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Drug repositioning of antipsychotic drugs for cisplatin-induced pica behavior in mice

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We aimed to clarify whether various antipsychotics ameliorate cisplatin-induced pica behavior in mice using a drug repositioning approach. Mice were administered cisplatin (12.5 mg/kg, *i.p.*) with or without olanzapine (1 mg/kg, *i.p.*), asenapine (4 mg/kg, *i.p.*), mirtazapine (5 mg/kg, *i.p.*) or standard three-drug antiemetics (granisetron [0.5 mg/kg, *i.p.*], fosaprepitant [25 mg/kg, *i.p.*], and dexamethasone [3 mg/kg, *i.p.*]). Kaolin, food, and water intake, and spontaneous motor activity on the day before and seven consecutive days after the cisplatin administration were measured using a telemetry system. At the primary endpoint, kaolin intake was significantly higher at day three in the cisplatin group than in the pre-treatment and saline groups ($p < 0.05$). Additionally, kaolin intake was not significantly higher in cisplatin with olanzapine, asenapine, and mirtazapine groups for seven days than in the pre-treatment group. At the secondary endpoint, cisplatin decreased the food and water intake, and spontaneous motor activity in a time-dependent manner. Three antipsychotics failed to improve the cisplatin-induced decrease in food and water intake, and spontaneous motor activity. The findings suggest that prophylactic administration of antipsychotics besides olanzapine may improve cisplatin-induced nausea and vomiting in a delayed phase and de-escalate standard 3-drug antiemetics.

1. Introduction

Cancer is a major cause of morbidity and mortality worldwide (Bray et al. 2018). In recent years, one in two Japanese patients was diagnosed with a type of cancer, while one in three people died of cancer. Thus, the effectiveness of cancer treatment and related management, including prophylactic management of adverse events, has increased. Currently, the first-line of treatment for relapse or advanced non-small cell lung cancer is a combination of immune checkpoint inhibitors and platinum-based regimens, such as cisplatin or carboplatin (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; West et al. 2019). Chemotherapy-induced nausea and vomiting (CINV) is the most severe side effect observed in patients that decreases their quality of life (QOL) (Carelle et al. 2002; Bloechl-Daum et al. 2006). The complete response (CR) rate, defined as no vomiting and no use of rescue medication, for platinum-based regimens remains low, ranging from 64 to 78% during the overall phase (0–120 h after chemotherapy administration) even when treated with the current standard antiemetics recommended by the national and international guidelines (Navari et al. 2016; Suzuki et al. 2016; Hashimoto et al. 2020). In the acute phase, defined as 0–24 h after chemotherapy administration, the CR rate is good, ranging from 86 to 95%, whereas the CR rate in the delayed phase, defined as 24–120 h after chemotherapy administration, remains poor, ranging from 67 to 79% (Navari et al. 2016; Suzuki et al. 2016; Hashimoto et al. 2020). Further, cisplatin induces CINV and fatigue (Martin 1996). Therefore, appropriate prophylaxis and management of CINV can maintain patients' QOL and avoid treatment discontinuation or dose reduction, further enhancing the effectiveness of platinum-based regimens.

Recently, olanzapine has been approved as an antiemetic drug for CINV in Japan. Pivotal phase III trials demonstrated that a four-drug combination of olanzapine and the standard triple antiemetic therapy was superior to the standard three-drug combination for CINV induced by highly emetogenic chemotherapy (Navari et al. 2016; Hashimoto et al. 2020). Although the detailed mechanism underlying the antiemetic effect of olanzapine remains unknown, it is suggested that olanzapine antagonizes serotonin 5-HT_{2c} receptors and dopamine D_2 receptors. Olanzapine is commonly called a multi-acting receptor-targeted antipsychotic (MARTA) that blocks multiple receptors. Other MARTAs with similar effects to olanzapine also exist. Thus, atypical antipsychotics other than olanzapine should be expected to have an antiemetic effect; however, this has not yet been investigated. Atypical antipsychotics have a long history in the field of psychiatry and exhibit a very high potential as safe and effective antiemetic agents for drug repositioning. In contrast, rats and mice do not vomit but do exhibit pica behavior, i.e., the ingestion of other non-nutritive substances (Mitchell et al. 1976; Yamamoto et al. 2011; Machida et al. 2015; Yamamoto and Yamatodani 2018; Jaime-Lara et al. 2021). When rats and mice are treated with emetogenic stimuli such as anticancer drugs, they ingest kaolin that contains a mineral (Mitchell et al. 1976; Yamamoto et al. 2011; Yamamoto and Yamatodani 2018). Kaolin consumption has been documented to reflect signs of visceral illness in rats and mice.

