The hype about hyper signals

Gadolinium based contrast agents (GBCA) are used worldwide to aid Magnetic Resonance Imaging (MRI). It has been well documented that exposure to some GBCAs for patients with renal failure can result in the life threatening disease Nephrogenic Systemic Fibrosis (NSF). Since the classification of GBCAs based on NSF risk, the incidence of the disease has dropped to almost zero. More recent studies, however, have reported an association between the cumulative number of some GBCAs and hyper signal intensities in specific brain regions on unenhanced T1 weighted images even in patients with normal renal function. Evidence to date suggests this is dependent on the GBCA structure and, as of yet, the clinical significance is not understood.

Background

The strong paramagnetic behavior of Gadolinium helps to reduce T1 relaxation times therefore increasing tissue contrast on MRI images. Gadolinium ions on their own are highly toxic and so they are typically chelated to an organic ligand. There are 2 ligand structures; linear and macrocyclic. The type of ligand and charge varies between all commercially available GBCAs. Macrocyclic, ionemic chelates are regarded as the most thermodynamically and kinetically stable in human serum while linear, non-ionic chelates are less so1. In 2014 Kanda et al.2 observed hyper signal intensities in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1 weighted brain images in patients with a history of multiple GBCA administrations (5 or more). Further investigation showed that there is a linear relationship between the extent of hyper signal intensities and number of contrast MRI examinations3. Mass spectrometry studies of autopsy brain specimens linked a build-up of Gadolinium to the observed hyper intensities4. An example of hyper signal intensities is given in Fig 1.

Pre-clinical, tissue and retrospective image analysis studies have all suggested that there is a higher likelihood of Gadolinium retention following the administration of linear agents rather than macrocyclic. The clinical effect of these hyper intensities is still unknown, however, recent case reports, in which patients have undergone extremely high numbers of linear contrast administrations, have reported the occurrence of neurological disorders such as aphasia, decreased vigilance and difficulties with executive function5.

Problem

Aim

The aim of this study is to investigate whether GBCAs, in particularly the macrocyclic gadodaterol meglumine (Dotarem), are causing increases in the signal intensity of specific brain regions on unenhanced T1 weighted brain images of patients with normal renal function. Signal intensity ratios of images prior to the administration of contrast will be compared to those from images taken following multiple administrations. Further analyses will include exploring associations with the cumulative dose, time intervals between injections and any potential reversibility. Potential links to other significant adverse reactions, in particular neurological and dermatological, will also be investigated.

Data Cohorts

Since 2009 NHS Tayside has predominantly used Dotarem, a macrocyclic, ionic chelate, for contrast enhanced MRI examinations. Information regarding each MRI examination, including contrast type and dose, is recorded in scanner specific lab books. The initial stage of the research is to compile an accurate database of all contrast enhanced MRIs that have taken place across NHS Tayside since 2009. This has been organised with the help of the Health Informatics Centre (HIC) and all information is stored in the HIC safehaven. The use of this electronic database to source patient cohorts has, thus far, not been reported in any other studies.

Patients are identified for analysis if they have undergone multiple contrast enhanced MRIs and their first and last examination are brain scans (i.e. of the scan codes MSKUH(C)/MIAMR(C)). There will be 3 cohorts; two positive groups in which patients have been exposed solely to either Dotarem or linear agents and one negative control group in which patients have undergone multiple unenhanced MRIs.

Further Work

Following this initial stage there are many further avenues this research will explore, such as:

• If there is any correlation between SNRs and the number of injections or cumulative dose;

• The effect of time intervals between administrations on SNRs and whether there is any evidence of reversibility;

• Whether Dotarem is associated with good tolerance and good diagnostic performance in paediatric patients (≤ 18yrs). 29 paediatric patients who have undergone 2 or more Dotarem enhanced MRI have been identified in the database;

• The incidence of adverse reactions (particularly neurological and dermatological) in at risk populations such as those at risk of developing nephrogenic fibrosing dermopathy and in those with/likely to develop impaired renal function;

• Potential other areas of interest to investigate GBCA accumulation e.g. liver;

• Novel imaging techniques e.g. susceptibility weighted imaging.

References:


Fig 1: Unenhanced axial T1 weighted images showing hyper signal intensity of the dentate nucleus (yellow ROI) and globus pallidus (green ROI) developing following linear contrast administrations. Adapted from McDonald.

Fig 2: a) Example of the cohort selection protocol for the Dotarem cohort. b) Example timeline for a patient who has undergone 5 Dotarem administrations with a baseline brain image and a final brain image.