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Differential action of ondansetron and dexamethasone to modify cisplatin-induced acute and delayed kaolin consumption (“pica”) in rats

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Abstract

The ability of cisplatin to induce acute (0–24 h) and delayed (24–48 and 48–72 h) phases of kaolin ingestion (pica) was investigated in the rat. Cisplatin 3 mg/kg, i.p., induced kaolin consumption during the 0–24- ($P<0.001$) and 48–72-h ($P<0.05$) periods that was antagonised by dexamethasone 1 mg/kg, i.p., administered every 12 h alone or in combination with ondansetron 2 mg/kg, i.p., administered every 12 h ($P<0.05$). As a single treatment, ondansetron 2 mg/kg, i.p., administered every 12 h potentiated cisplatin-induced kaolin consumption by 41% ($P<0.05$) during the 0–24-h period but had no action to modify the delayed response ($P>0.05$). Dexamethasone 1 mg/kg, i.p., administered every 12 h and cisplatin 3 and 6 mg/kg, i.p., but not ondansetron 2 mg/kg, i.p., administered every 12 h ($P>0.05$) reduced food consumption and decreased rat weight. The highest dose of cisplatin 6 mg/kg, i.p., induced acute ($P<0.001$) but not delayed kaolin ingestion ($P>0.05$). The action of cisplatin to induce acute and delayed pica is complicated and may be affected by drugs that modify appetite.

Keywords: Cisplatin; Kaolin; Pica; Emesis; Delayed

1. Introduction

Chemotherapy using cisplatin-containing regimens may induce episodes of acute and delayed emesis in man (Martin, 1996). The acute response occurs on the first day of treatment and is particularly sensitive to 5-HT_3 receptor antagonists such as ondansetron (Kris et al., 1998). The delayed phase occurs on days 2–5 and may be less sensitive to the action of 5-HT_3 receptor antagonists (Tsukada et al., 2001). The control of both phases is improved by the combination of anti-emetics with glucocorticoids such as dexamethasone (Gralla et al., 1996). However, no single agent is effective to reduce satisfactorily delayed nausea and vomiting in man.

There have been several attempts to develop animal models of cisplatin-induced acute and delayed emesis. The studies have used the ferret (Rudd et al., 1994), piglet (Milano et al., 1995), cat (Rudd et al., 2000) and pigeon (Tanihata et al., 2000). Performing the emesis experiments is particularly time consuming and labour-intensive. The experiments are also expensive to conduct because they also utilise non-rodent laboratory animals that possess the emetic reflex.

Common laboratory animals that do not possess the emetic reflex are also useful to anti-emetic research (Morita et al., 1988). In particular, the rat has been used in acute studies of drug- and motion-induced pica (i.e. eating non-nutritive substance such as kaolin) in an attempt to mimic mechanisms activated during vomiting (Takeda et al., 1993; Uno et al., 1997). Many toxins and emetic agents (including cisplatin) induce kaolin ingestion and the model also successfully identifies agents that have anti-emetic activity (Takeda et al., 1995). The kaolin ingestion model may offer a simplistic approach to studying the mechanisms that may be relevant to the emetic action of cisplatin.

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Recently, it was shown that the rat exhibits acute and delayed pica activity following the intraperitoneal administration of cisplatin (10 mg/kg, i.p.; Saeki et al., 2001). In the model, daily injections of ondansetron, and ondansetron plus dexamethasone, reduced the acute but not the delayed phase of kaolin consumption. Further studies revealed that the tachykinin NK_1 receptor antagonists, CP-99,994 ((2*S*, 3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine) and HSP-117 ((2*S*,3*S*)-3-[(5-isopropyl-2,3-dihydrobenzofuran-7-yl)methyl]amino-2-phenylpiperidine) reduced both phases of kaolin consumption; the reductions were seen following the single administration of the tachykinin NK_1 receptor antagonists prior to the administration of cisplatin (Saeki et al., 2001).

In the ferret, the single administrations of ondansetron and CP-99,994 are ineffective to control cisplatin-induced acute and delayed emesis and a successful anti-emetic treatment usually requires multiple doses over the course of both phases of the response (Rudd et al., 1996b; Rudd and Naylor, 1996). In the present studies, therefore, we re-investigate the profile of cisplatin to induce kaolin consumption and study the effect of multiple doses of ondansetron and dexamethasone on acute and delayed pica behaviour. The effect of drug treatment on food consumption was also investigated.

