J. Pharm. Pharmacol. 1998, 50 (Supplement): 195

Effect of liver diseases on the urinary metabolic pattern and salivary clearance of caffeine in children

ADNAN EL-YAZIGI, SOUHEIL SHABIB, SAMEER AL-RAWITHI, AHMED YUSUF, ERLINDA S. LEGAYADA AND ABDULKARIM AL-HUMIDAN

Pharmacokinetics Laboratory, Department of Biological and Medical Research, and Paediatric Gastroenterology, Department of Paediatrics, King Faisal Specialist Hospital, PO Box 3354,Riyadh 11211, Saudi Arabia

Conventional liver function tests such as measurement of serum levels of endogenous tracers including albumin and various enzymes are of limited value for assessing liver dysfunction, since they reflect increased hepatocellular permeability rather than functional capacity. Determination of salivary clearance and urinary metabolites of caffeine is an excellent, non-invasive tool for assessing liver function, particularly, the activity of cytochrome P4501A2 (CYP1A2), N-acetyltransferase (NAT), and xanthine oxidase (XO), Varagnolo et al (1989). This study was undertaken to measure the clearance of caffeine using saliva as a biological fluid and to assess the activities of the above mentioned enzymes in healthy children and pediatric patients with liver diseases using urinary molar ratios of different caffeine metabolites. Nine pediatric patients with liver diseases (LD) and nine healthy children were included in this study. The subject refrained from caffeine intake for a 72-hour period, then received orally 2 mg/kg of caffeine in the form of caffeinated cola beverage at least 3 hours after ingestion of the last meal. After chewing on parafilm for 5-10 min, saliva samples (1-2 mL) were collected from the subject at 4-5 hr (i.e., evening sample) and 16-17 hr (i.e. morning sample) (time of sampling was exactly recorded) after drug administration and stored in a specimen container at -80° until analysis. Caffeine was analyzed in saliva samples by high performance liquid chromatography, El-Yazigi et al (1989). Caffeine Clearance (Cl_{caf}) was calculated by use of the following equation: $Cl_{caf} = V_d [\ln C_{t1}/C_{t2}]/ \tau$ where V_d is the volume of distribution (V_d) which is assumed to be equivalent to 0.6 liters per kg body weight, C_{t1} is the concentrations of caffeine in saliva in the first (i.e., evening) sample, C_{t2} is the concentrations of caffeine in saliva in the second (i.e., morning) sample, and τ is the time interval separating the two collections, assuming first-order kinetics for caffeine. Urine was also collected from these subjects for 48 hr after caffeine ingestion in a 2-liter container containing 2 g of sodium meta-bisulfite as an antioxidant stabilizer and was kept refrigerated throughout the collection. At the end of this period, the urine volume was measured and an adequate aliquot (10 mL) was taken and stored frozen at -80° until analysis. The caffeine metabolites were measured in urine by HPLC, and urinary molar ratios of 5-acetylamino-6-formylamino-3-methyluracil (AFMU), 1-methylxanthine (1X), 1-methyluric acid (1U), and 1,7-dimethyluric acid (17U) were employed to estimate the activities of CYP1A2, NAT, and XO. The caffeine salivary clearance and the percent of dose excreted in the form of various metabolites were significantly ($p < 0.034$) smaller in the LD patients than those in healthy children. The urinary molar ratio of [AFMU+1U+1X]/17U which reflect the activity of CYP1A2 was also significantly ($p < 0.001$) reduced in these patients. However, there was no significant difference between the two groups in the ratios of AFMU/1X and 1U/1X which estimate the activities of NAT and XO, respectively. Thus, the data obtained suggest that the activity of CYP1A2 was significantly suppressed in the patients with liver diseases as compared to the healthy subjects, whereas, the activities of N-acetyltrasferase and xanthine oxidase appear to be unaffected, although the latter enzyme tended to be more active in the patients. Further studies involving more patients and control subjects preferably of a different ethnic background are needed to expand on these findings and explore their clinical implication.

El-Yazigi, A., Chaleby, K., Martin, C. R. (1989) Clin. Chem. 35:848-851

Varagnolo, M., Plebani, M., Mussap, M., Nemetz, L., Paleari, C. D., Burlina A., (1989) Clinica Chemica Acta 183:91-94