The present study aimed to clarify whether various antipsychotics ameliorate cisplatin-induced pica behavior in mice using a drug repositioning approach.

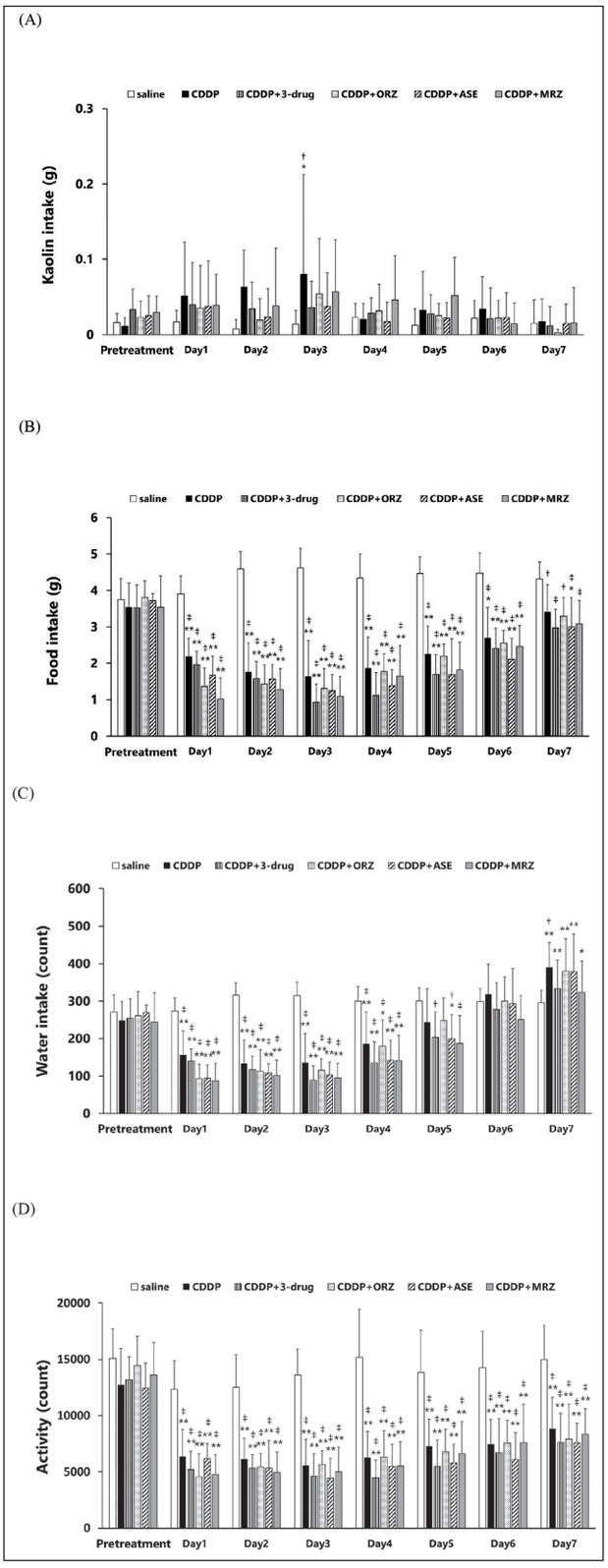

Fig. 1: Effects of (A) kaolin, (B) food and (C) water intake, and (D) spontaneous motor activity in mice with or without the administration of olanzapine, asenapine, mirtazapine or standard three-drug antiemetics (granisetron, fosaprepitant, and dexamethasone) on the day before and seven consecutive days after the administration of cisplatin. CDDP: cisplatin; three-drug; granisetron, fosaprepitant, and dexamethasone, ORZ: olanzapine; ASE: asenapine; MRZ: mirtazapine. Data are expressed as mean ± SD (n = 12–16 per group). *p < 0.05 and **p < 0.01 for the comparison with the pre-treatment (one-way ANOVA followed by Dunnet's post-hoc test) and †p < 0.05 and ‡ p < 0.01 for the comparison with the saline group (two-way ANOVA followed by Tukey's post-hoc test).

