Ocular Administration of Palonosetron in the Prevention of Cisplatin-Induced Nausea and Vomiting

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Received September 9, 2022; accepted December 19, 2022

ABSTRACT

Cancer treatments are frequently associated with nausea and vomiting despite greatly improved preventive medication. Administration of antinausea agents as eye drops might provide easy and rapid access to the systemic circulation for prevention of nausea and vomiting and for the treatment of breakthrough nausea, but the ocular administration route has rarely been evaluated. Palonosetron is a second-generation 5-hydroxytryptamine 3 receptor antagonist approved for prevention and treatment of chemotherapy-induced nausea and vomiting. We compared ocular administration of palonosetron to non-active vehicle eye drops and to intravenous palonosetron in the prevention of cisplatin-induced nausea and vomiting in beagle dogs. Palonosetron ocular drops at the dose of 30 μg/kg reduced cumulative nausea over time as measured with the area under the visual analog scale curve by 98% compared with the vehicle and reduced nausea-associated dog behavior by 95%. Vomiting was completely prevented with repeated palonosetron ocular dosing. Hydroxypropyl-β-cyclodextrin (HP-β-CD) palonosetron formulation was well tolerated locally at the palonosetron concentration of 3 mg/ml. Absorption of palonosetron from eye drops was fast. Ten minutes after ocular administration, palonosetron plasma concentrations were similar compared with intravenous administration, and remained similar for six hours. We conclude that palonosetron is rapidly absorbed into the systemic circulation from eye drops. Ocularly administered palonosetron was well tolerated in the HP-β-CD formulation and was highly effective in the prevention of cisplatin-induced nausea and vomiting. Evaluation of the safety and efficacy of ocular administration of palonosetron is warranted in the prevention and treatment of chemotherapy-induced nausea and vomiting in clinical trials.

SIGNIFICANCE STATEMENT

Palonosetron, an effective and well-tolerated antiemetic drug was rapidly absorbed into the systemic blood circulation when administered as eye drops. The achieved palonosetron blood concentrations prevented cisplatin-induced nausea and vomiting in beagle dogs. Palonosetron eye drops might provide an easy and quick method for administering palonosetron when parenteral administration is desired and intravenous administration is not feasible.

Introduction

Systemic cancer treatments are commonly associated with nausea and vomiting, (Piechotta et al., 2021), and radiotherapy-induced and cancer surgery-related nausea and vomiting are also frequent. Several effective agents are available for prophylaxis of nausea and vomiting. The antinausea treatments recommended for patients who receive moderately or highly emetogenic chemotherapy regimens often include a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist, a neurokinin-1 receptor antagonist, olanzapine, and dexamethasone, whereas patients treated with a regimen that has a low risk for nausea and vomiting are often treated with a single prophylactic agent, either with dexamethasone, metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist (National Comprehensive Cancer Network, 2022).

The first-generation 5-HT3 receptor antagonists, such as ondansetron, granisetron, and dolasetron, and the second-generation antagonist palonosetron are recommended both for the prevention of acute chemotherapy-induced nausea and vomiting (CINV) that occurs within 24 hours after chemotherapy administration and for delayed CINV (National Comprehensive Cancer Network, 2022). Palonosetron is an allosteric 5-HT3 receptor antagonist with a neurokinin-1 signaling interfering property (Rojas et al., 2010). The dual mode of action of palonosetron, its highest affinity to the 5-HT3 receptor in its class, and the long elimination half-life of about 40 hours are compatible with its efficacy for both acute and delayed nausea. Palonosetron has shown superior efficacy compared with first-generation 5-HT3 antagonists for both acute and delayed CINV in meta-analyses of randomized trials (Likun et al., 2011; Jin et al., 2013). Palonosetron is usually administered...
only once (Giralt et al., 2011). It is generally well tolerated, the most common adverse effects are headache (4% to 27% of patients) and constipation (1% to 16%) (Zhou et al., 2015).

