Altered Irinotecan Pharmacokinetics in Diet-Induced Obesity

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ABSTRACT

Purpose: Irinotecan (CPT-11) is a topoisomerase I inhibitor that has been shown to be highly effective in treatment of colon, stomach, pancreas, and non-small cell lung cancers. It has recently been shown that CPT-11 administration is associated with liver toxicity and this effect is compounded by baseline obesity. It was found that patients with a BMI index of >25 were twice as much susceptible to developing liver toxicity than patients with BMI index of <25. CPT-11 metabolizes to form SN-38, which then undergoes glucuronidation by the enzyme, uridine glucuronosyl transferase (UGT) 1A1 to form SN-38 glucuronide (SN-38G). Excess accumulation of the toxic metabolite SN-38 is known to cause fatal diarrhea in cancer patients. We hypothesize that accumulation of SN-38 is associated with increased liver toxicity of CPT-11 in obesity. **Methods:** For drug metabolism studies, liver S9 fractions were prepared from diet-induced obese (DIO, 60% Kcal diet fed mice) and lean mice (10% Kcal diet fed mice). UGT1A-mediated metabolism of SN-38 was determined in liver S9 fractions (2 mg/ml protein) incubated with SN-38 (15 µmol) for 60 min. For pharmacokinetic studies, mice were injected with a single oral dose of 10 mg/kg CPT-11 and blood samples were collected from 0-480 minutes. Plasma and feces samples were analyzed for CPT-11 and SN-38 concentrations using LC-MS/MS. Liver tissues were harvested for real-time PCR studies. The mRNA and serum TNF-α levels were measured in liver and plasma samples, respectively. **Results:** We found that the rate of formation of SN-38G was ~2 fold lower in the DIO mice compared to the lean controls. This corresponded with reduced expression of UGT1A1 in DIO mice livers. We did not observe significant changes in the area under the curve (AUC) or clearance of CPT-11 between the DIO and lean mice. However, plasma and fecal exposure (AUC) of SN-38 was increased by ~2 folds in the DIO mice compared to the lean controls. We also observed significantly higher mRNA and serum levels of TNF-α in the DIO mice as compared to the lean mice. Higher TNF-α levels are known to be associated with liver toxicity. **Conclusions:** CPT-11 dosage should be closely monitored for effective and safe

chemotherapy in obese patients who are at a higher risk of developing liver toxicity.

KEY WORDS: Irinotecan, Pharmacokinetics, Obesity, Liver Toxicity