Investigating into the Emetic Mechanism of Irinotecan-Induced Emesis in *Suncus murinus*

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Introduction

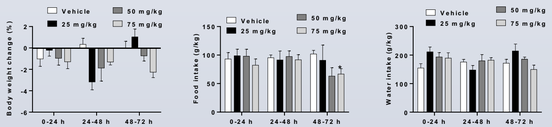
The use of irinotecan in the treatment of cancer may be associated with the side effects of nausea and emesis. The aim of present study is to develop an animal model of irinotecan-induced emesis to investigate the contribution of the abdominal vagus and the role of 5-HT_3 and NK_1 receptors in the mechanism of action.

Methods

Adult male *Suncus murinus* (60-80 g) were used. In pilot studies, animals were administered irinotecan 25-75 mg/kg, p.o., or vehicle (2 % carboxymethylcellulose; 2 ml/kg, p.o.) to determine an optimal dose to use in the mechanism of action studies. Thereafter, some animals underwent bilateral abdominal vagotomy, or a sham vagotomy, 7 days before irinotecan, 75 mg/kg, p.o. In other studies, animals were administered palonosetron (0.01-0.1 mg/kg, p.o.) or aprepitant (0.1-1 mg/kg, p.o.), or their respective vehicles (2 ml/kg, p.o.), 1 h before irinotecan 75 mg/kg, p.o. All behavioural recordings were conducted in a whole-body plethysmography chambers, with assessment of body weight, and food and water intake made at 24 h intervals for up to 72 h.

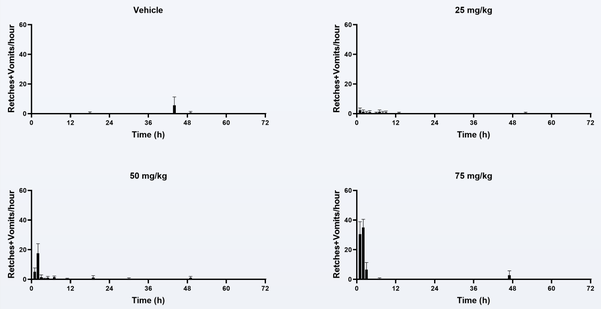
Results

Effects of irinotecan on body weight, food and water intake

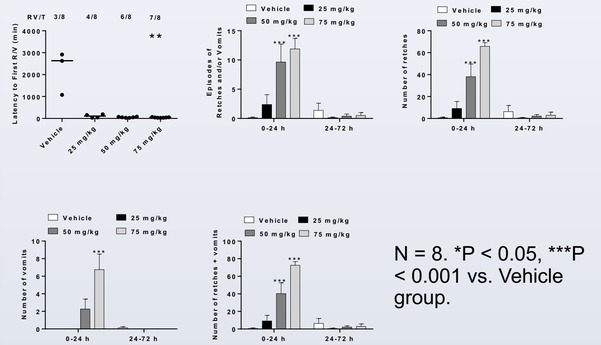


N = 8. *P < 0.05 vs. Vehicle group. Two-way ANOVA followed by Bonferroni's post-hoc test

Emesis profile of animals received irinotecan treatment



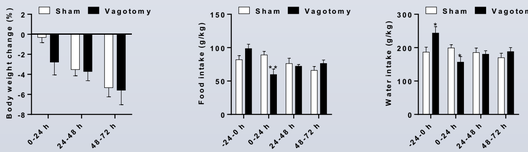
Effects of irinotecan on emesis in Suncus murinus over 72 h



N = 8. *P < 0.05, ***P < 0.001 vs. Vehicle group.