Breakthrough nausea and vomiting that occurs despite prophylactic antinausea medication may be sudden and may be challenging to treat. The recommended agents for breakthrough nausea and vomiting include olanzapine, 5-HT\textsubscript{3} receptor antagonists, metoclopramide, haloperidol, lorazepam, and dexamethasone (National Comprehensive Cancer Network, 2022). Rectal, subcutaneous, or intravenous administration is often needed, since oral agents may be ineffective due to vomiting. Few studies have evaluated palonosetron in the treatment of breakthrough nausea and vomiting. In one study, 50% of the patients were successfully treated with the second dose of palonosetron (Musso et al., 2010). A small, randomized trial that compared single-agent palonosetron to single-agent ondansetron and to olanzapine plus ondansetron combination in the treatment of breakthrough CINV in patients undergoing hematopoietic stem cell transplantation, concluded that a single dose of palonosetron effectively reduced breakthrough nausea for 24 hours after its administration (Nakagaki et al., 2017).

We hypothesized that 5-HT\textsubscript{3} receptor antagonists could be successfully administered via the ocular route as eye drops, which might provide easy and rapid access to the systemic blood circulation for prevention of CINV and for the treatment of breakthrough nausea. We investigated palonosetron eye drops in the prevention of cisplatin-induced nausea and vomiting in the dog that is an appropriate species for this purpose (du Sert et al., 2012). We found that therapeutic palonosetron serum concentrations could be achieved surprisingly quickly after ocular administration and that ocular administration was highly effective in the prevention of cisplatin-induced nausea and vomiting. To our knowledge, this is the first study to investigate pharmacokinetics and efficacy of a 5-HT\textsubscript{3} receptor antagonist when administered via the ocular route.

Materials and Methods

Experimental Animals. The experiments were carried out using non-naïve adult, purpose bred, male Beagle dogs (Supplemental Table 1). The animals were housed in social groups of two to three animals in appropriate kennels under standard conditions. Other than palonosetron and cisplatin, no other drugs or vaccines were administered to the dogs during the study. At the end of the experiments, the animals were not sacrificed and were returned to their kennels.

Dogs were weighed the day before each dosing for calculation of the appropriate drug dose. The dog body surface area was calculated using the following formula:

\[ \text{Body surface area (BSA in m}^2\text{)} = 10.1 \times \frac{\text{BW}}{\text{BW in kg}} \]

where BW is the body weight in kilograms. Prior to each cisplatin dosing, blood cell counts and blood biochemistry (potassium, urea, creatinine, aspartate aminotransferase, and alanine aminotransferase) were measured, and a urine analysis was carried out (urine leukocytes, nitrites, urohelinogen, protein, pH, hemoglobin, specific gravity, glucose, ketones, and bilirubin).

The study was conducted according to European Directive (European, 2010) and U.S. guidelines (National Research Council 2011) of animal welfare. The palonosetron eye drop formulation study was approved by the National Animal Experiment Board of Finland (ESAVU/91890/4, Oct 7, 2015).

Low-Dose Cisplatin Model. The efficacy of ocular palonosetron administration in the prevention of cisplatin-induced nausea and vomiting was studied in a low-dose cisplatin model. The model was originally introduced by Kenward et al. (2014). Six male Beagle dogs were used for the testing. Each of the six dogs received sequentially the three eye drop treatments using a crossover design (Table 1). A washout period of at least 14 days was kept between the treatments to ensure complete recovery of the dogs for the second treatment. Cisplatin 18 mg/m\textsuperscript{2} was administered as an intravenous infusion (2 ml/min) over 20 minutes. Cisplatin was purchased from Accord Healthcare Limited (Didkot, U.K.) and was freshly dissolved in 0.9% NaCl (CDM Lavoisier, Paris, France) before dosing. To reduce cisplatin nephrotoxicity, all dogs were infused first with saline (0.9% NaCl, 25 ml/kg/h) into the cephalic vein for 1 hour, followed by mannitol infusion (0.5 mg/kg over 15 minutes), and then saline again for 15 minutes before the start of cisplatin administration. The dogs were treated with either four doses of eye drop vehicle consisting of 2% polyvinylpyrrolidone (PVP, Povidone K-30, ISP Technologies Inc., TX, USA) in 0.9% sodium chloride administered 5 minutes apart (the vehicle group), one dose of the palonosetron eye drops 30 \( \mu \text{g/kg} \) plus three doses of the eye drop vehicle (the palonosetron 30 \( \mu \text{g/kg} \) group), or four doses of the palonosetron eye drops 30 \( \mu \text{g/kg} \) (the palonosetron 120 \( \mu \text{g/kg} \) group; Fig. 1).

