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13C-Methacetin Breath Test: Metabolic Basis, Analytical Methods and Clinical Applications in Liver Diseases

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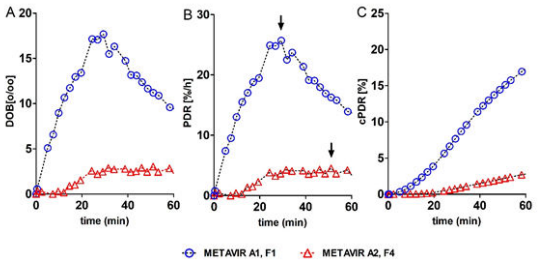
Introduction

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 oxygenase 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 ass essment 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 intravenous preparation (2mg/kg bw) must be operated simultaneously with a special LiMAx breathing mask and a FLIP® device. The oral application (75 mg dissolved in 100-200 ml water) can be obtained as a pharmacy preparation in some European countries. The metabolism of 13C-methacetin can be detected by means of 13CO2 in the exhaled air after the 13-carbon labelled methyl group of CYP1A2 enzymes has been cleaved via the rate-liniting 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.The first step, the reaction of formaldehyde to formic acid, is initiated by formaldehyde dehydrogenase, a glutathione-dependent cytosolic enzyme or by mitochondrial aldehyde dehydrogenase. 13C formic acid is oxidized to 13CO2 via 10-formyl tetrahydrofolate and appears in the exhaled air. (1,4) Here, a typical 13CO2/12CO2 exhalation curve, parameterized with the delta value used in mass spectrometric analysis, is recorded. From this exhalation curve, assuming a constant CO2 production under resting conditions with 300 mmol CO2/m2 body surface area, the metabolized proportion of the applied dose per unit of time (PDR = percentage dose recovery rate in %/h of the applied dose) can be calculated (Figure 1). The dose recovery rate can also be converted from the molecular weight of the test substance and the CO2 production into a substrate metabolic rate normalized to body weight in µg/kg/min. The maximum percentage dose recovery rate detected after intravenous bolus application is also called the LiMAx value and corresponds to the maximum rate of CO2 predominantly generated by CYP1A2.(1) This is a quantitative approach is commonly used for planning of liver resection in hepatobiliary surgery.(5) After integration of the PDR curve (expressed as cPDR in %) the amount of substrate appearing in the exhaled air can be calculated directly. The recovery of a substrate never reaches 100 %, since 13C degradation products can escape into alternative metabolic pathways independently of the CO2-generating metabolic pathway to be investigated and thus a physiological marker loss occurs (e.B. integration into bone, adipose tissue).(1, 6) Various analytical systems are available for measuring the 13C/12C isotopic ratio: 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. For the analysis, about 5 ml of breathing air is needed. The carbon isotope ratio can be determined with NDIRS devices to an accurate 0.1‰. Interval sampling in containers (glass tubes or breathing bags) also makes it possible to send samples to a laboratory. Molecular correlation spectroscopy, also a direct infrared spectroscopy method, like the FLIP method, enables continuous 13C respiratory gas analysis via a nasal canula or a mask under capnometric control. (7) The infrared spectrometric methods have been well validated using IRMS.(7, 8)

Figure1:



Results

A Typical 13CO2 exhalation curves expressed as delta over baseline (DOB) after oral application of 75mg 13C-Methacetin

dissolved in 100 ml water in 2 patients with chronic hepatitis C infection(12) and different liver biopsy proven fibrosis stages (according to METAVIR classification(13)). The 13C/12C isotopic ratio was determined about all 3 minutes by molecular correlation spektroscopy (BreathID®). B and C: describe the metabolic process as percentage dose rate (PDR) and cumulative PDR (cPDR). Arrows: maximal PDR (PDRmax) corresponding to a maximal 13C-methacetin metabolisation rate of 298 µg/kg bw/min (METAVIR F1) and 41 µg/kg bd/min (METAVIR F4).

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