2. Methods

2.1. Animals

Male Wistar rats (Charles River Japan, Yokohama, Japan) weighing 200–240 g were housed individually in cages (23 × 23 × 20 cm) in a room with a 12-h light/12-h dark cycle (lights on between 07:00 and 19:00 h) at a constant temperature (23 ± 1 °C) and humidity (50 ± 5%). Pelleted food (MF, Oriental Yeast, Osaka, Japan) and water was available ad libitum. Each cage had a wire-mesh floor to permit collection of spilt kaolin and food.

2.2. Preparation of kaolin pellets

Kaolin pellets were prepared according to the methods described Takeda et al. (1993). Briefly, gum Arabic and hydrated aluminium silicate (kaolin) were mixed together (1:100 on a weight:weight basis) with distilled water to form a thick paste. Pellets of the resulting kaolin mixture were shaped to resemble the dimensions of the rats' normal laboratory diet. The pellets were dried completely at room temperature.

2.3. Measurement of kaolin and food consumption and drug administration

The kaolin pellets were introduced into the cages 3 days prior to drug administration. They were held in identical stainless-steel containers (7 × 8 × 3 cm, attached to the side of the cage) to the food pellets. The kaolin and food containers were removed each day (at 10:00 h) and the spilt kaolin and food collected, to determine the rats' consumption, during each 24-h period, up to a total 72 h observation time. Rat weight was also recorded on a daily basis.

In preliminary experiments, cisplatin (3–6 mg/kg) or vehicle (saline 0.9% w/v, 5 ml/kg) was injected intraperitoneally and animals returned to the experiment cages. In subsequent experiments, rats were injected with ondansetron (2 mg/kg, i.p.), and/or dexamethasone (1 mg/kg, i.p.), or their respective vehicles (saline 0.9% w/v, 1 ml/kg, i.p.) immediately following the administration of cisplatin (3 mg/kg, i.p.) at 10:00 h. Ondansetron and/or dexamethasone, or their respective vehicles, were administered at regular 12-h intervals for the remainder of the observation time. In a final set of experiments, the effect of ondansetron (2 mg/kg, i.p., administered every 12 h) and dexamethasone (1 mg/kg, i.p., administered every 12 h) were examined alone on kaolin and food consumption. Kaolin and food intake and rat weight was measured at 24, 48 and 72 h post-cisplatin. All experiments were approved by the Animal Care Committee of Osaka University, The Faculty of Medicine.

2.4. Statistical analysis

Kaolin and food consumption was calculated to the nearest 0.1 g and rat weight to the nearest 1 g. Data were analysed using a repeated measures two-factor analysis of variance (ANOVA; factor 1 = time, factor 2 = treatment) with comparisons of specified means by Planned Contrasts (SuperANOVA®, Version 1.11, Abacus Concepts, USA). This procedure is useful for testing hypotheses about data that are more specific than the hypothesis automatically tested for by each term in the ANOVA model. Differences were considered significant when $P < 0.05$.

2.5. Drugs used

Cisplatin (Sigma-Aldrich, St. Louis, USA) was formulated in saline (0.9% w/v) and administered in a volume of 5 ml/kg. Ondansetron hydrochloride dihydrate (Glaxo Smith Kline, Tokyo, Japan) and dexamethasone 21-phosphase disodium salt (Sigma-Aldrich) were formulated in saline (0.9% w/v) and administered in a volume of 2 ml/kg. Gum Arabic and hydrated aluminium silicate were from Katayama Chemical, Osaka, Japan. Doses are expressed as the free base.

