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Ondansetron, dexamethasone and an NK_1 antagonist block radiation sickness in mice

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Abstract

Radiation sickness is frequently observed in total body irradiation (TBI). We have reported that the kaolin ingestion behavior "pica" may be analogous to nausea and vomiting in mice. We evaluated the effects of anti-emetics on the prevention of radiation-induced pica in mice. After the intraperitoneal injection of ondansetron (OND: 2 mg/kg), dexamethasone (DEX: 2 mg/kg) or CP-99,994 (CP: 15 mg/kg), mice received 9 Gy of TBI, and then kaolin consumption was measured after 24 h. Radiation-induced pica was slightly inhibited by pretreatment with a single administration of OND or DEX, but not by CP (control: 0.69±0.19 g, OND: 0.33±0.06 g, DEX: 0.39±0.07 g, CP: 0.66±0.09 g); it was significantly inhibited by the combination treatment of OND and DEX (control: 0.55±0.09 g, OND+DEX: 0.30±0.06 g, OND+CP: 0.70±0.04 g, DEX+CP: 0.58±0.02 g). The combination of the three drugs completely abolished the behavior (control: 0.67±0.08 g, OND+DEX+CP: 0.10±0.05 g). These results suggest that radiation-induced pica in mice may be useful to evaluate drugs for treatment of radiation sickness and that the combination therapy of a serotonin 5-HT_3 receptor antagonist and a glucocorticosteroid with a neurokinin NK_1 receptor antagonist is effective in reducing the symptom.

Keywords: Anti-emetic drugs; Mice; Nausea and vomiting; Pica; Radiation sickness; Total body irradiation

1. Introduction

Bone marrow transplantation is a valid treatment in patients with hematological malignancies (Costello et al., 2003; Johnson et al., 1998). Prior to bone marrow transplantation, patients often receive total body irradiation (TBI) in order to eliminate malignant cells, and it is a highly emetogenic regimen (Barrett, 1982; Bieri et al., 2001; Buchali et al., 2000). Therapy-induced nausea and vomiting, referred to as radiation sickness, does not result in death, but it can impair the quality of life of the patients and may lead to a discontinuation of therapy. Since serotonin 5-HT_3 receptor antagonists such as ondansetron and granisetron combined with a glucocorticosteroid such as dexamethasone are recommended for prophylaxis during highly emetogenic-radiation therapy in the anti-emetic guidelines for radiation sickness (ASHP Therapeutic Guidelines, 1999; Antiemetic Subcommittee of the MASCC, 1998), these drugs are widely used as the current standard therapy (Kusnierczyk et al., 2002; Tonini et al., 2003; Prentice, 2003; Kirkbride et al., 2000; Abbott et al., 1999). However, many patients receiving anti-emetic drugs still suffer from nausea and vomiting (Tramer et al., 1998). Although recent investigations have suggested that 5-HT_3 receptor antagonists combined with a glucocorticosteroid and neurokinin NK_1 receptor antagonists are useful in preventing chemotherapy-induced emesis (Cocquyt et al., 2001; de Wit et al., 2003), relatively few clinical studies have examined the efficacy of this combination therapy in radiation therapy.

Rodents, e.g. rats and mice, which are the most common laboratory animals, are known as an animal species that do not vomit. However, Takeda et al. previously reported that pica, i.e., an eating disorder that involves the satisfaction of

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a craving by eating kaolin, in rats may be analogous to gastrointestinal discomfort such as nausea and vomiting (Takeda et al., 1993, 1995). Actually, we have found that highly emetogenic X-ray irradiation (i.e., TBI and abdominal irradiation) induced pica in mice and that the increased kaolin consumption was partially inhibited by pretreatment with ondansetron (Yamamoto et al., 2002a). These results indicate that radiation-induced pica could be useful as a behavioral index for the severity of radiation sickness in rats. We have also reported that mice showed pica after administration of an emetic anti-cancer agent, cisplatin (Yamamoto et al., 2002b). In the present study, we examined the radiation-induced pica in mice and investigated the effects of ondansetron (5-HT_3 receptor antagonist), dexamethasone (glucocorticosteroid) and CP-99,994 (NK_1 receptor antagonist) on the behavior.

