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Gadofosveset

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Contents

Abstract

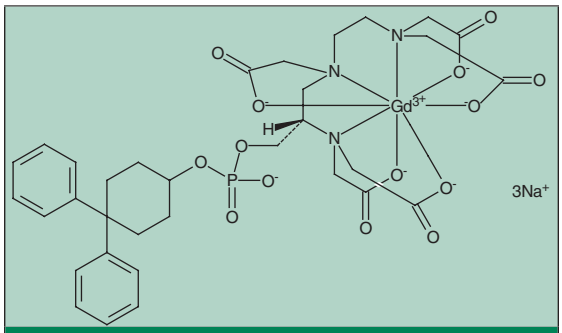
▲ Gadofosveset is the first gadolinium-based magnetic resonance (MR) imaging agent designed to image the blood pool. At clinically relevant concentrations, gadofosveset is highly bound to human serum albumin, which has the effect of increasing its signal-enhancing properties above that of non-protein bound imaging agents, as well as increasing its plasma half-life, allowing for increased imaging times.

▲ The use of gadofosveset-enhanced MR angiography was compared with non-enhanced MR angiography in four open-label, multicentre studies in adults with known or suspected arterial disease. Significant improvements in the accuracy and specificity of diagnosis were seen with gadofosveset in patients with aortoiliac disease in two studies. Sensitivity was also improved, with all three readers in one study, and two of three readers in the other study, showing significant improvements with gadofosveset use.

▲ Significant improvements in sensitivity, specificity, and accuracy were also seen with gadofosveset in a renal artery disease study. Specificity was significantly improved in patients with pedal artery disease across all readers, with accuracy and sensitivity significantly improved in two of three and one of three readers.

▲ Gadofosveset was generally well tolerated in clinical trials, with most adverse events being mild or moderate in severity.

Features and properties of gadofosveset (Vasovist™)	
Indication	
Contrast-enhanced magnetic resonance angiography for visualisation of abdominal or limb vessels in adults with suspected or known vascular disease	
Mechanism of action	
Binds to human serum albumin and shortens intravascular longitudinal relaxation	
Dosage and administration	
Dosage	0.03 mmol/kg
Route of administration	Intravenous
Frequency of administration	Single dose
Pharmacokinetic profile (single intravenous dose of 0.03 mmol/kg)	
Binding to human serum albumin	80–90%
Area under the plasma concentration-time curve	732 μg • h/mL
Volume of distribution at steady state	148 mL/kg
Total body clearance	6.57 mL/h/kg
Elimination half-life	18.5h
Adverse events (most frequent)	
Paraesthesia, pruritus, hyperglycaemia, feeling hot, headache, burning sensation, nausea	



Gadofosveset

X-ray angiography is commonly used to diagnose vascular disease due to its accuracy, but there are several disadvantages to its use, including the potential for vascular injury, nephrotoxicity, nerve damage and stroke.[1] Magnetic resonance (MR) angiography is a less invasive technique than x-ray angiography, being derived from signals produced by the protons in water; the relaxation of protons releases signals in the form of radiowaves, and this relaxation occurs in both the longitudinal (T_1) and transverse (T_2) directions.[1] Differences in signal intensity create contrast in MR images, which is enhanced further by the use of contrast agents, allowing even better tissue resolution than non-enhanced MR imaging.[2,3]

The majority of MR imaging contrast agents are complexes of the heavy metal gadolinium, which act to shorten the T_1 of water protons wherever they localise;[3,4] the degree of relaxation enhancement is determined primarily by the rate of rotation of the complex.[4] Most currently used contrast agents are hydrophilic and extracellular,[5,6] causing them to diffuse through extracellular fluids rather than bind selectively to a target. As a result, these agents possess a very short vascular half-life, allowing only a small window for imaging the vasculature unless multiple doses are administered.[7,8]

Gadofosveset (Vasovist™)[1] is the first gadolinium-based MR imaging agent designed to image the blood pool; it binds reversibly and non-covalently to human serum albumin in plasma.[1,4] The use of gadofosveset offers potential advantages such as an extended imaging time, with a single dose allowing the imaging of multiple body regions. This profile examines the pharmacological properties of gadofosveset and discusses its clinical use in patients undergoing MR angiography for arterial disease.