3. Results

3.1. Effect of cisplatin on pica behaviour

On the first day of adaptation, rats ingested approximately 0.7–1.2 g of kaolin and approximately 15.8–19.2 g

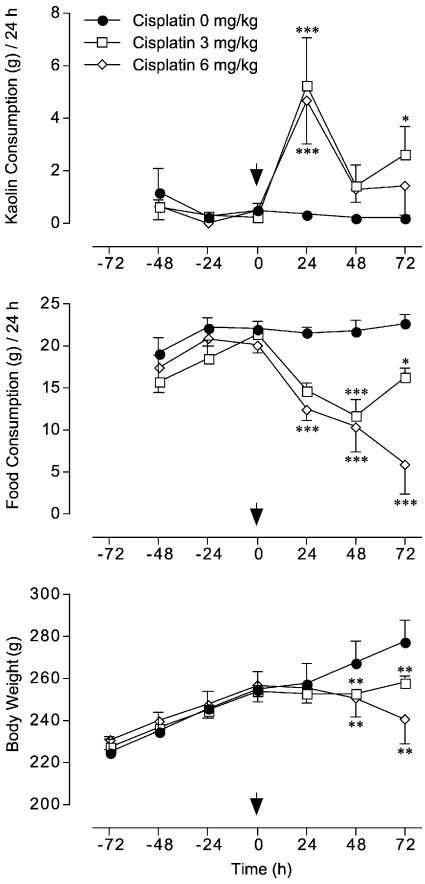

Fig. 1. Action of cisplatin to modify kaolin and food ingestion in the rat and its impact on rat weight. Cisplatin or vehicle (saline 0.9%w/v, 10 ml/kg, i.p.) was administered at $t=0$ (indicated by the arrows). Data represent the means ± S.E.M of 5–6 determinations. Data significantly different from the respective vehicle-treated cisplatin animals are indicated as $*P<0.05$, $**P<0.01$, $***P<0.001$ (repeated measures ANOVA with pre-planned contrasts of specified means).

of food. Generally, kaolin ingestion decreased to approximately 0.3–0.5 g on the remaining second and third days before cisplatin administration and food ingestion increased to approximately 20.2–21.5 g (Fig. 1).

Compared to the saline-treated animals, cisplatin at 3 and 6 mg/kg increased significantly kaolin consumption by 1365% ($P<0.001$) and 1326% ($P<0.001$), respectively (i.e. rats consumed approximately 4.7–5.3 g), during the 0–24-h period but did not significantly increase kaolin intake during the 24–48-h period ($P>0.05$). Only cisplatin at 3 mg/kg significantly increased kaolin consumption during the 48–72-h period (a 1054% increase relative to the saline treated animals was recorded; $P<0.05$). Conversely, cisplatin at 3 and 6 mg/kg decreased food consumption by 32% (non-significant: $P>0.05$) and 42% ($P<0.001$), respectively, during the 0–24-h period, by 46% ($P<0.001$) and 53% ($P<0.001$), respectively, during the 24–48-h period and by 28% ($P<0.05$) and 74% ($P<0.001$), respectively, during the 48–72-h period (Fig. 1).

Control rats generally gained approximately 10 g in weight each day but cisplatin at 3 mg/kg prevented the increase: this was evident 48 and 72 h after treatment ($P<0.01$). Rats injected with cisplatin at 6 mg/kg lost weight (approximately 5–10 g/day) and this was particularly evident 72 h after treatment ($P<0.01$; Fig. 1).

3.2. Effect of ondansetron and/or dexamethasone on cisplatin-induced kaolin ingestion

Cisplatin 3 mg/kg was selected as the most reliable dose to induce both acute and delayed phases of kaolin ingestion. In these experiments, rats consumed approximately 0.2–0.6 g of kaolin and approximately 16.7–18.0 g of food, on the first day of adaptation. On the day before cisplatin (3 mg/kg) administration, rats consumed approximately 0.1–0.7 g of kaolin and 21.0–22.5 g of food (Fig. 2). Control vehicle treated rats receiving cisplatin consumed 3.5 ± 1.2 g of kaolin during the 0–24-h period, 1.4 ± 0.7 g of kaolin