2. Materials and methods

2.1. Animals

Eight-week-old male mice of *ICR* strain (30–36 g) obtained from Japan SLC (Shizuoka, Japan) were housed in individual home cages (23 × 23 × 20 cm) in a room with a regular light/dark cycle (lights on 7:00–19:00) at a constant temperature (23 ± 1 °C) and humidity (50 ± 5%). They had free access to standard laboratory chow (MF, Oriental Yeast, Osaka, Japan), water and kaolin pellets during the acclimatized period. The kaolin and chow pellets were provided in their respective stainless steel containers (7 × 8 × 3 cm) placed in the home cage. The protocol of this experiment was approved by the Animal Care Committee of Faculty of Medicine, Osaka University and conducted in accordance with the Animal Experiment Guideline of the Committee.

2.2. Preparation of kaolin pellets

Kaolin pellets were prepared according to the previously reported method (Yamamoto et al., 2002b). Briefly, pharmaceutical grade kaolin (hydrated aluminum silicate; Sigma Aldrich Japan, Tokyo, Japan) was mixed with 0.5% (w/w) carmine (Sigma, St Louis, MO, USA) and 1% (w/w) gum arabic (Sigma Aldrich Japan) in distilled water to form similar shapes to chow pellets and then these kaolin pellets were completely dried at room temperature.

2.3. Total body X-ray irradiation

Mice were adapted to the experimental environment for 4 days, and on the day before the experiment kaolin and chow pellets were removed. On the day of the experiment, mice were restrained individually in an acrylic holder (diameter: 2 cm), and then received TBI using a medical linear accelerator (EXL-6SP, Varian Medical Systems K.K., Tokyo, Japan) at a single 3, 6 or 9 Gy (n = 4: each group) dose of 4 MV X-rays at a dose rate of 1.8 Gy/min delivered at a depth of 1 cm with a source target distance of 100 cm. Sham irradiation (n = 4) as a control was performed by placing the mice in an irradiation room surrounded by 10 cm lead shield bricks. Kaolin and chow pellets were provided again immediately after the irradiation, and kaolin pellets were presented for 24 h. The feces of each mouse were collected individually for 2 days after total body irradiation and stored at −20 °C in a refrigerator until analysis.

2.4. The effects of a single anti-emetic drug on radiation-induced pica

Since all mice that received TBI at a single dose of 9 Gy significantly increased kaolin consumption after the irradiation, the dose was selected for further experiments. Ondansetron (2 mg/kg: n = 4), dexamethasone (2 mg/kg: n = 4) or CP-99,994 (15 mg/kg: n = 4) were injected intraperitoneally (i.p.) at 30 min before the total body irradiation of a dose of 9 Gy. The doses of these anti-emetic drugs were selected from our preliminary studies. Control animals (n = 4) received an i.p. injection of saline. Then, kaolin and chow pellets were provided and feces were collected as described above.

2.5. The effects of the combination of anti-emetic drugs on radiation-induced pica

Mice were administered three sets of two anti-emetic drug combinations, i.e., ondansetron (2 mg/kg, i.p.) and dexamethasone (2 mg/kg, i.p.) (OND + DEX), dexamethasone and CP-99,994 (15 mg/kg, i.p.) (DEX + CP), and ondansetron and CP-99,994 (DEX + CP) (n = 4, each group) before 30 min of 9 Gy X-ray TBI. Control animals (n = 4) received an i.p. injection of saline twice. Kaolin and chow pellets were provided after irradiation and the feces were collected as described above.