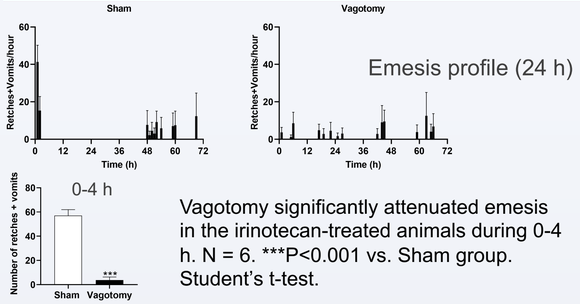
Irinotecan dose-dependently induced emesis in *Suncus murinus.*

Effects of vagotomy on body weight, food and water intake in irinotecan-treated animals



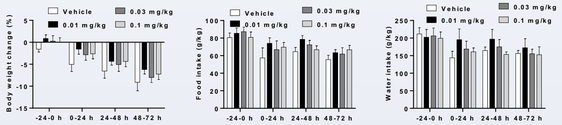
N = 6. *P < 0.05, **P < 0.01 vs. Sham group. Two-way ANOVA followed by Bonferroni's post-hoc test.

Effects of vagotomy on emesis of irinotecan-treated animals



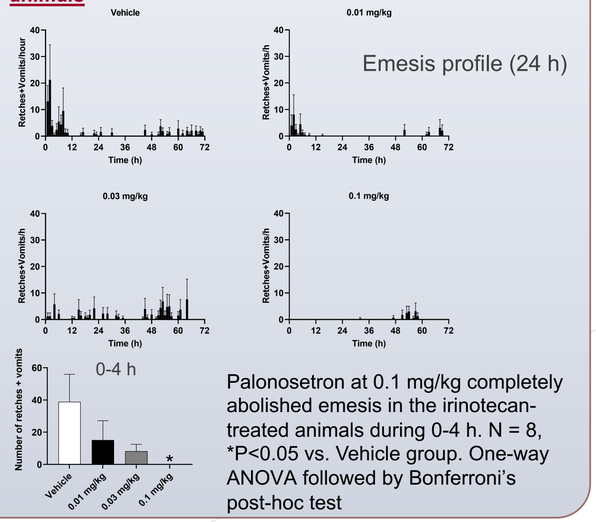
Vagotomy significantly attenuated emesis in the irinotecan-treated animals during 0-4 h. N = 6. ***P<0.001 vs. Sham group. Student's t-test.

Effects of palonosetron on body weight, food and water intake in irinotecan-treated animals



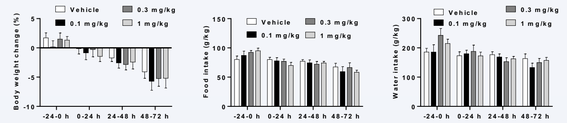
N = 8. Two-way ANOVA followed by Bonferroni's post-hoc test

Effects of palonosetron on emesis of irinotecan-treated animals



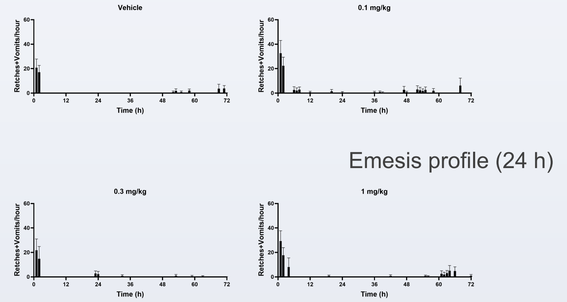
Palonosetron at 0.1 mg/kg completely abolished emesis in the irinotecan-treated animals during 0-4 h. N = 8, *P<0.05 vs. Vehicle group. One-way ANOVA followed by Bonferroni's post-hoc test

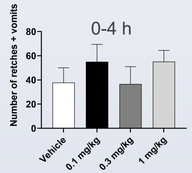
Effects of aprepitant on body weight, food and water intake



N = 8. Two-way ANOVA followed by Bonferroni's post-hoc test

Effects of aprepitant on emesis of irinotecan-treated animals





Aprepitant had no effects on emesis in the irinotecan-treated animals during 0-4 h. N = 8. Two-way ANOVA followed by Bonferroni's post-hoc test.

Conclusions

Irinotecan induces emesis over a three-day period, with the most intense response occurring during the first 4 h and involving 5-HT_3 receptors and abdominal vagi. Surprisingly, irinotecan-induced emesis in *Suncus murinus* appears to be resistant to treatment with the NK_1 receptor antagonist, aprepitant.