Reveal Pharmaceuticals

NEWS RELEASE
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SAFER MRI BY DESIGN

If you're battling a life-threatening disease, you shouldn't have to worry about the safety of your diagnostic procedures. That's why biotech startup Reveal Pharmaceuticals, in collaboration with researchers at Massachusetts General Hospital, is developing a safer contrast agent for magnetic resonance imaging (MRI). A recent study published in the journal *Investigative Radiology* shows that, in a rat model of renal impairment, Reveal's gadolinium-free MRI contrast agent (RVP-001), was efficiently eliminated from the body even if kidney function is impaired.

Contrast-enhanced MRI is an important tool for diagnosing disease, guiding treatment decisions, and monitoring treatment response. Patients receiving contrast-enhanced MRI are injected with a gadolinium-based contrast agent (GBCA). The GBCA contains chelated gadolinium ion, a rare earth metal with magnetic properties that increases the signal in MRI scans, making it easier to visualize details of blood vessels, organs, and tumors. Contrast-enhanced MRI is used to detect and stage many cancers, to diagnose and monitor neurodegenerative diseases like multiple sclerosis, detect aneurysms or narrowed arteries, and for insight into many other diseases. Over 30 million contrast-enhanced MRI scans are carried out worldwide every year.

However, GBCAs are not without risks. Although GBCAs use a stable chelated form of gadolinium, small amounts can accumulate in the brain and other tissues. Gadolinium in some forms can be highly toxic. In people with severe kidney impairment, gadolinium from GBCAs can trigger a devastating condition called nephrogenic systemic fibrosis (NSF), where patients develop fibrosis of the skin and internal organs . Despite these safety concerns, there are currently no approved alternatives to GBCAs for general purpose use in MRI. Reveal aims to change that.

"My motivation when I began this work really came from these at-risk patients with chronic kidney disease or acute kidney injury that couldn't receive gadolinium-based contrast agents because of the risk of NSF," says Peter Caravan, Co-Director of the Institute for Innovation in Imaging at Massachusetts General Hospital, Professor of Radiology at Harvard Medical School, co-inventor of RVP-001, and one of Reveal's co-founders.

Reveal's new manganese-based agent, RVP-001 (referred to as Mn-PyC3A in scientific literature), was designed to provide the same magnetic contrast enhancement as the leading GBCAs. Similarly to GBCAs, RVP-001 uses a chelator to stabilize the molecule, minimize manganese release, and avoid manganese accumulating in tissues. However, unlike gadolinium, manganese is essential for life, naturally found in the body, and the body has innate mechanisms to manage manganese levels and eliminate excess manganese. Other manganese contrast agents such as Mn-DPDP (mangafodipir) are designed to release manganese and have it transiently accumulate in the liver in order to highlight liver tumors.

A major goal of this study was to understand how renal impairment affects the elimination of RVP-001 and how that compares to the state of the art GBCA gadoterate (Gd-DOTA). The researchers used a rat model of end stage kidney disease to examine how much injected manganese from RVP-001 remains in the body after a week in these rats. They found that RVP-001 was more completely eliminated than gadoterate: there was three times less injected manganese from RVP-001 remaining than gadolinium from gadoterate.

To help take some of the load off of the kidneys, RVP-001 was designed to eliminate partially through the liver and into the bowel. This is exactly what the researchers found – in fact, positron emission (PET) imaging combined with MRI showed that the fraction of RVP-001 eliminated through the liver was doubled in rats with decreased kidney function compared to normal rats.

The researchers also used PET to compare the fate of manganese from RVP-001 with that of Mn-DPDP, a manganese contrast agent used in liver imaging, in rats to examine where each compound travels in the body and how rapidly the injected manganese is eliminated. Manganese from Mn-DPDP was still detectable in the liver, bones, and other tissues after 7 days, while RVP-001 was rapidly cleared into the bladder and bowel, and almost completely eliminated within a day after injection.

As anticipated, RVP-001 "remains intact and moves around the body the same way as GBCAs which means that RVP-001 provides the same imaging function, but importantly there is no accumulation or build up of injected manganese in the body," says Eric Gale, Assistant Professor of Radiology at Harvard Medical School, senior author of the study, co-inventor of RVP-001, and Reveal co-founder.

Gale calls the results from this new study "another proof of concept that this technology may be a very effective and potentially very safe alternative to gadolinium." Future work will continue to develop RVP-001 and file an IND in support of human clinical trials.

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Reveal Pharmaceuticals, Inc. was founded in 2016 by CEO Vera Hoffman and Massachusetts General Hospital / Harvard Medical School researchers Eric Gale and Peter Caravan with the aim of providing a safe, effective replacement for gadolinium MRI contrast agents.

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Positron Emission Tomography-Magnetic Resonance Imaging Pharmacokinetics, In Vivo Biodistribution, and Whole-Body Elimination of Mn-PyC3A
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