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Detection of maleate-induced Fanconi syndrome by decreasing accumulation of ^{125}I-3-iodo-α-methyl-L-tyrosine in the proximal tubule segment-1 region of renal cortex in mice: a trial of separate evaluation of reabsorption

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Objective: Fanconi syndrome is a renal dysfunction characterized by various combinations of renal tubular transport dysfunction involving amino acids, glucose, protein and other substances. Most reabsorption of amino acids occurs in proximal renal tubule segment 1 (S1). The present study evaluated the possibility of early detection of drug-induced Fanconi syndrome, based on decreased renal accumulation of ^{125}I-3-iodo-α-methyl-L-tyrosine (^{125}I-IMT), an amino acid transport marker, in the S1 region of renal cortex. The present experimental model used maleate (MAL)-induced Fanconi syndrome in mice. Results were compared between ^{125}I-IMT and 3 other clinical renal radiopharmaceuticals: ^{99m}Tc-2,3-dimercaptosuccinic acid (^{99m}Tc-DMSA); ^{99m}Tc-mercaptoacetylglycylglycylglycine (^{99m}Tc-MAG$_3$); and ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA). ***Methods:*** Male ddY mice (age, 6 weeks; body weight, 25 g) were used to create a Fanconi model of renal dysfunction. A single dose of maleate disodium salt was administered by intraperitoneal injection (6 mmol/kg). Hematoxylin and eosin (HE) staining of the renal cortex, renal autoradiography and measurement of renal radioactivity of labeled compounds were performed at 30, 60, 90 and 120 min after MAL injection. At 5 min after injection of labeled compounds (18.5 kBq for accumulation experiment, 670 kBq for autoradiography), animals were sacrificed by ether overdose and kidneys were removed. For the accumulation experiment, radioactivity was measured using a well-type scintillation counter. For autoradiography, 20-μm sections of frozen kidney were used with Bio-Imaging Analyzer. ***Results:*** At 30 min after MAL injection, HE staining showed pyknosis in some proximal tubule cells. At that time, accumulations of ^{125}I-IMT and ^{99m}Tc-DMSA in the S1 region were approximately 67% and 55% of control levels ($p < 0.005$). MAL increased accumulation of ^{99m}Tc-DTPA in the S1 region, but had no effect on accumulation of ^{99m}Tc-MAG$_3$ in the S1 region. ***Conclusions:*** Decreased accumulation of ^{123}I-IMT in the S1 region appears to represent a useful marker for detection of MAL-induced Fanconi syndrome. In future, we plan to assess the efficacy of using ^{125}I-IMT to monitor renal dysfunction induced by nephrotoxic clinical drugs.

Key words: reabsorption, 3-iodo-α-methyl-L-tyrosine, maleate-induced Fanconi syndrome, renal cortex, proximal tubule segment 1