1. Pharmacodynamic Profile

Gadolinium causes signal enhancement by shortening the T_1 of water molecules that interact with it.[1,3] The rate of rotation of the contrast agent complex primarily determines the magnitude of relaxation enhancement; most agents have less than optimal relaxation-enhancing properties because of their high rate of rotation.[4] Binding of a contrast agent such as gadofosveset to a target protein increases relaxation enhancement by slowing down the rate of rotation of the gadolinium complex.[4] This increase in relaxation enhancement only occurs with binding, producing an improved target-to-background ratio.[4]

- Gadofosveset is highly and reversibly bound to human serum albumin (see section 2); the targeting of gadofosveset to the blood pool allows selective enhancement of the vascular system.
- Binding of gadofosveset to human serum albumin enhances relaxivity, resulting in improved contrast. The relaxivity seen with gadofosveset use was 6- to 10-fold greater than that seen with non-protein bound gadolinium chelates.[9] In another comparative study, the relaxivity of gadofosveset in whole blood at 37°C was 19.0 mmol/L/sec, up to 5-fold the relaxivity of non-protein bound chelates, and the highest of all currently available MR contrast agents.[10]
- Over a dose range of up to 0.05 mmol/kg of gadofosveset, relaxivity in plasma was 33.4–45.7 mmol/L/sec (at 20 MHz).[11] A dose of gadofosveset of 0.1 mmol/kg was 96% bound to human serum albumin in ultrafiltration experiments, leading to a relaxivity of 48 mmol/L/sec (at 20 MHz).[12]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• In clinical studies, intravenous injection of gadofosveset has been shown to shorten T_1 values for up to 4 hours post-injection.[11] In a dose-ranging study in 27 healthy volunteers, plasma relaxation rates increased significantly with gadofosveset use at all doses (0.01–0.05 mmol/kg; p-value not reported).[1] In another study, the change in plasma relaxation rate in patients with arterial disease who were receiving warfarin was not significantly different when compared with patients not receiving warfarin.[1]

• Binding to albumin increases the half-life of gadofosveset, allowing extended imaging time. Indeed, gadofosveset administration increased the time over which high quality MR images could be obtained in peripheral,[1,8] carotid[1,8,13] and abdominal[1] arteries in healthy subjects,[1,8] and patients with confirmed or suspected arterial disease.[13] At doses of 0.03 and 0.05 mmol/kg, interpretable steady-state images were obtained up to 1 hour after initial injection of gadofosveset in all studies, although the quality of images obtained at 50–60 minutes was decreased compared with images obtained at 5–15 minutes.[1,8,13]

2. Pharmacokinetic Profile

The pharmacokinetics of gadofosveset were determined in six clinical trials (total n = 167).[1] All were single-dose studies administering intravenous gadofosveset 0.01–0.15 mmol/kg. Participants included healthy volunteers, patients with renal impairment, patients with moderate hepatic impairment, and patients with vascular disease, some of whom were receiving warfarin therapy.[1]

• In healthy volunteers, intravenous gadofosveset had an area under the plasma concentration-time curve (AUC) from time zero to infinity of 732 μg • h/mL following administration of a single 0.03 mmol/kg dose (the approved dose).[1] The plasma concentration-time profile of gadofosveset conformed to a two-compartment open model; the distribution phase had a mean half-life of 0.48 hours, with a steady-state volume of distribution of 148 mL/kg, following administration of gadofosveset 0.03 mmol/kg.[1,11]

• Ultrafiltration experiments have shown that at clinically relevant concentrations of 0.1–1.0 mmol/L (corresponding to 0.01–0.1 mmol/kg doses), 80–96% of gadofosveset is bound to human serum albumin.[9,12] Gadofosveset 0.03 mmol/kg was 80–90% bound to human serum albumin.[1]

• Gadofosveset is not metabolised at a detectable level.[1,11] In healthy volunteers, gadofosveset is primarily eliminated in the urine, with a small proportion (4.7%) excreted in the faeces.[1] Of a dose of gadofosveset 0.03 mmol/kg, 84% was eliminated in the urine within 14 days, with 94% of that excreted within 72 hours.[1] Renal clearance after administration of gadofosveset 0.03 mmol/kg was 5.51 mL/h/kg; total clearance was 6.57 mL/h/kg, while mean terminal elimination half-life was 18.5 hours.[1]

• Concomitant administration of gadofosveset 0.05 mmol/kg and warfarin did not alter the pharmacokinetics of either agent.[1] In *in vitro* studies, gadofosveset did not inhibit enzymes of the cytochrome P450 system, or the protein binding of piroxicam, diazepam, ibuprofen, ketoprofen, naproxen, diclofenac, digoxin, propanolol or verapamil.[1] An increase in the proportion of unbound warfarin was found in one *in vitro* study, but this effect was not seen in other studies.[1,4]

