Effects of Paclitaxel Exposure on Food Intake and Body Weight Gain in Adult Rats

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Abstract: For the therapeutic management of various types of cancer, paclitaxel (PTX) is commonly used for chemotherapy. Peripheral neuropathy, neuropathic pain, behavioral changes and emotional depression are all side effects of PTX therapy, but their effect on food consumption and body weight gain in adult patient have not been well reported so far. Therefore, present study aimed to evaluate the impact of PTX on food consumption and body weight gain in adult female Wistar rats. In this study, selected equivalent therapeutic doses of PTX (1.6 and 3.2 mg/kg bw) were administered intermittently for six weeks (once a week) intravenously in tail vein via catheter. During experiment, food consumption and body weight of PTX exposed and control rats were recorded. During six weeks of intermittent exposure, our results revealed dose-dependent substantial reduction in food consumption and body weight except first week of PTX exposure in adult Wistar female rats. The effect of equivalent therapeutic doses of PTX was found to be associated with feeding pattern (anorexia) and body weight loss (body mass index) involving multifactorial regulatory mechanisms for controlling the food consumption and body weight changes.

Keywords: Anticancer drug, Paclitaxel, Chemotherapy, Food intake, Weight gain, Rats


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Introduction

Paclitaxel (PTX) is a chemotherapeutic drug of the taxane family commonly used to treat neoplastic illnesses such as breast, lung, and ovarian (WHO, 2021). Paclitaxel's anti-tumor activity is achieved by its attachment to cytoskeleton microtubules and promoting tubulin polymerization (Jordon and Wilson, 2004; Altmann and Gretsch, 2007), leading to cell cycle arrest and then apoptotic cell death (Malingre et al., 2001). PTX has received FDA approval to treat Kaposi’s sarcoma linked to HIV infection, advanced non-small-cell lung cancer, melanoma, and ovarian cancer (Stinchcombe, 2007). Despite PTX’s beneficial effects on cancer patients’ overall progression-free survival, it causes several side effects including gastrointestinal and metabolic disorders like anorexia and weight loss after each progressive intermittent treatment regimens. Additionally,
hematological toxicity, peripheral sensory neuropathy, hypersensitivity reactions, myalgia or arthralgia (Sullivan et al., 2021) and emotional deficits (Dranitsaris et al., 2015) are some of the significant adverse pharmacological effects associated to PTX, despite its use for two decades alone or in conjunction with other chemotherapeutics (Ghadi and Dand, 2017). Due to its low permeability and poor water solubility, oral delivery of PTX is challenging (Green et al., 2006; Marupudi et al., 2007; Zhang et al., 2014), hence intravenous (i.v.) route of drug administration is recommended.

Several reports demonstrated that majority of anticancer drugs induced decreased food intake, followed by subsequent weight loss after chemotherapy (Malik et al., 2006; Miyoshi et al., 2015; Nicolini et al., 2017). In a clinical study, PTX has been found to induce slight decrease of food consumption and body weight in adults of both sexes (Turcott et al., 2016). In a preclinical trial Tohgo et al. (2006) reported significant deduction in food consumption and weight gain in rodents after exposure to PTX. Although paclitaxel and cisplatin are often used to treat female patients with tumours like breast, cervical, and ovarian cancer, the majority of laboratory investigations on the neuropathic pain caused by chemotherapy have been carried out on male animals (Naji-Esfahani et al., 2016). Various clinical studies have proposed that women are oversensitive to pain than men (Hwang et al., 2012). Harley and Adams (2018) and Fillingim et al. (2009) demonstrated that female rodents show lower threshold to pain (Fearon et al., 2012; Hiura et al., 2012). However, several preclinical studies on rodent models demonstrated combined effects of anticancer drugs with PTX exposure as polytherapy on food consumption and weight loss, but studies on use of PTX alone on females in clinical and preclinical regimens are limited. Therefore, present study was aimed to evaluate the effect of equivalent therapeutic doses of PTX on food consumption and weight gain in adult female rats as rodent model mimicking with chemotherapy regimens of PTX in humans.