Ocular palonosetron (or its vehicle) administration was started 45 minutes after the end of the cisplatin infusion. At each treatment session, the dogs received an identical volume of ocular drops (50 \( \mu \)l) on each eye every 5 minutes for four times (i.e., a total volume of 200 \( \mu \text{l/eye} \)) using a micropipette. The palonosetron ocular drops contained palonosetron at the concentration of 3 mg/ml, and the drops were sterile filtered and ready-to-use. The dose for ocular instillation was selected based on a pilot pharmacokinetic study carried out in dogs. The target was to achieve a comparable plasma exposure level compared with the human effective dose. The palonosetron doses are expressed as the base.

Observation and Response Evaluation. After the end of the cisplatin infusion the dogs were observed for nausea-like behavior over a time period of 420 minutes (7 hours). They were housed individually during the two hours that preceded cisplatin infusion, during the infusion, and during the 7-hour observation period that followed the completion of the cisplatin infusion. For hydration, a bolus of saline was administered hourly starting 60 minutes after the end of the cisplatin infusion until the end of the 7-hour follow up period to a cumulative total volume of 27.5 ml/kg.

Dog nausea-like behavior was rated and the episodes of vomiting were counted within 15-minute time bins during the observation period starting from the end of the cisplatin infusion and continuing to the end of the 7-hour observation period. Nausea was rated by a single server assessed the severity of the dog nausea-like behavior based on a 100 mm visual analog scale (VAS) which ranged from 0 mm (no nausea) to 100 mm (the worst possible nausea). The observer was blinded to the type of eye drop treatment given. The observer assessed the severity of the dog nausea-like behavior based on the presence or absence of salivation, exaggerated swallowing motions, lip licking, lethargy, and restlessness or turning behavior signaling imminent vomiting, and their frequency.

Pharmacokinetic Study. Ocular administration was performed as described in the low-dose cisplatin model. Intravenous palonosetron (10 \( \mu \text{g/kg} \), US Pharmacopeial Convention, Rockville, MD, USA) was administered at the concentration of 0.02 mg/ml as one injection into the jugular vein. For pharmacokinetics assessment, 1 ml blood samples were collected into pre-cooled K\textsubscript{2}EDTA tubes before and after ocular or intravenous administration of palonosetron. The blood samples collected at 2, 5, 10, 20, 30, and 45 minutes, 1 hour, and 2 hours after administration were drawn from the cephalic vein, whereas the predose blood sample, and samples collected at 4, 6, 8, 12, 24, and 48 hours after administration were sampled from the jugular vein. Samples were immediately labeled, placed on ice, and centrifuged within 30 minutes at the speed of 2,500 g at +5 °C for 10 minutes. After centrifugation, the plasma (250 \( \mu \)l) was stored in upright position in polypropylene tubes at -80 °C until analyzed.

