

Clinical Evaluations in the Diagnosis of Liver Disease

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Description

4-O-13C methacetin (13C-methacetin) is a compound, which has no previously described toxicity and is the most commonly used substrate for the clinical evaluation of human mixed functional hepatic oxygenize function in dynamic liver function tests. 13C-methacetin can be administered orally or intravenously. In a recently published European guideline the diagnostic approach of the 13C-methacetin breath test and several other 13C stable isotope breath tests commonly used for the assessment of gastroenterological symptoms and diseases have been harmonized. Methacetin cannot be used in case of hypersensitivity to the substrate and its metabolite acetaminophen. Strong inhibitors of the CYP1A2 system such as ciprofloxacin or fluvoxamine can have an influence on hepatic methacetin metabolism and thus on the test results. The metabolism of 13C-methacetin can be detected by means of 13CO₂ in the exhaled air after the 13C labelled methyl group of CYP1A2 enzymes has been cleaved *via* the rate-limiting step of O-dealkylation as formaldehyde together with the formation of acetaminophen. The formed 13C-formaldehyde is oxidized *via* presumably the same degradation processes as in the N-dealkylation of 13C-aminopyrine to 13CO₂.

Various analytical systems are available for measuring the 13C/12C isotopic ratio is the Isotope Ratio Mass Spectrometry (IRMS) represents the gold standard for the high-precision determination of the 13C/12C isotope ratio. Infrared spectroscopic procedures are more practicable in routine clinical and laboratory use. Molecular correlation spectroscopy, also a direct infrared spectroscopy method, enables continuous 13C respiratory gas analysis *via* a nasal canula or a mask under capnometric control.

In patients with chronic liver disease, currently used biomarkers demonstrate limited mid-to long-term predictive value for deterioration requiring liver transplantation or liver related death. Several prospective clinical studies using the MBT with a larger number of cases on prognostic value have already been published. In 2015, the predictive value of the 13C-Methacetin Breath Test (MBT) over 60 minutes test time for survival and hepatic decompensation was prospectively analyzed for the first time in 139 patients with liver cirrhosis of various etiologies and MELD<19. The MBT was able to predict survival better than the MELD value over 1-13 months of follow-up, the relative mortality risk was 5-fold increased using a cut-off of cPDR 20 min below 0.55%. These initial data were confirmed in another study in 123 cirrhosis patients with three years of follow-up. In a recently published 7-years follow-up study in 132 patients with chronic hepatitis-c virus infection the MBT by means of a real-time point-of-care analyzer was non-inferior to liver biopsies analyzed by two experienced liver pathologists for the prediction of liver-related death and transplantation.

These studies show that the MBT, as a non-invasive liver function test, can predict mid-to long-term liver deterioration leading to clinical relevant endpoints as liver transplantation or liver associated death in chronic liver disease patients. These results may extend the utilization of this well-known dynamic liver function test beyond its use a surrogate for estimation of liver fibrosis and encourage clinical research in new fields such as monitoring and estimating critical of liver function leading to decompensation in non-surgical therapies of primary and secondary liver tumors or liver toxic chemotherapies in other oncological diseases and assessment of prognosis of evolving liver diseases.