2.6. The effects of the combination of three anti-emetic drugs on radiation-induced pica

Mice were administered the three anti-emetic drugs, i.e., ondansetron (2 mg/kg, i.p.), dexamethasone (2 mg/kg, i.p.) and CP-99,994 (15 mg/kg, i.p.) (OND + DEX + CP) (n = 4) before 30 min of 9 Gy X-ray TBI. Control animals (n = 4) received an i.p. injection of saline three times. Kaolin and chow pellets were provided after irradiation and the feces were collected as mentioned above.

2.7. Quantification of kaolin consumption in mice

To determine the exact amount of kaolin consumption in mice, we measured the contents of carmine, a dye not

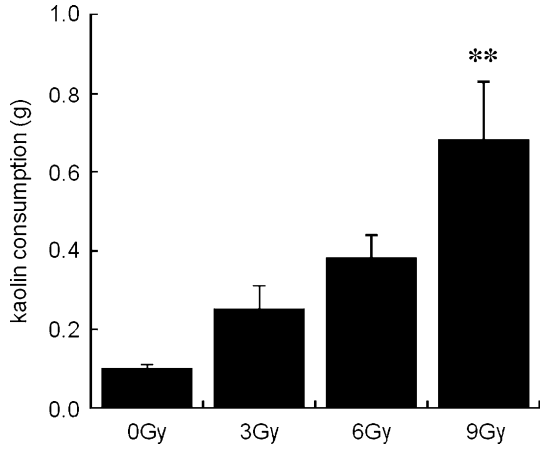

Fig. 1. Effects of total body X-ray irradiation on kaolin intake in mice. Mice received total body irradiation (TBI) at a single 3, 6 or 9 Gy dose of X-ray using a medical linear accelerator. Columns and bars represent the mean±S.E.M. of the kaolin consumption measured at 24 h after TBI. The data were analyzed for any significant differences using a one-way analysis of the variance (ANOVA), followed by post hoc Newman–Keuls multiple comparison tests. *$p<0.05$ vs. sham irradiation (0 Gy).

absorbed in the gastrointestinal tract, in the feces according to the previously described method (Yamamoto et al., 2002b). Briefly, after drying completely, collected feces were weighed, soaked in distilled water (19 ml/g of feces) for 1 h and homogenized by sonication (Sonifire, Branson, Danbury, CT, USA). After the addition of 3 N NaOH (1 ml/g of feces), the homogenate was mixed vigorously and centrifuged at 35,000 $\times g$ for 10 min. An 80 μl aliquot of the supernatant was diluted with 920 μl of distilled water. The absorbances at 550 and 700 nm of the fecal extract were measured using a spectrophotometer (U-2000, Hitachi, Tokyo, Japan) to determine the fecal carmine contents. The kaolin consumption was calculated from the carmine content in the feces.

2.8. Drugs used

Ondansetron hydrochloride (GlaxoSmithKlein, Tokyo, Japan), dexamethasone 21-phosphate disodium salt (Sigma-Aldrich) and CP-99,994 (+)-[(2S,3S)-3-(2-methoxy-benzyl-amino)-2-phenylpiperidine] (Pfizer, Groton and New London, CT, USA) were formulated in saline and administered in a volume of 10 ml/kg. Doses are expressed as the free base.

2.9. Data analysis

The data were represented as means±S.E.M. of kaolin consumption and analyzed for any significant differences using a one-way analysis of the variance (ANOVA), followed by post hoc Newman–Keuls multiple comparison tests. Differences were considered significant when $p<0.05$.

3. Results

3.1. The effect of total body irradiation on pica in mice

In the experiments, we did not use mice that ate more than 0.10 g of kaolin during the acclimatization period, because these mice bite and break kaolin pellets into small pieces maybe out of curiosity during the experimental period. As shown in Fig. 1, the kaolin consumption estimated by the fecal carmine content was increased by TBI in a dose-dependent manner (sham: 0.10±0.01 g, 3 Gy: 0.25±0.06 g, 6 Gy: 0.38±0.06 g, 9 Gy: 0.68±0.15 g, $F(3,12)=6.13$, $p<0.01$). Since a dose of 9 Gy of TBI significantly increased kaolin consumption by approximately 680% compared to the sham-irradiated mice, this dose was selected for the subsequent evaluation of the effect of anti-emetic drugs on the radiation-induced pica.