To measure palonosetron plasma concentration, the plasma was first fractionated using liquid chromatography using a Waters Aesy-Unity UPLC HSS T3 column (Waters Corp, Milford, MA, USA) followed by an electrospray ion source. Palonosetron was subsequently detected using a selective reaction monitoring technique using a
the control group (cisplatin + vehicle only), the VAS score for nausea started to increase 160 minutes (range, from 143 to 173 minutes) after the end of cisplatin infusion and peaked at 215 minutes (range, 188 to 233 minutes) with a maximum mean VAS score of 88 mm (S.D., 14 mm), whereas ocular palonosetron prevented dose-dependently cisplatin-induced nausea (Fig. 2A). Palonosetron eye drops with the dose of 30 μg/kg reduced cumulative nausea over time as measured with the area under the VAS curve (VAS-AUC) by 98% (S.D., 2%), and nausea was completely prevented with the 120 μg/kg dose of palonosetron (four times 30 μg/kg; Fig. 2B).

In the palonosetron 30 μg/kg group, small transient non-significant increases in the VAS score were observed at 368 minutes and 398 minutes (mean, 5 mm and 8 mm, respectively) from the end of cisplatin infusion. These were due to a dog that had a vomiting episode and restlessness at 360 to 375 minutes and another dog that vomited at 390 to 405 minutes (the VAS score 50 mm), whereas the remaining four dogs showed no signs of nausea.

### Nausea-Associated Behavior in the Cisplatin Model

In the vehicle group nausea-associated behavior started 173 to 308 minutes after the end of cisplatin infusion, peaking at 233 minutes. Lip licking (14 [S.D., 4] observations per dog, a maximum of 27) and exaggerated swallowing (four observations [S.D., 1] per dog, a maximum of nine) were observed in all dogs. Salivation (five out of the six dogs) and restlessness started at 180 minutes from the end of cisplatin infusion and were observed up to three times per dog. Salivation and restlessness were frequent also during the 300 to 315-minute interval (three observations per dog). Substanceinduced restlessness occurred in four out of the six dogs during the 203 to 278-minute time period after the end of cisplatin infusion, and turning behavior was observed in three out of the six dogs. Abnormal salivation, lethargy, restlessness, and turning behavior ceased by 360 minutes from the end of cisplatin infusion, but exaggerated swallowing and lip licking were observed until the end of the observation period.

Ocular administration of palonosetron at the dose of 30 μg/kg reduced nausea-associated behavior by 95% (S.D., 5%). No

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**Fig. 1.** The time sequence of hydration, cisplatin administration, and ocular drops administration in the low dose cisplatin model. White symbols with dot inside stand for vehicle and green symbols ocular drops containing palonosetron.
turning behavior or lethargy was observed in this group. Lip licking was observed sporadically in four out of the six dogs. Also exaggerated swallowing was sporadically observed in two out of the six dogs during the follow up. In addition, restlessness was observed in two out of the six dogs, in each case during only one observation interval. Salivation was recorded once in one dog.

After ocular administration of palonosetron 120 µg/kg, the only nausea-associated behavior recorded was lip licking, which was observed sporadically in three out of the six dogs. During the peak cisplatin-induced nausea period, lip licking was observed once in a dog and twice in another dog.

**Efficacy on Vomiting in the Cisplatin Model.** In the vehicle group, the dogs started to vomit 158 minutes to 323 minutes after the end of cisplatin infusion. Vomiting peaked at 218 minutes, at which time the dogs had a mean of two (S.D., 2; range, 0 to 6) vomiting episodes. No vomiting was observed 368 minutes after the end of cisplatin infusion. In the vehicle group, each dog had 5 to 17 vomiting episodes during the entire observation period.

The 30 µg/kg dose of palonosetron reduced significantly vomiting; only one vomiting episode occurred in one dog (during the 360- to 375-minute interval), and another vomiting episode in another dog (the 390- to 405-minute interval; P < 0.0001). The 120 µg/kg dose of palonosetron prevented vomiting completely throughout the entire observation period (P < 0.0001; Fig. 3).

**Palonosetron Plasma Exposure.** At the end of the study (6 hours after administration of the ocular drops) the mean plasma palonosetron concentration was 0.23 ng/ml (S.D., 0.12 ng/ml) in the 30 µg/kg once group and 0.70 ng/ml (S.D., 0.33 ng/ml) in the four times 30 µg/kg group (n = 6 in each group).

