewers were blinded to the type of contrast agent. Exam quality was recorded with regards to signal suppression in the stomach, duodenum and proximal small bowel and with regards to pancreatic duct and biliary ducts visualization. In vitro, the signal characteristics of several commercially available brands of PJ were assessed using T1W, T2W and MRCP sequences. Signal intensity was correlated with the manganese concentration measured using atomic absorption spectrometry. Finally, the reviewers compared the taste of PJ and ferumoxsil.

RESULTS:

On MRCP sequences, results were similar with regards to signal suppression in the stomach, duodenum and proximal small bowel with PJ and ferumoxsil. Visualization of the pancreatic duct, intrahgepatic bile ducts and CBD was similar with PJ and ferumoxsil. The signal intensity of commercially available brands of PJ on T2W and MRCP sequences correlated well with the measured manganese concentration on spectroscopy. Variations in manganese concentration were observed, with values ranging from 3.65 to 27.24 mg/L. The reviewers noted that PJ tasted "good" or "very good" and that ferumoxsil tasted "bad" or "very bad".

CONCLUSION:

Ingestion of PJ provides effective signal suppression in the GI tract on MRCP, similar to paramagnetic contrast agents. Because manganese concentration is highly variable in commercially available PJ brands, a brand with high manganese concentration should be selected.

Abdom Imaging. 2012 Jun;37(3):447-56. doi: 10.1007/s00261-011-9761-6.

Use of pineapple juice with gadopentetate dimeglumine as a negative oral contrast for magnetic resonance cholangiopancreatography: a multicentric study.

Duarte JA[1], Furtado AP, Marroni CA.

Author information

Abstract

We evaluated the efficacy of pineapple juice with gadopentetate dimeglumine as a negative oral contrast agent for magnetic resonance cholangiopancreatography (MRCP). Images were obtained before and after the intake of a negative oral contrast agent. Images obtained from six different areas of the biliary tree were analyzed by three different radiologists, who were blind to the exams; scores regarding image quality were given to each area. The statistical analysis showed a significant difference between images before and after the use of the contrast agent ($P < 0.001$) for the three radiologists (R1-R3). Mean scores given by radiologists before the intake of the contrast agent were 2.49 ± 0.42 (R1), 2.62 ± 0.32 (R2), and 2.22 ± 0.46 (R3). After the intake, mean scores were 3.38 ± 0.62 (R1), 3.48 ± 0.55 (R2), and 2.89 ± 0.69 (R3). The ducts that showed the highest scores were the common bile duct and duct of Wirsung, the distal portion of the common bile duct and the cystic duct. We suggest herein that the contrast agent pineapple juice with gadopentate dimeglumine constitutes an efficient negative oral contrast agent for MRCP, for it efficiently eliminates the signal of the digestive tube in MRCP images.