

Editorial

Potential Uses of Ferumoxytol in the Magnetic Resonance Imaging of Epilepsy

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EDITORIAL

Ferumoxytol (Feraheme ®) is an iron oxide nanoparticle approved by the Food and Drug Administration (FDA) in 2009 for treating anemia, but has found excellent off-label uses as contrast agent in the magnetic resonance imaging (MRI) of many neurological disorders, in particular multiple sclerosis [1], brain tumor [2], and stroke [3]. These MRI studies take advantage that ferumoxytol remains mainly in the blood pool for a long time (half-life: 15 hours). Two types of ferumoxytol-based brain MRI have been described [4] :a) cerebral blood volume (CBV) measurement at high spatial and temporal resolutions within the first few hours after ferumoxytol injection, and b) iron concentration measurement to detect abnormal iron uptake from blood to parenchyma at 24-48 hours after ferumoxytol injection. However, these uses have not come to the full attention of radiologists and neurologists, as only short time has passed since the clinical approval of ferumoxytol.

In this perspective, we aim to raise the awareness of ferumoxytol to radiologists and neurologists interested in epilepsy, which is the third most common neurological disorder in the United States. To the best of our knowledge, there is currently no study of epilepsy using ferumoxytol. A major challenge in epilepsy is to treat patients with medically refractory partial seizures. Neurosurgical resection, often the only definitive treatment option, requires accurate localization of the epileptogenic focus during presurgical evaluation. This is usually achieved through neuroimaging including magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). MRI is much more available, safer and higher in spatial resolution than PET and SPECT, but is mainly used to detect anatomical abnormalities, whereas PET and SPECT are used to measure brain metabolism and perfusion, respectively. Although MRI-based perfusion measurement in epilepsy was described over a decade ago [5], at that time it was inferior to SPECT in the performance of localizing epileptogenic focus [6]. With the arrival of ferumoxytol, however, now is a prime time to expand the MRI applications in epilepsy. We have contemplated several uses of ferumoxytol in epilepsy, as described below.

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Imaging cerebral blood volume

In the first few hours immediately following injection, ferumoxytol remains within the blood pool at a relatively stable concentration, owing to its large molecular size and long half-life (15 hours). This feature makes ferumoxytol an excellent agent for measuring the total amount of blood in tissues, in particular the cerebral blood volume (CBV). Measurement can start as soon as one minute after the injection, when a steady state of ferumoxytol distribution in the brain is reached [7]. A whole-brain map of CBV can be acquired at very high resolutions (0.6 mm in-plane, 1.2 mm thickness) in just 6 minutes [8]. Alternatively, by using echo-planar imaging (EPI) in the fashion of functional MRI, whole-brain qualitative maps of CBV can be acquired at lower resolutions (3-4 mm) but much faster (2-3 s) and consecutively in time, allowing for measurements of dynamic CBV changes [9].

CBV and cerebral blood flow (CBF) are both measurements of brain perfusion and are closely correlated to the level of neural activities. Therefore, mapping of CBV and CBF has long played a critical role in epilepsy diagnosis. CBV and CBF increase focally at and near the epileptogenic focus during an epileptic seizure event (the ictal period), and decrease focally in the time between seizure events (the interictal period). Ictal measurements are usually difficult because of vehement head motion, but with the significant exception of SPECT with technetium-99m (99mTc) radioactive agent. Distribution of 99mTc in the brain is correlated only to the CBF distribution at the time of injection, thus injecting the agent during the ictal period captures the ictal CBF, which can be mapped by SPECT conducted after the seizure. A previous study at our epilepsy center indicates that ictal-interictal SPECT subtraction is the most sensitive neuroimaging method to localize the epileptogenic focus, whereas interictal measurements alone made by either SPECT or PET are less sensitive [10].

Ferumoxytol has the promise of improving both the sensitivity and the accuracy of interictal neuroimaging in localizing epileptogenic focus. The main advantage lies in that ferumoxytol-based MRI can acquire high-quality whole-brain CBV maps at high spatial and temporal resolutions, specifically, at 4 mm and 2 s resolutions with a contrast-to-noise ratio of 60 [11]. In comparison, the average CBF map obtained from a half-hour session of SPECT with 99mTc has a spatial resolution of 1 cm

and a contrast-to-noise ratio of 30 [6,12]. In other words, with the same imaging time, the average CBV map from ferumoxytol-based MRI likely has 2.5 times better spatial resolution and 60 times better image quality than the average CBV map from ^{99m}Tc SPECT. Thus it is likely that ferumoxytol-based MRI is much more sensitive to interictal perfusion abnormalities than SPECT and other neuroimaging modalities are.

Imaging intrinsic functional connectivity

With the excellent temporal resolution of ferumoxytol-based CBV mapping, it becomes feasible to measure the dynamic fluctuations in CBV in the fashion of functional MRI. Dynamic fluctuations in blood oxygen level dependent (BOLD) signals are strongly correlated across cortical regions that engage in the same function, a phenomenon known as intrinsic (also known as resting-state) functional connectivity. Analysis of intrinsic functional connectivity from BOLD data has been very fruitful in understanding various neurological and psychiatric disorders, including epilepsy [13]. Intrinsic functional connectivity can be similarly analyzed from ferumoxytol-based CBV fluctuations. Compared to BOLD, ferumoxytol provides a small but definite gain (about 1.5-2 times) in both image quality and the quality of functional connectivity results [9,11]. Furthermore, ferumoxytol allows high-quality measurement of CBV using spin-echo MRI, which gives much heavier weight to the microvasculature, compared to conventional gradient-echo MRI that gives more weight to larger vessels [14]. This may be particularly beneficial to studying epilepsy, where the pathophysiological processes are most likely in the parenchyma and involve mainly small blood vessels.

Imaging iron uptake

The long half-life (15 hours) of ferumoxytol provides an excellent window for cellular uptake before its eventual excretion. Since ferumoxytol is fundamentally iron, its uptake is closely related to the activity of macrophages and microglia, and therefore inflammation in the brain. Based on this rationale, ferumoxytol has been used to image the iron uptake in many neuroinflammation diseases, in which it has shown spectacular advantages compared to the conventional gadolinium contrast agent [1-3]. This type of imaging needs to be conducted 24-48 hours after the ferumoxytol injection to allow for microglia's uptake and washout in non-inflammatory tissues.

Epilepsy is not usually seen as a neuroinflammatory disease. However, there are strong accumulating evidences from animal studies that neuroinflammation is involved in the pathogenesis of epilepsy [15]. A PET study in a single epilepsy patient using PK-11195, a ligand specifically binding activated microglia, has shown higher ligand uptake in the epileptogenic focus, though its sensitivity appears lower than that of conventional interictal PET [16]. Given the advantages of MRI over PET and SPECT that we discussed above, it is attractive to explore the ferumoxytol-based MRI marking of activated microglia in epilepsy, by imaging the iron distribution in brain a day after ferumoxytol injection. It remains an open question whether the neuroinflammation marker in MRI can better localize the epileptogenic focus than the metabolism and perfusion markers, which have been thoroughly explored using PET and SPECT respectively.

CONCLUSION

In conclusion, we envision that ferumoxytol, a novel MRI contrast agent that has been approved for human use, can be highly useful in the MRI of epilepsy. The advantages of ferumoxytol are most significant in the imaging of CBV, which is an established marker of the epileptogenic focus. Ferumoxytol can also benefit the study of intrinsic functional connectivity and neuroinflammation in human epilepsy patients.

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