3.2. The effects of a single anti-emetic drug on radiation-induced pica

Ondansetron at 2 mg/kg, dexamethasone at 2 mg/kg or CP-99,994 at 15 mg/kg alone did not induce pica (data not shown). As shown in Fig. 2, the radiation-induced kaolin consumption was slightly reduced by a single treatment of ondansetron at a dose of 2 mg/kg and by dexamethasone at a dose of 2 mg/kg to 48% and 57% of the control, respectively, but there were no statistical significances. A single treatment of CP-99,994 at a dose of 15 mg/kg did not produce any change in the kaolin

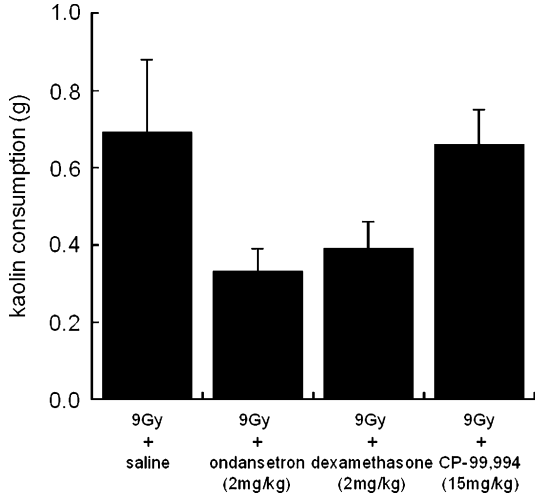

Fig. 2. Effect of single therapy of anti-emetic drugs on radiation-induced pica after 9 Gy of TBI in mice. Anti-emetic drugs ondansetron (2 mg/kg), dexamethasone (2 mg/kg) and CP-99,994 (15 mg/kg) were intraperitoneally injected 30 min before 9 Gy of TBI. Columns and bars represent the mean±S.E.M. of the kaolin consumption measured at 24 h after TBI. The data were analyzed for any significant differences using a one-way analysis of the variance (ANOVA), followed by post hoc Newman–Keuls multiple comparison tests.

consumption. The average kaolin consumptions in each treatment were: 0.69±0.19, 0.33±0.06, 0.39±0.07 and 0.66±0.09 g, respectively. However, all the treatments did not affect their food consumption significantly (data not shown).

3.3. The effects of combination treatments of anti-emetic drugs on radiation-induced pica

No paired combinations of anti-emetic drugs alone induced pica in mice ($n=4$, each groups) (data not shown). As shown in Fig. 3, OND+DEX produced a significant reduction in TBI-induced kaolin consumption to 54% of the control, but no significant changes were seen in the combination of OND+CP or DEX+CP. The average kaolin consumptions in each treatment were; control: 0.55±0.09 g, OND+DEX: 0.30±0.06 g, OND+CP: 0.70±0.04 g, and DEX+CP: 0.58±0.02 g. However, these treatments did not affect their food consumption significantly (data not shown).

On the other hand, as shown in Fig. 3, TBI-induced kaolin consumption was significantly and completely suppressed by pretreatment with a combination of the three drugs (control: 0.67±0.08 g, OND+DEX+CP: 0.10±0.05 g, $F(5,18)=12.21$, $p<0.01$). The inhibitory effect of the three drug combination was superior to that of the combination of ondansetron plus dexamethasone ($p<0.05$). However, this treatment did not affect their food consumption significantly (data not shown).

4. Discussion

The vomiting reflex is one of the visible criteria for emesis (AGA Technical Review, 2001). Thus, laboratory animals that possess a vomiting reflex in response to radiation, such as dogs, ferrets, monkeys and *Suncus murinus* have been used in the study of radiation-induced vomiting (King, 1990; Torii et al., 1993). Nausea, in contrast, is a subjective and unpleasant symptom usually described as recognition of the need to vomit (AGA Technical Review, 2001). Visual Analogue Scales that are based on verbal communication have been usually used to assess nausea in human subjects (Boogaerts et al., 2000), but no reliable methods are available to determine the severity of nausea in animals.