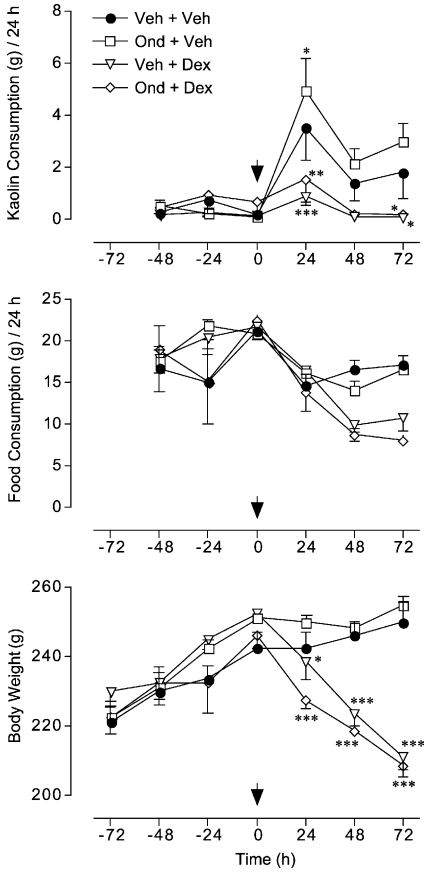

Fig. 2. Action of ondansetron and dexamethasone on the ability of cisplatin (3 mg/kg, i.p.) to modify kaolin and food ingestion in the rat and its impact on rat weight. Cisplatin was administered at $t=0$ (indicated by the arrows). Ondansetron and/or dexamethasone, or the respective vehicles, were administered immediately after cisplatin injection and then at regular 12-h intervals. Data represent the means ± S.E.M of four determinations. Data significantly different from vehicle-treated cisplatin animals are indicated as $*P<0.05$, $**P<0.01$, $***P<0.001$ (repeated measures ANOVA with pre-planned contrasts of specified means).

during the 24–48-h period and 1.8 ± 1.0 g kaolin during the 48–72-h period. Animals administered ondansetron 2 mg/kg, twice per day, consumed 41% more kaolin than the control treated rats during the 0–24-h period ($P<0.05$); ondansetron did not modify significantly kaolin consumption during the remaining periods ($P<0.05$).

However, animals administered dexamethasone 1 mg/kg, twice per day, consumed 74.3% ($P<0.001$) and 94% ($P<0.05$) less kaolin respectively than the control animals during the 0–24- and 48–72-h periods. Animals that received the combination treatment of ondansetron 2 mg/kg, twice per day, plus dexamethasone 1 mg/kg, twice per day, similarly consumed 56% ($P<0.01$) and 89% ($P<0.05$ less kaolin respectively compared to control animals) during the 0–24- and 48–72-h periods. None of the drug treatments modified the cisplatin-induced kaolin consumption during the 24–48-h period ($P>0.05$). In addition, animals that received dexamethasone in combination with cisplatin, or the combination of ondansetron plus dexamethasone in combination with cisplatin, lost weight (range 8.8–18.8 g/day) during each 24-h period ($P<0.05$); ondansetron as a single regimen combined with cisplatin had no action when compared to the cisplatin vehicle treated controls ($P>0.05$; see Fig. 2). There was also trend for animals receiving cisplatin and dexamethasone (alone or in combination with ondansetron) to eat less food than the other treatment groups, but the differences were not statistically significant ($P>0.05$; Fig. 2).

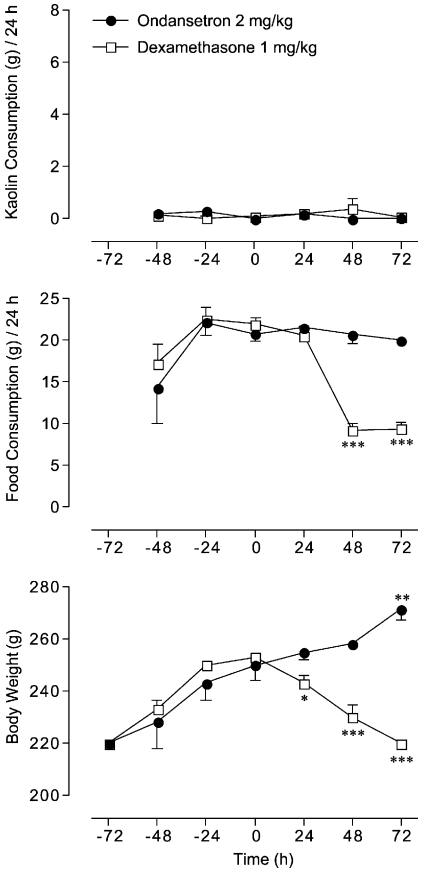

Fig. 3. Action of ondansetron and dexamethasone on kaolin and food ingestion in the rat and their impact on rat weight. Drugs were administered at $t=0$ and then at regular 12-h intervals for the duration of the experiment. Data represent the means ± S.E.M of three determinations. Data statistically different from the respective drug treatments at time = 0 h are indicated as $*P<0.05$, $**P<0.01$, $***P<0.001$ (repeated measures ANOVA with pre-planned contrasts of specified means).