• Pooled data from 64 healthy volunteers showed that the pharmacokinetics of gadofosveset were not influenced by age or sex.[1] Mild renal or moderate hepatic impairment also did not significantly alter the pharmacokinetics of gadofosveset, although a slight decrease in faecal excretion was seen in patients with moderate hepatic impairment compared with those without hepatic impairment (2.7% vs 4.8%).[1] The pharmacokinetics of gadofosveset in patients with severe hepatic impairment have not been studied.[1]

• The half-life of gadofosveset increased in patients with moderate to severe renal impairment.[1] Plasma clearance decreased as the severity of renal impairment increased; the AUC increased in patients with moderate and severe renal impairment by 2- and 3-fold.[1]

3. Clinical Use

Two phase II trials investigating the use of intravenous gadofosveset in patients with known or suspected aortoiliac and carotid arterial disease have been published. [13,14] These dose-ranging studies will not be discussed further, since phase III trial data is widely available.

Four phase III trials have investigated the use of intravenous gadofosveset in adults (where stated, mean patient age was ≈65 years[7,15]) with known or suspected arterial disease. Two of these studies have been published[7,15] and two have yet to be published.[1] The two published studies were designed as open-label, multicentre phase III trials that investigated aortoiliac arterial disease in 178[15] and 274[7] patients. One of the unpublished trials was an open-label study with the same design as the published studies, and evaluated the use of gadofosveset in the detection of disease in the renal arteries in 145 patients.[1] The other unpublished study was a randomised, open-label, two-dose study that evaluated gadofosveset use in 185 patients with pedal arterial disease.[1]

Non-enhanced MR angiography was selected as the comparator in all phase III studies, using conventional x-ray angiography as the standard of reference.[1,7,15] Three blinded readers in each study evaluated the MR images, while the x-ray angiograms were read by at least two additional blinded readers to obtain the standard of reference.[1,7,15] The dosage of gadofosveset was based on the results from the phase II trials,[13,14] and was a single intravenous bolus of 0.03 mmol/kg in three of the four studies.[1,7,15] The trial investigating the use of gadofosveset in pedal artery disease[1] used two single doses, 0.03 and 0.05 mmol/kg, based on the results of Perreault et al.[14] This study showed almost equivalent performance between the 0.03 and 0.05 mmol/kg doses, with the suggestion that the higher dose may show greater efficacy in the slower flow environment of the pedal vessels.[1] Each patient underwent three scans: a baseline, non-enhanced MR angiogram; a gadofosveset-enhanced MR angiogram; and a conventional x-ray angiogram, performed within 3–30 days of the MR angiography.[1,7,15] Dynamic MR images were obtained within 30–45 seconds of gadofosveset administration, while steady-state MR images were obtained within 15 minutes.[7,15]

The primary efficacy endpoints were the accuracy, sensitivity and specificity of the detection of clinically significant stenosis, comparing gadofosveset-enhanced MR angiography with non-enhanced MR angiography using conventional x-ray angiography as the diagnostic standard of reference.[1,7,15] The definition of accuracy was the percentage of correct diagnoses (the number of correctly identified vessels of the total number of examined vessels); sensitivity was defined as the percentage of correctly identified stenoses (number of correctly identified abnormal vessels of the total number of abnormal vessels diagnosed by x-ray angiography); and specificity was defined as the percentage of correctly identified normal vessels (number of correctly identified normal vessels of the total number of normal vessels diagnosed by x-ray angiography).[7,15] Clinically significant stenosis was defined as a narrowing of 50% or more of the target vessels.[1,7,15] For all analyses, an intent-to-treat method was used, whereby uninterpretable MR angiograms were deemed inaccurate.[1,7,15] In the aortoiliac artery studies, 251[7] and 173[15] patients (1646[7] and 1164[15] vessels) were evaluable for accuracy, 140[7] and 85[15] patients (237[7] and 146[15] vessels) were evaluable for sensitivity and 250[7] and 172[15] patients (1409[7] and 1018[15] vessels) were evaluable for specificity. In the renal artery study, 127, 40 and 116 patients (282, 53 and 229 vessels) were evaluable for accuracy, sensitivity and specificity, and 80, 72 and 53 patients (316, 200 and 116 vessels) were evaluable for accuracy, sensitivity and specificity in the pedal artery study.[1]

Accuracy

- Imaging with gadofosveset improved the accuracy of diagnosis when compared to non-enhanced MR images.[1,7,15] All readers showed significant improvements ($p < 0.001$) in accuracy with gadofosveset-enhanced MR images in the smaller aortoiliac study.[15] Across the three readers, accuracy was