2. Investigations and results

2.1. Primary endpoint

As shown in Fig. 1 (A), kaolin intake was significantly increased at day three (delayed phase, i.e., 0–120 h) in the cisplatin group compared with the pre-treatment and saline groups ($p < 0.05$). In contrast, no significant differences were observed on day one (acute period, i.e., within 24 h). Additionally, kaolin intake in cisplatin treated with olanzapine, asenapine, mirtazapine, and standard three-drug antiemetics group did not significantly increased for seven days after the administration of cisplatin compared with that in the pre-treatment and saline groups. However, there were no statistically significant differences between the cisplatin group and these groups, i.e., standard three-drug antiemetics, as well as the three antipsychotics included in this study, slightly suppressed the kaolin intake induced by cisplatin.

2.2. Secondary endpoint

As shown in Fig. 1 (B), food intake in the cisplatin group significantly decreased from day one to seven (acute and delayed phase) following the administration of cisplatin compared with the pre-treatment and saline groups ($p < 0.05$). Similar results were obtained for standard three-drug antiemetics and the three antipsychotics included in this study, i.e., standard three-drug antiemetics and the three antipsychotics failed to improve the cisplatin-induced decrease in food intake. As shown in Figs. 1 (C) and (D), the water intake and spontaneous motor activity (SMA) showed similar results. Cisplatin tended to decrease the food and water intake, and SMA in a time-dependent manner.

3. Discussion

The present study showed that prophylactic administration of antipsychotics (olanzapine, asenapine, and mirtazapine) may improve cisplatin-induced CINV, especially in the delayed phase, and has the potential to de-escalate standard three-drug antiemetics, which are traditionally used in clinical practice. These results support our original hypothesis based on clinical observation. In contrast to pica behavior, we found that cisplatin greatly decreased the food and water intake and SMA lasting up to day seven with or without the administration of antipsychotics. To our knowledge, this is the first pre-clinical study to investigate whether various antipsychotics ameliorate cisplatin-induced pica behavior for seven days in mice using a drug repositioning approach.

In this study, we found that olanzapine slightly reduced cisplatin-induced kaolin consumption. This indicates that prophylactic administration of olanzapine may prevent cisplatin-induced CINV. This result is inconsistent with that of a previous pre-clinical study. Jaime-Lara et al. (2021) showed a statistically significant difference in cisplatin-induced kaolin consumption with or without the administration of olanzapine in rats. In their study, olanzapine was administered four times, two days after the administration of cisplatin, whereas olanzapine in this present study was administered only once after the administration of cisplatin. Thus, a single dose of olanzapine may lack the power to improve cisplatin-induced kaolin consumption. This finding suggests that it is important to consider the frequency and number of olanzapine administrations. Furthermore, we confirmed that other antipsychotics, such as asenapine and mirtazapine, have similar effects. Asenapine, unlike other MARTAs, can be used in patients with diabetes. This suggests that asenapine may be effective as an antiemetic for CINV in patients with diabetes who cannot use olanzapine. Mirtazapine, but not MARTAs, also suppressed kaolin consumption. However, the inhibition of kaolin consumption was relatively smaller than that induced by other antipsychotics, thus the antiemetic effect may be weaker. The antiemetic effect of olanzapine is thought to be due to its affinity for 5-HT_3 and 5-HT_{2c} receptors (Navari 2015; Jaime-Lara et al. 2021); however, mirtazapine has a similar high affinity for 5-HT_3 and 5-HT_{2c} receptors according to the package insert. Therefore, it is speculated that the antiemetic effect of olanzapine is also related to other receptors. Further studies are needed to examine the receptors directly involved in CINV regulation.