Materials and Methods

Animals:
Adult female Wistar rats of 8-10 weeks of age, weighing 180±10 g were used. All experimental rats were housed in plastic cages with rice bran as the bedding material and maintained under standard laboratory conditions (22±2ºC, 24±2 % RH and 12h L/D cycle). Tap water was supplied ad libitum throughout the experiment. Animals were used in accordance with the Animal Welfare Act and protocol for use of experimental rats was approved by the Institutional Animal Ethics Committee (IAEC), UoA.

Experimental design and drug exposure:
All female control and experimental rats were randomized into three groups, Group-I (control/vehicle treated, n=12), Group-II (1.6 mg/kg bw PTX, n=12), and Group-III (3.2 mg/kg bw PTX, n=12). The drug manufactured by Beta Drugs Ltd. and marketed by Cadila Pharmaceuticals Ltd. Ahmadabad, India was purchased from the pharmaceutical market. PTX solution was diluted prior to infusion in 0.9% normal saline water. Rats received standard dosing regimen (Polomano et al., 2001; Flatters and Bennett, 2004, 2006) for 42 days. The volume of the doses (0.5 ml to 1.0 ml) was calibrated as per weight gain or loss of the individual rat for subsequent exposure regimens. As per protocol, individual rat was anesthetized with ketamine (2 mg/kg bw, ip) and placed in a constrainer chamber, then selected doses of vehicle or PTX were administered intravenously (i.v.) in the rat’s lateral tail vein through a catheter. All the control and experimental rats were exposed once a week at 09.00 h for six weeks. During experiment, daily record of food intake and body weight of each individual rat was maintained for six weeks consecutively.

Statistical analysis:
All data are represented as mean and standard error of mean (Mean± SEM). Daily food intake and body weight of each rat was analyzed using two-way analysis of variance (ANOVA) between drug
Fig.1: Effect of PTX exposure on food consumption in adult female rats. Data are expressed as mean ± SEM (n=12 per group). *, ** and *** indicate level of significance at p<0.05, p<0.01, p<0.001, respectively between control and PTX exposed groups for two-way ANOVA followed by Tukey's multiple comparison test at different exposure weeks (time point) in comparison to control rats.

(doses) and exposure period (time) followed by Tukey's multiple comparison post-hoc tests to determine differences amongst groups. For all statistical values, significance level of p<0.05, p<0.01 and p<0.001 were used. All data calculations were done with the support of Microsoft Excel and Prism 8.0 software.

Results

Effect of paclitaxel exposure on food intake:

Figure 1 shows effect of intermittent six weeks exposure to PTX (once per week) on weekly food intake by adult female rats. Two way ANOVA [treatment (doses) and time (weeks) interaction] followed by Tukey's multiple comparison post-hoc test displayed a non-significant [F(10,198)=1.78, p>0.05] dose-dependent decrease of food intake in treated groups as compared to vehicle or control group, whereas two way ANOVA also displayed significant effects of treatment [F (5, 198) =7.22, p<0.001] and time [F (2,198)=63.0, p<0.001] on food consumption. These results indicated that time effect was more prominent than dose effect. The post-hoc analysis also revealed that drug induced food intake was significantly decreased (p<0.05 to p<0.001) in a dose-dependent manner from weeks 2-6 (Fig.1). Thus, drug induced anorexia /hypoplasia was developed after first exposure of the drug and substantially prevailed up to 6th weeks of PTX exposure.

Effect of PTX exposure on body weight:

Figure 2 displays a dose-dependent pattern in body weight reduction after PTX exposure from weeks 2 to 6, intermittently. Two way ANOVA [treatment (doses) and time (weeks) interaction] followed by Tukey's multiple comparison post-hoc test displayed a non-significant [F(10,198)=1.80, P>0.05] dose-dependent decrease of body weight in PTX treated groups when compared with control group, whereas two way ANOVA also expressed significant effects of treatment [F(5,198)=2.70, p<0.05] and time [F(2,198)=60.8, p<0.001] on body weight reduction. These results indicated that time effect was more noticeable than dose effect. The post-hoc analysis also revealed that drug induced body weight deficit was significantly decreased (p<0.05 to p<0.001) in a dose-dependent way from different exposure periods, weeks 2-6 (Fig. 2). Thus, drug induced body weight loss was developed after first exposure of the drug and substantially prevailed...
Fig. 2: Effects of PTX on body weight reduction in adult female rats. Data are expressed as mean ± SEM (n=12 per group). *, ** and *** indicate level of significance at p<0.05, p<0.01, p<0.001, respectively between control and PTX exposed groups for two-way ANOVA followed by Tukey’s multiple comparison test at different exposure periods (time point in weeks) in comparison to control rats.