3.3. Effect of ondansetron and dexamethasone on kaolin and food ingestion

It was decided to investigate if ondansetron (2 mg/kg) and dexamethasone (1 mg/kg) had actions to modify kaolin and food intake when administered twice daily, in the absence of cisplatin. In these experiments, rats consumed approximately 0.2 g of kaolin and approximately 14.3–17.2 g of food, on the first day of adaptation. The rats consumed approximately 0.0–0.1 g of kaolin and 21.0–22.0 g of food in the 24-h period prior to drug administration. Ondansetron and dexamethasone had no action to modify kaolin consumption ($P>0.05$). Ondansetron was also inactive to modify food consumption ($P>0.05$) but dexamethasone produced 58.1% ($P<0.001$) and 57.2% ($P<0.001$) reductions in food consumption at 48 and 72 h, respectively, post-drug administration at $t=0$ (Fig. 3). Rats treated with ondansetron continued to gain weight ($P<0.01$) but animals treated with dexamethasone lost approximately 10–13 g/day ($P<0.05$), starting 24 h post-treatment (Fig. 3).

4. Discussion

Previous studies in the rat have used cisplatin at a dose of 10 mg/kg to induce an acute (0–24 h) phase of kaolin consumption that may be analogous to emesis seen in other species (see Introduction). In this regard, cisplatin-induced kaolin intake in the rat (Saeki et al., 2001; Takeda et al., 1993), and the early vomiting induced by cisplatin in other species (see Naylor and Rudd, 1996) is antagonised by ondansetron, to implicate a common role for 5-HT_3 receptors in the mechanisms mediating both pica behaviour and emesis. Yet studies in the ferret, a species with the vomiting reflex, have shown that it is not possible to study delayed emesis when cisplatin is used at 10 mg/kg, because the associated toxicity probably interferes with the development of the retching and vomiting response (Rudd et al., 1994). Further, ondansetron and dexamethasone do not interact predictably in the cisplatin 10 mg/kg model (Rudd and Naylor, 1997). These were concerns of the present studies, where the aim was to investigate if cisplatin could induce acute and delayed phases of kaolin ingestion, that is similar to the pharmacological sensitivity of emetic response exhibited in man.

Using a lower dose of cisplatin 5 mg/kg in the ferret provides a model of acute and delayed emesis where repeated administration of ondansetron and dexamethasone

provide a control of retching and vomiting that is similar to their anti-emetic activity in man (Rudd and Naylor, 1996). For these reasons, and other concerns about the potential non-specific toxicity associated with the use of cisplatin over extended observation periods, we decided to investigate the potential of similar doses of cisplatin to induce acute and delayed phases of kaolin ingestion in the rat. Using this approach, we discovered that cisplatin at 3 mg/kg induced kaolin consumption during the 0–24- and 48–72-h periods, which may be referred to as acute and delayed phases, respectively. Importantly, we also observed that cisplatin decreased food consumption and the rate of weight gain of the rats; a similar situation is seen with the use of cisplatin in the ferret (Fukunaka et al., 1998). Whilst the higher dose of cisplatin 6 mg/kg also induced kaolin consumption during the 0–24-h period, it was associated with a marked suppression of food intake and a consistent weight loss over the 3-day period that we interpreted as an unacceptable toxicity in the model. In addition, and importantly, cisplatin at 6 mg/kg failed to induce delayed kaolin ingestion. Therefore, we decided to focus only on the mechanism of kaolin consumption induced by the lower dose of cisplatin 3 mg/kg. Interestingly, cisplatin at 3 mg/kg represents the threshold dose for rats to exhibit conditioned taste aversions (discussed later) (Rudd et al., 1998).