Moreover, we investigated the food intake and SMA. Olanzapine, asenapine, and mirtazapine failed to improve the cisplatin-induced decrease in food intake. The present result is consistent with a previous pre-clinical study (Jaime-Lara et al. 2021). This indicates that these three antipsychotics have no potential for the improvement of cisplatin-induced anorexia, i.e., loss of appetite. Similarly, standard three-drug antiemetics and the three antipsychotics used in this study failed to improve the cisplatin-induced decrease in SMA. This was also consistent with the results of another previous pre-clinical study (Malik et al. 2006). This indicates that these three antipsychotics do not have potential for the improvement of cisplatin-induced fatigue. In contrast, antipsychotic-induced sedation was not observed because no significant difference occurred between the cisplatin and antiemetic groups.

In the present study, we investigated the cisplatin-induced pica behavior in mice for seven days. The investigation period of our study differs from those of previous pre-clinical studies (e.g., two or three days) (Malik et al. 2007; Machida et al. 2015; Yamamoto and Yamatodani 2018; Jaime-Lara et al. 2021). In clinical studies, the investigation period of CINV ranged from five to seven days (Tamura et al. 2015; Navari et al. 2016; Suzuki et al. 2016; Hashimoto et al. 2020). Additionally, the peak time of CINV will be on days four or five in humans following cisplatin-based regimens (Tamura et al. 2015). Taken together, a delayed phase of at least five days should be evaluated.

The present study has some limitations. First, mice tend to show more individual differences than rats. To overcome this, we used 12–16 mice per group. Second, we calculated the dose of three antipsychotics from the human equivalent dose and administered it once as a premedication. We were concerned about the sedation induced by olanzapine in the present study (Navari et al. 2016; Hashimoto et al. 2020). Hence, other doses and frequencies should be investigated to determine the appropriate antipsychotic dose for antiemetics. Third, we investigated only three antipsychotics: olanzapine, asenapine, and mirtazapine. To fully understand the antiemetic mechanism of antipsychotics, different types of antipsychotics should be explored. Finally, our single-dosing methods differed in clinical practice. However, we speculated that antipsychotics have the potential to de-escalate standard three-drug antiemetics. This may lead to a significant reduction in the cost of antiemetic therapy. For instance, in Japan, the cost of 5 mg olanzapine is reasonable, compared with costs of 0.75 mg palonosetron and 150 mg fosaprepitant (US $1.4, US $137.5, and US $122.5, respectively (US $1 = ¥108.93 [May 24, 2021])). In contrast, clinicians are interested in steroid sparing because immune checkpoint inhibitors in combination with platinum-based regimens are the first-line treatment for advanced non-small cell lung cancer (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; West et al. 2019). Additionally, fosaprepitant and aprepitant exhibit drug-drug interactions via cytochrome P450 3A4. Thus, clinicians must pay attention to concomitant drugs in cancer patients undergoing chemotherapy treatment using fosaprepitant or aprepitant.

In conclusion, this pre-clinical study examined whether the antipsychotic drugs ameliorate cisplatin-induced pica behavior as well as food and water intake, and SMA for seven days using a drug repositioning approach. The findings suggest that prophylactic administration of antipsychotics besides olanzapine may improve cisplatin-induced nausea and vomiting in the delayed phase and has the potential to de-escalate standard three-drug antiemetics. In the future, clinicians can use prophylactic administration of various antipsychotics as antiemetics, and should evaluate appropriate de-escalation of antiemetics in clinical practice. Clarification of the antiemetic mechanism of antipsychotics is warranted.

4. Experimental

4.1. Animals

Male DBA/2 mice aged 6–7 weeks (weighing 18–24 g) were purchased from the Sankyo Laboratory Service Co., Ltd. (Shizuoka, Japan) and individually housed in wire-bottom housing cages in a room with a regular light/dark cycle (lights on at 8:00 and lights off at 20:00) at a constant temperature (approximately 25 °C) and humidity (approximately 50%). All mice had free access to food and tap water throughout the study, except when specified otherwise.