**Pharmacokinetic Study And Palonosetron Eye Drop Ocular Tolerance.** Absorption of palonosetron from ocular drops was fast. Palonosetron plasma concentrations were similar 10 minutes after palonosetron ocular administration compared with intravenous administration (Fig. 4A), and the palonosetron plasma concentrations were generally similar for six hours after ocular administration and intravenous administration (Fig. 4B). The bioavailability of 30 µg/kg palonosetron was significantly better from the hydroxypropyl-β-cyclodextrin (HP-β-CD) formulation than from the PVP formulation (Table 2).

When applied using the PVP formulation, palonosetron caused increased blinking of the eye, eye itching (pawing of the eye), and mild conjunctival hyperemia in most dogs. The HP-β-CD formulation, in turn, was well tolerated at the palonosetron concentration of 3 mg/ml, but at a higher palonosetron concentration (6 mg/ml) the HP-β-CD formulation was associated with increased blinking (Table 3). No signs of ocular irritation were recorded following vehicle administration.

**Discussion**

Palonosetron ocular drops reduced substantially cisplatin-induced vomiting and nausea-like behavior at the dose of 30 µg/kg, and vomiting was completely prevented with the dose of 120 µg/kg. Palonosetron was rapidly absorbed into the systemic circulation after ocular administration. Plasma concentrations corresponding to intravenous administration were reached as early as 10 minutes after ocular administration. Palonosetron eye drops were well tolerated and caused little conjunctival irritation when the HP-β-CD formulation was used.

To our knowledge, the ocular route has not been studied earlier for administration of 5-HT₃ antagonists. Since 5-HT₃
antagonists can be administered intravenously, orally, and intramuscularly for the prevention or for the treatment of chemotherapy-related nausea and vomiting, finding a niche for the ocular administration could be questioned. Nevertheless, eye drops are quick and easy to administer even by non-professionals, and no special equipment is needed. Eye drops can be administered when the patient is already nauseous and vomiting, making oral administration challenging and unreliable. Since plasma concentrations of palonosetron corresponding to intravenous administration can be achieved within a few minutes of ocular administration, palonosetron eye drops may be an appealing option when rapid relief of nausea is required.

We selected to investigate palonosetron in the present study instead of other 5-HT3 receptor antagonists, because palonosetron has a high affinity to the 5-HT3 receptor and high efficacy for both acute and delayed nausea (Likun et al., 2011; Jin et al., 2013) and also has efficacy for breakthrough nausea (Nakagaki et al., 2017). In addition, palonosetron is generally well tolerated. Although palonosetron is typically used as a single dose for the prevention of nausea and vomiting, its repeat administration seems to be safe (Musso et al., 2010).

Palonosetron was better tolerated locally in the HP-β-CD formulation than in the PVP formulation. PVP is a frequently used pharmaceutical ingredient in eye drops, where it is intended for relieving eye redness or dryness. In dogs, palonosetron frequently caused mild local ocular irritation with the PVP formulation, increasing blinking of the eyes and itching (eye pawing), and caused conjunctival hyperemia. These adverse effects could largely be overcome with the HP-β-CD formulation. Cyclodextrins are often used to increase solubility of poorly soluble drugs. We discovered that although palonosetron is highly soluble, the cyclodextrin formulation could prevent palonosetron-induced ocular intolerance without having a major effect on the absorption kinetics of palonosetron. Most of the detected signs of ocular intolerance were mild, and, therefore, might have gone unnoticed unless specifically monitored and scored.

The study has some limitations. We studied the safety and efficacy of palonosetron eye drops only in one species, the Beagle dog. The dog was selected for testing, because it is considered to resemble man in emetic sensitivity. The number of dogs tested in each experiment was relatively small, but since the efficacy of ocular palonosetron in the prevention of nausea and vomiting turned out to be high, statistically significant differences between groups could be achieved. We administered moderate hydration during the follow-up period to protect the kidneys from cisplatin-related damage and to main the urine flow, which could have a small diluting effect on the blood palonosetron concentrations. We did not investigate ocular administration of other 5-HT3 inhibitors, such as ondansetron, granisetron, and dolasetron in the present study, which remains a topic for future research.