Discussion

The present study revealed that prolonged exposure to PTX at selected equivalent therapeutic doses induced dose-dependent significant reduction of food consumption and body weight in experimental rats. The present findings corroborate well with those investigators who have reported significant reduction of food consumption and weight loss in PTX exposed subjects during chemotherapy (Legakis et al., 2018; Ekici and Balkaya, 2021). Furthermore, Takeda et al. (2008) also reported reduction of food consumption due to the cisplatin during chemotherapy. Several studies demonstrated that treatment of anticancer drugs such as cisplatin induced reduction in body weight and food consumption in mice/rat (Grossberg et al., 2010; Lin et al., 2018). Additionally, various anticancer drugs used in chemotherapy also causes anorexia that associated with chemotherapy induced cachexia (Tohgo et al., 2002; Laviano et al., 2008; Fearon et al., 2012).

Several investigators have postulated that the management of chemotherapy is associated with anxiety and depression (Lyon et al., 2015), which may cause reduced appetite (Brenne et al., 2013). High anxiety levels could reduce the motivation for food intake and the amount of pleasure during a meal (Santa et al., 2017). Another possible mechanism of anticancer drugs induced reduction of food uptake and body weight could be associated with cytotoxicity after every session of chemotherapy which may reduce the numbers of smell and taste receptors, resulting into taste loss (Marinho et al., 2017). Additionally, the cytotoxic treatment causes hypothalamic inflammation and suppresses the activation of the orexin neurons in the hypothalamus (Weymann et al., 2013). Orexin, a neuropeptide found in hypothalamus, is linked with regulation of feeding behavior, sleep/wake cycle and spontaneous physical activity. However, the mechanisms of appetite loss during chemotherapy have not been completely elucidated. Few studies have displayed that blood ghrelin level decreases after chemotherapy in animals and humans (Takeda et al., 2008; Malik et al., 2008; Hiura et al., 2012). Ghrelin is an orexigenic hormone that has been proposed to prevent anorexia (Shiomi et al., 2018). Recently, Ekisi et al. (2021) reported that food intake decreased due to stress induced from repeated PTX therapy and another reason could be due to significant anorexigenic effect of anticancer agents (Ekici and Balkaya, 2021). Other possible reasons for loss of taste involve alterations in the rate of
receptor cells turnover, structure of receptors that affect the delivery of smell and taste molecules to their respective receptors in the re-establishment of synaptic connections at the end of treatment (Mattes et al., 1990; Marinho et al., 2017). Legakis et al. (2018) revealed that suppression of food consumption and weight loss in PTX treated rats expressed emotional behavioral especially depression due to neuropathic pain. Kadota et al. (1994) and Polomano et al. (2001) reported that intravenous exposure of PTX in rats shown a dose-dependent toxicity that causes suppression of locomotor activity due to neuropathic pain and sedation that resulted in reduced feeding and weight loss. The current study hypothesizes that multifactorial processes may not be entirely ruled out in regulating consumption of food and body weight modulation following subsequent exposure to PTX.

**Conclusion**

The present study concluded that prolonged exposure to equivalent therapeutic doses of PTX induces dose-dependent substantial reduction in food consumption and body weight in adult female rats; and involvement of multifactorial mechanisms for controlling the food consumption and body weight changes. Therefore, alternate therapies based on immuno protective agents and molecular medicines may be used to avoid severe adverse effects related to metabolic deregulations.

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**References**


Turcotte C, Blanchet MR, Laviolette M and Flamand N.