The previous studies have clearly shown that a single injection of ondansetron 1–2 mg/kg can reduce the acute kaolin ingestion induced by cisplatin 10 mg/kg (Takeda et al., 1993). However, in the present studies, ondansetron at 2 mg/kg, administered twice per day, potentiated cisplatin (3 mg/kg, i.p.)-induced kaolin ingestion during the 0–24-h period. Ondansetron was inactive to modify cisplatin-induced kaolin ingestion during the delayed phase of the response and was also inactive to modify kaolin and food intake when administered alone. The reason(s) for the unexpected action of ondansetron to potentiate cisplatin (3 mg/kg, i.p.)-induced kaolin consumption is unknown. However, it is possible that repeated handling of the rats to administer the second injection of ondansetron or vehicle may have stimulated kaolin ingestion via 5-HT_3 receptor resistant mechanisms that were conditioned at the start of the experiment (i.e. the process of 'handling' acted as the conditioned stimulus to cisplatin). Certainly, cisplatin-induced conditioned taste aversions are not sensitive to 5-HT_3 receptor antagonists and pica can be conditioned (Mele et al., 1992; Mitchell et al., 1977; Rudd et al., 1998). Alternatively, another possible explanation is that different doses of cisplatin may evoke kaolin consumption via different mechanisms. It is possible that activation of 5-HT_3 receptors may serve to reduce kaolin intake in the low-dose cisplatin model, but may potentiate kaolin consumption when cisplatin is used at higher doses. Certainly, it is known that the 5-HT_3 receptor agonist, *m*-chlorophenylbiguanide, can inhibit emesis when administered intravenously (Ravenscroft et al., 1992), but is emetic when administered intraperitoneally (Kamato et al., 1993) and some 5-HT_3 receptor antagonists are emetic and anti-emetic in the pigeon (Preziosi et al., 1992) and *Suncus murinus* (Torii et al., 1991). Whilst the mechanism may be complex, the present studies revealed that the ondansetron-induced potentiation of the cisplatin-induced kaolin consumption is prevented by dexamethasone, to tentatively suggest the involvement of eicosanoids in the mechanism (Vane and Botting, 1996).

The present studies also used dexamethasone as another reference anti-emetic drug. The doses of dexamethasone used in the present studies antagonise cisplatin (5 mg/kg)-induced emesis in the ferret (Sam et al., 2001) and cisplatin- (Mele et al., 1992) and radiation (Cairnie and Leach, 1982)-induced conditioned taste aversions in the rat. Perhaps an ability to reduce conditioned behaviour (set-up by handling) contributes to the action of dexamethasone to reduce the cisplatin-induced kaolin intake in the present studies. However, we are not sure about the specificity of action of dexamethasone, since dexamethasone administered alone, or in combination with ondansetron and cisplatin, caused a reduction of food intake and a marked weight loss. Indeed, dexamethasone also prevents apomorphine-induced kaolin consumption in the rat (Takeda, unpublished observations) and this is not expected since dexamethasone is ineffective to prevent apomorphine-induced emesis in the ferret (Rudd et al., 1996a). Conversely, studies in the ferret show that dexamethasone in combination with granisetron actually improves appetite and reduces weight loss induced by cisplatin (Fukunaka et al., 1998), to suggest that important species differences exist in the ability of glucocorticoids to regulate appetite.

It is possible that treatments reducing appetite may interfere with the usefulness of the pica model by non-selectively reducing kaolin consumption. This may be the case in the present studies where dexamethasone reduced food intake and caused weight loss via mechanisms probably relating its known action to increase carbohydrate catabolism and to generally increase animal behaviour (Beatty et al., 1971; Simpson et al., 1974). However, the action of ondansetron on food ingestion ranges from negligible to the complex (Cooper et al., 1993; Higgins et al., 1992; Kaya et al., 1992) so its action to modify cisplatin-induced kaolin ingestion is difficult to rationalise.

In conclusion, low-dose cisplatin (3 mg/kg) induced acute and delayed phases of kaolin consumption that was prevented by repeated administrations of dexamethasone. Conversely, repeated administration of ondansetron potentiates cisplatin-induced acute kaolin consumption via a dexamethasone-sensitive mechanism. The pharmacological sensitivity of the kaolin ingestion model is therefore different from the clinical situation of nausea and vomiting. The studies also revealed the action of dexamethasone to reduce food intake that may complicate an interpretation of the data with regard to its anti-emetic potential. We advise caution when using multiple drug administrations in the model and in predicting the anti-emetic potential of drugs that have additional properties to modify food consumption. Further

investigations are required to develop the pica model to detect drugs to prevent delayed emesis in man.

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