Conclusions

We conclude that palonosetron administration as ocular drops resulted in fast absorption of palonosetron into the

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**TABLE 2**

<table>
<thead>
<tr>
<th>Dosing route</th>
<th>Palonosetron dose</th>
<th>Formulation</th>
<th>C₀ / Cmax</th>
<th>C₁₀min</th>
<th>C₅₀</th>
<th>AUC₀₂₅</th>
<th>t½</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>10 µg/kg</td>
<td>Saline</td>
<td>13.2 ± 4.9</td>
<td>4.7 ± 1.4</td>
<td>0.27 ± 0.12</td>
<td>9.2 ± 3.9</td>
<td>4.6 ± 5.0</td>
<td>—</td>
</tr>
<tr>
<td>Ocular</td>
<td>30 µg/kg</td>
<td>PVP</td>
<td>4.9 ± 1.5</td>
<td>3.5 ± 1.1</td>
<td>0.53 ± 0.22</td>
<td>11.4 ± 1.6</td>
<td>8.6 ± 1.8</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>Ocular</td>
<td>30 µg/kg</td>
<td>HP-β-CD</td>
<td>5.7 ± 1.3</td>
<td>2.8 ± 1.6</td>
<td>0.96 ± 0.47</td>
<td>19.0 ± 5.3</td>
<td>3.2 ± 1.0</td>
<td>76 ± 20</td>
</tr>
<tr>
<td>Ocular</td>
<td>60 µg/kg</td>
<td>HP-β-CD</td>
<td>7.3 ± 3.2</td>
<td>4.7 ± 2.1</td>
<td>2.0 ± 2.6</td>
<td>37.5 ± 30.8</td>
<td>5.3 ± 2.5</td>
<td>63 ± 26</td>
</tr>
</tbody>
</table>

Repeate one-way ANOVA followed by multiple comparisons test.

BA, bioavailability; t½, half-life.

*n* = 6 dogs per treatment.  
*<sup>2</sup>p<sup>*</sup> = 0.05 compared with intravenous administration.

*<sup>2</sup>P < 0.01, compared with intravenous administration.
Table 3: Local tolerance of the ocular formulations tested

<table>
<thead>
<tr>
<th>Dose, µg/kg</th>
<th>Formulation</th>
<th>Palonosetron, mg/ml</th>
<th>Increased blinking rate</th>
<th>Narrowing of the palpebral fissure/closed eyelid</th>
<th>Eye itching (pawing of the eye)</th>
<th>Conjunctival hyperemia</th>
<th>Conjunctival swelling</th>
<th>Conjunctival discharge</th>
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<tbody>
<tr>
<td>10</td>
<td>Vehicle</td>
<td>0</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>30</td>
<td>PVP</td>
<td>3</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>30</td>
<td>HP-β-CD³</td>
<td>3</td>
<td>1/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
<tr>
<td>60</td>
<td>HP-β-CD³</td>
<td>6</td>
<td>4/6</td>
<td>1/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
<td>0/6</td>
</tr>
</tbody>
</table>

Repeated one-way ANOVA followed by multiple comparisons test.
¹ 0.9% NaCl.
² 2% (w/v) Povidone K30 in saline (pH 4.8).
³ 10% hydroxypropyl-β-cyclodextrin/2.5% mannitol/20 mM citrate buffer (pH 4.8).

Systemic circulation in dogs. Palonosetron ocular drops either as a single 30 µg/kg dose or with repeated dosing (four times the 30 µg/kg dose) effectively and dose-dependently prevented nausea and vomiting in the low-dose cisplatin model. Palonosetron was well tolerated with the HP-β-CD formulation. Evaluation of the safety and efficacy of ocular administration of palonosetron in the prevention and treatment of chemotherapy-induced nausea and vomiting warrants clinical trials.

References


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