80.3–87.6% versus 68.4–74.5% for gadofosveset-enhanced versus non-enhanced MR images, an absolute difference of 10.5–13.1%.[15] In the larger aortoiliac study,[7] reader accuracy was 83.8–90.3% versus 70.6–82.2% for gadofosveset-enhanced versus non-enhanced images, an absolute difference of 8.1–19.7% ($p < 0.001$ for all three readers).[7]

- Similar results were obtained in the studies concerned with renal and pedal artery disease.[1] In the renal arterial disease study, reader accuracy was 73.4–79.1% for gadofosveset-enhanced MR images, and 44.7–55.7% for non-enhanced MR images,[1] with absolute accuracy improvements for gadofosveset-enhanced images ranging from 23.0 to 28.7% ($p < 0.001$ for all three readers). In the pedal artery disease study, accuracy was 72.8–80.7% for gadofosveset-enhanced images, and 59.8–66.5% for non-enhanced MR images. Absolute accuracy improved by 7.0–17.7%, a significant difference in two of three readers ($p < 0.005$).[1]

Sensitivity

- Diagnostic sensitivity also increased with gadofosveset use in most studies. Compared with non-enhanced MR images, absolute improvements in sensitivity with gadofosveset use in patients with aortoiliac disease in the smaller study ranged from 21.9 to 30.8% ($p < 0.001$ for all three readers),[15] corresponding to sensitivities of 70.5–84.2% for gadofosveset-enhanced images versus 48.6–60.3% for non-enhanced MR images.[15] In the larger aortoiliac study,[7] sensitivity was 60.8–80.2% and 41.8–66.7% for gadofosveset-enhanced and non-enhanced MR images,[7] an absolute difference of 6.3–19.0%; a significant ($p < 0.001$) improvement was seen for two out of three readers.[7]
- In the renal artery disease imaging study, sensitivity increased with gadofosveset use, with results less consistent in the pedal artery disease study.[1] In renal arteries, sensitivity ranged from 56.6 to 66.0% and from 22.6 to 41.5% for gadofosveset-enhanced and non-enhanced MR images;[1] absolute sensitivity improved by 24.5–41.5% ($p < 0.01$ for all three readers).[1] Sensitivity in the pedal artery study was 77.5–93.0% for gadofosveset-enhanced MR images and 77.0–86.5% for non-enhanced MR images; one of three readers showed a significant increase in sensitivity of 16.0% with gadofosveset use ($p < 0.001$).[1]

Specificity

- The specificity of diagnosis was increased with gadofosveset use in all studies. In patients with aortoiliac artery disease, the range of specificity was 80.0–90.1%[15] and 84.5–95.3%[7] for gadofosveset-enhanced images versus 70.7–78.2%[15] and 75.1–84.8%[7] for non-enhanced MR images. Gadofosveset significantly ($p \leq 0.001$) improved specificity across all three readers in both studies; absolute differences in specificity were 8.5–11.9%[15] and 8.4–19.9%.[7]
- Specificity was also increased with gadofosveset use in the renal and pedal artery studies.[1] Specificity ranged from 77.3 to 82.5% for gadofosveset-enhanced images and from 48.0 to 59.0% for non-enhanced MR images in the renal artery study, with specificity in the pedal study ranging from 59.5 to 66.4% and from 28.4 to 38.8% for gadofosveset-enhanced and non-enhanced images.[1] These ranges corresponded to an absolute increase in specificity of 22.7–29.3% ($p < 0.001$ for all three readers) and 20.7–34.5% ($p \leq 0.01$ for all three readers) for the renal and pedal artery imaging studies.[1]

Other Endpoints

- In both studies in patients with aortoiliac disease, all three readers reported significantly ($p < 0.05$) greater confidence in the interpretation of images obtained with gadofosveset use, compared with unenhanced MR angiography.[7,15]
- In one study, significantly fewer images were deemed uninterpretable with gadofosveset-enhanced MR imaging than with unenhanced MR imaging (0.4–1.2% vs 4.7–21.9% of images; all $p < 0.05$).[7] In the other study, 1.7–2.6% of vessels were uninterpretable with gadofosveset-enhanced MR angiography, compared with 12.4–19.5% of vessels with unenhanced MR angiography (statistical analysis not reported).[15]

4. Tolerability

This section will concentrate on the tolerability data summarised in the published phase III trials (see section 3 for study design details).[7,15]

