Aim: Limitations to the use of chemotherapeutic agents are the often severe side-effects which may lead to early discontinuation of treatment. In previous work we have shown that 3 days of fasting prior to treatment with a high dose of irinotecan prevents the occurrence of side-effects in C26 colon carcinoma bearing mice, while the antitumor activity is not abrogated. To elucidate the mechanism of fasting induced resistance against adverse side effects, we have examined the pharmacokinetics of irinotecan in both fasted and ad libitum fed mice in plasma, liver and tumor.

Methods: Tumor bearing BALB/c mice were divided into three groups (n=18/group). Two groups were fasted for 3 days and one group was fed ad libitum. The ad libitum fed group and one group of fasted animals were treated with 100 mg/kg irinotecan. The other fasted group received a flat dose (i.e., the same dose as ad libitum fed mice). Plasma, liver, and tumor tissue were collected at 1, 4, 8, 12 and 24 hours after injection. Tissues were homogenized and concentrations of irinotecan and its active metabolite SN-38 were determined using a validated reversed-phase high-performance liquid chromatography (HPLC) system.

Results: AUC curves were made to compare the results between groups. The highest, intermediate and lowest AUC value for each group was plotted. No significant differences were found for irinotecan concentrations between ad libitum fed, fasted and flat dosed fasted groups in plasma, liver and tumor. Significant differences were found in plasma and liver for SN-38. SN-38 levels in plasma were significantly lower in fasted animals (p=0.02). SN-38 levels in the liver were significantly lower in both fasted groups (p=0.003). SN-38 concentrations in tumor tissue did not differ between the groups.

Conclusions: Our data demonstrate that 3 days of fasting prior to irinotecan administration significantly reduced SN-38 levels in plasma and liver. Importantly, SN-38 levels in the tumor did not differ between groups. These data suggest that the reduction of side effects by fasting is due to the lower systemic exposure to SN-38. Therefore, fasting before chemotherapy treatment may improve its therapeutic index, and improve treatment of colorectal carcinoma patients.

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