4.2. Drugs and reagents

Cisplatin, fosaprepitant dimeglumine, olanzapine, and dexamethasone phosphate sodium were purchased from Sigma-Aldrich Japan (Tokyo, Japan); granisetron was purchased from Santa Cruz Biotechnology Inc. (Dallas, TX, USA), asenapine was purchased from Toronto Research Chemicals Inc. (Toronto, ON, Canada), and mirtazapine was purchased from Alomone Labs Ltd. (Jerusalem, Israel). Standard laboratory chow pellets (CE-2) were purchased from CLEA Japan, Inc. (Tokyo, Japan). Kaolin pellets (K50001), which included 1% (w/w) acacia gum, were purchased from Research Diets, Inc. (New Brunswick, NJ, USA) (Jaime-Lara et al. 2021).

4.3. Experimental procedure

The intraperitoneal (*i.p.*) injections, cisplatin, fosaprepitant, dexamethasone, granisetron, and asenapine were dissolved in saline just prior to administration. Olanzapine and mirtazapine were dissolved in 0.1 M hydrochloric acid, and the solution was diluted with saline according to previous studies (Aoyama et al. 2014; Nagata et al. 2016). The dose for mice was based on the following criteria: 1) a previous study (Yamamoto and Yamatodani 2018), 2) ten-fold of the human equivalent dose, and 3) 50% lethal dose as-needed. On the day of the experiment, mice received a single *i.p.* injection of cisplatin (12.5 mg/kg) with or without antipsychotics or standard three-drug antiemetics. Each dose of antipsychotics was as follows: 1) olanzapine (1 mg/kg), asenapine (4 mg/kg), and mirtazapine (5 mg/kg). Each dose of standard three-drug antiemetics was as follows: 1) granisetron (0.5 mg/kg), fosaprepitant (25 mg/kg), and dexamethasone (3 mg/kg). In contrast, control mice received a single *i.p.* injection of saline (1 mL/100 g of body weight). As shown in Fig. 2, cisplatin or saline was administered to mice at 16:00. Additionally, olanzapine, asenapine, mirtazapine, granisetron, and dexamethasone were administered to mice 30 min prior to the administration of cisplatin (at 15:30). Fosaprepitant was administered to mice 1 h prior to cisplatin administration (at 15:00).

At the end of the experiment all mice were euthanized by inhalation of carbon dioxide gas. Each group consisted of 12–16 mice. The animals were not used more than once.

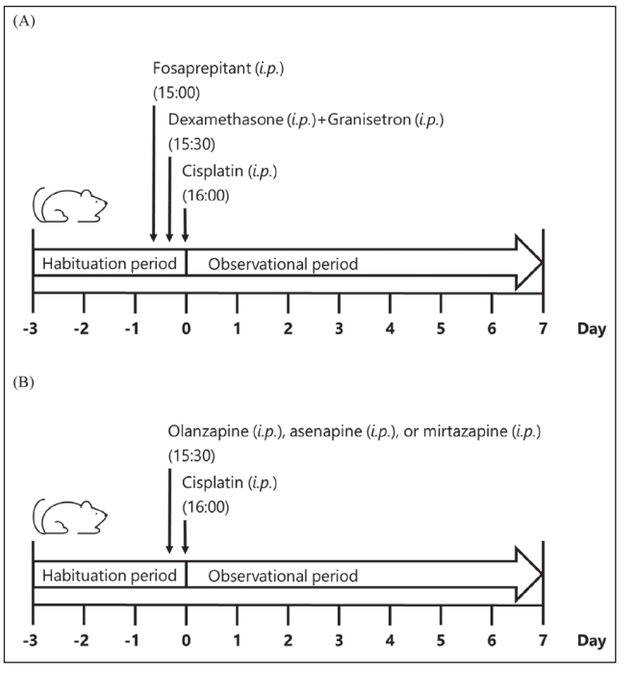

Fig. 2: A schematic presentation of the experimental time-line of cisplatin treatment along with (A) standard three-drug antiemetics and (B) olanzapine, asenapine, or mirtazapine.

