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Editorial for « Noninvasive Assessment of APAP-Induced Hepatotoxicity Using Multiple MR
Parameters in an Experimental Rat Model. »

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Dealing with Drug Induced Liver Injury (DILI) is a major public health issue in so called *advanced economies* in which the consumption of painkiller such as Tylenol or Paracetamol is increasing. Among DILI, acetaminophen or N-acetyl-p-aminophenol (APAP) induced hepatotoxicity, represents half of all acute liver failures¹.

As we all know, the liver *gold-standard* biopsy, is not always so shiny in a clinical practice, due to its invasiveness and its chancy sparse spatial sampling. The need of reliable non-invasive DILI biomarkers has been stressed out by American and European health institutions². Magnetic Resonance Imaging techniques are natural candidates to provide such biomarkers while they have shown their potential ability to estimate quantitatively liver function, inflammation, fibrosis, necrosis, fat fraction, perfusion or stiffness.

In this preclinical study performed at 3T with an eight-channel phased-array coil in an experimental rat model, Chen *et al.*³ propose to combine in a multi-parametric MR approach, diffusion and dynamic contrast-enhanced (DCE-MRI) derived parameters as a potential tool to assess APAP hepatotoxicity.

Indeed, IVIM and Gd-EOB-DTPA DCE-MRI parameters are both particularly related to cellular and (micro)-vascular status of the liver.

Using an animal model is really interesting whereas designing a clinical study is a real challenge in such acute and often unpredictable idiosyncratic DILI. Of 33 Wistar rats, 21 received a single toxic dose of APAP while 12 other animals constituting the control group received an equivalent dose of vehicle alone. MR protocol includes anatomical T2-weighted images, intravoxel incoherent motion (IVIM) acquisitions including 12 *b-values* and DCE-MRI acquisitions with *pre-contrast* T1 mapping. Gadolinium-ethoxybenzyl chelate (Gd-EOB-DTPA) distribution was monitored during 50 min with a variable sampling rate going from 30 s during the first 5 min up to 10 min during the thirty last minutes. MRI findings were confronted to histologic analysis, Reverse-Transcription Polymerase Chain Reaction (RT-PCR) and Transmission Electronic Microscopy (TEM).

The single APAP dose injection led to 13 mild and 8 moderate histologic changes according to the necrosis score, as well as a significant decreased activity of *oatp1* in APAP group. While IVIM perfusion related parameters D^* and f were not statistically different in the three groups, diffusion parameters D and ADC showed a good ability to distinguish moderate from mild necrosis. If *pre-contrast* T1 measurements also show a significative positive correlation with necrosis severity, the time period from $\Delta T1\text{-max} [\%]$ to 2/3 value of $\Delta T1\text{-max} [\%]$ ($\Delta T1\text{-T2/3}$) presents a significant ability to discriminate between normal, mild and moderate necrosis. This quite unusual semi-quantitative parameter seems of potential interest since it could be related to hepatocyte uptake and biliary excretion in accordance with morphological changes observed in bile duct with TEM. However, a DCE-MRI quantitative analysis even based on empirical model or on more sophisticated physiological pharmacokinetic models^{4,5} should be performed to confirm the results presented here.

To conclude, if such an animal study, confirming similar prior results, must of course be completed by new experimental and clinical efforts based on methodological approach such as that

recommended by the International Society for Magnetic Resonance in Medicine (ISMRM) quantitative MR study group⁶, the work of Chen et al. is of real interest to identify biomarkers and improve drug development process as well as DILI diagnosis and management.

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