- Although head-to-head trials have not been conducted, it appears that the tolerability profile of gadofosveset is similar to that of extracellular MR contrast agents.[15] Gadofosveset was generally well tolerated in patients undergoing diagnostic imaging, with the majority of adverse events being of mild or moderate severity.[7,15]
- Adverse events considered by the investigator to be either possibly or probably related to gadofosveset were reported by approximately 1 in 5 patients with aortoiliac disease: 41 of 178 patients in one study (63 events reported) [15] and 59 of 274 patients in the other study (87 events reported).[7] The most common events included paraesthesia,[15] pruritus,[15] hyperglycaemia,[15] feeling hot,[7] headaches,[7] a burning sensation[7,15] and nausea[7,15] (figure 1).
- Only one serious adverse event, an anaphylactoid reaction which lasted approximately 3 minutes, was reported in the smaller study[15] and was judged to be probably related to gadofosveset. The investigator considered the reaction to be mild in severity, and the patient went on to complete the study.[15]
- During the MR imaging period of the larger study, none of the four reported serious adverse events were considered to be related to gadofosveset. However, one serious adverse event (atrial fibrillation) reported during the monitoring period for conventional angiography was considered possibly related to gadofosveset, despite this event occurring 11 days after administration of the imaging agent and outside of the MR monitoring period.[7]
- In both studies of aortoiliac patients,[7,15] no clinically important[15] or serious[7] changes in laboratory parameters were found. In the smaller study, there were also no important changes from baseline in vital signs, pulse oximetry data or ECG parameters.[15] In the larger study, four patients, each with a history of cardiovascular disease, had abnormal ECG readings that were considered by investigators to be possibly related to gadofosveset, although no pattern emerged over time.[7]

5. Dosage and Administration

In adults undergoing MR angiography, the recommended dose of gadofosveset is 0.03 mmol/kg, administered intravenously as a single bolus injection either manually or via the use of an automatic injector.[11] The duration of injection should be up to 30 seconds, followed by a flush of 25–30mL of

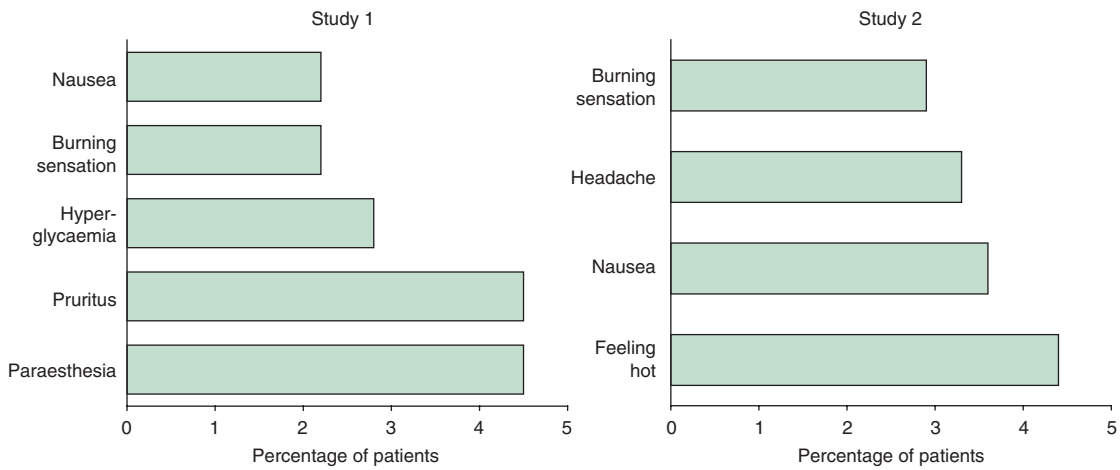


Fig. 1. Tolerability of gadofosveset in patients with aortoiliac artery disease. Results of open-label, multicentre phase III trials in 178 (Study 1[15]) and 274 (Study 2[7]) patients. Most commonly occurring adverse events possibly or probably related to intravenous administration of a single dose of gadofosveset 0.03 mmol/kg.

normal saline.[11] Local prescribing information should be consulted for contraindications and special precautions relating to gadofosveset use.

6. Gadofosveset: Current Status

Gadofosveset is approved for use in the EU in adults with suspected or known vascular disease undergoing contrast-enhanced MR angiography for visualisation of abdominal or limb vessels,[1] and in Switzerland for use in contrast-enhanced MR angiography in patients with suspected or known vascular disease.[16] In phase III trials, gadofosveset use significantly improved the sensitivity, specificity and accuracy of diagnosis of aortoiliac and renal artery disease, and the specificity and accuracy of diagnosis in pedal artery disease, compared with non-enhanced MR images. Gadofosveset was generally well tolerated.

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