4.4. Measurement of kaolin, food, and water intake and SMA

Mice were acclimatized to the housing conditions for three days before the start of the experiment. In our preliminary experiments, mice in behavioral studies recognized the following two containers of kaolin and food for at least three days (data not shown). Kaolin, food, and water intake and SMA on the day before (pre-treatment control) and seven consecutive days after the administration of cisplatin (day 0 at 16:00) were automatically measured using a telemetry system for mice (FDM-300AW with a controller [cFDM-CTL], software [Feedam], drink sensor [DS-30], and activity sensor [AS-10]; Melquest Ltd., Toyama, Japan) in accordance with a previous study (Yamamoto and Yamatodani 2018). SMA in the home cage was measured using a pyroelectric infrared activity sensor above the cage in accordance with a previous study (Nakamura et al. 2014; Iuchi et al. 2017). The sensor detects thermal radiation from the mouse and counts all movements, including horizontal locomotion, rearing, and hanging on the lid. Figure 3 shows the automatic measurement system. This system consists of a wire-bottom housing cage (140 mm [width] × 192 mm [depth]

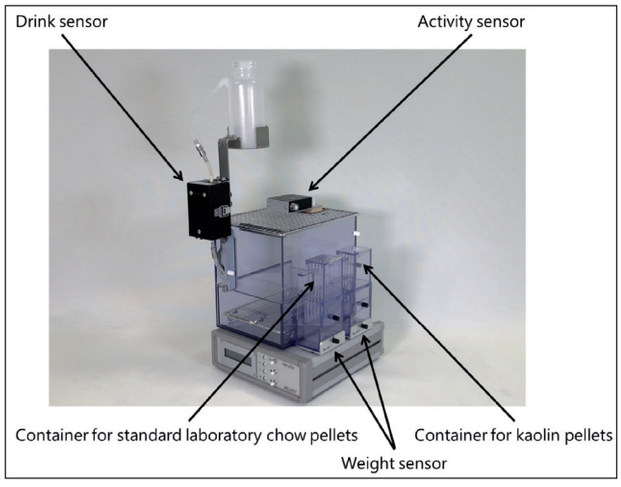

Fig. 3: Automatic measurement system for mice.

× 182 mm [height]), two containers for kaolin and standard laboratory chow pellets, tap water with a drink sensor, an activity sensor for SMA, and a controller equipped with two weight sensors. Kaolin and standard laboratory chow pellets were provided in their respective containers facing the housing cage. Kaolin and food intake was monitored hourly to the nearest 0.01 g, and the data were stored and analyzed using a laptop computer. The results were reported as cumulative daily amounts (g) per day for up to seven days after the administration of cisplatin. Similarly, water intake and activity were measured hourly to 1 (count) each, and the data were analyzed using a laptop computer. The results were reported as cumulative daily amounts (counts) per day for up to seven days after the administration of cisplatin. In a drink sensor, a total of 60 counts amounts to 1 mL of water.
The primary endpoint was the kaolin intake. The secondary endpoint was food and water intake and SMA during the seven days following the administration of cisplatin.

4.5. Statistical analysis

Data are expressed as the mean±standard deviation. Differences in the results from behavioral experiments were analyzed using a one-way analysis of variance (ANOVA) followed by Dunnett's post-hoc test, and a two-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. All statistical analyses were performed using JMP version 15.0.0 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a two-sided p-value < 0.05.

4.6. Ethics

All animal care and experimental procedures were approved by the Laboratory Animal Committee of Keio University (approval No. 18089-(0) and 18089-(1)). All animal experiments were conducted in accordance with the Guidelines for Proper Conduct of Animal Experiments issued by the Science Council of Japan.

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Contributions of authors statement: Hitoshi Kawazoe conceived the idea, designed, and supervised the study. Mayu Sekiguchi, Nanami Sagano, and Hitoshi Kawazoe performed the experiments, collected the data, and analyzed the data. Mayu Sekiguchi and Hitoshi Kawazoe wrote the initial manuscript and edited and revised the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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