Conditioned taste aversion (CTA) has often been used in anti-emetic research and the behavioral change may be representative of gastrointestinal discomfort in species that are capable/non-capable of vomiting (Welzl et al., 2001; Smith et al., 2001). However, it is known that the acquisition of CTA needs a pairing of a learned aversion with a subsequent stimulus which induces illness. Pica was found in a variety of animal species with or without the vomiting reflex in response to emetic stimuli (Takeda et al., 1993; Mitchell et al., 1976; Walker et al., 1985; Houpt, 1982; Krishnamani and Mahaney, 2000). The etiology of pica has been hypothesized to supply deficient essential substances such as zinc, calcium and iron by eating earth, but a previous report indicated that

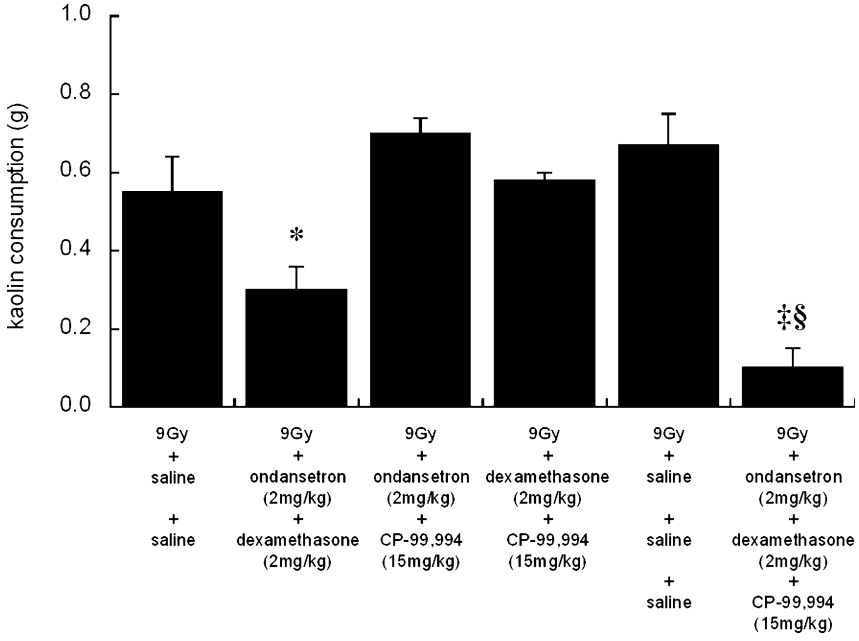

Fig. 3. Effect of the combination therapy of anti-emetic drugs on radiation-induced pica after 9 Gy TBI in mice (2 or 3 anti-emetic drugs study). Anti-emetic drugs (ondansetron (2 mg/kg), dexamethasone (2 mg/kg) and CP-99,994 (15 mg/kg)) were intraperitoneally injected 30 min before the 9 Gy of TBI. Columns and bars represent the mean±S.E.M. of the kaolin consumption measured at 24 h after TBI. The data were analyzed for any significant differences using a one-way analysis of the variance (ANOVA), followed by post hoc Newman–Keuls multiple comparison tests. *$p<0.05$ vs. TBI 9 Gy+saline+saline. ‡$p<0.01$ vs. TBI 9Gy+saline+saline+saline. §$p<0.05$ vs. TBI 9Gy+ondansetron+dexamethasone.

the behavior has a role in the detoxification of dietary toxins or elimination of gastrointestinal discomfort by ingesting clay (Johns and Duquette, 1991). Therefore, the behavior may be used as a behavioral index for the assessment of gastrointestinal discomfort, i.e., nausea and vomiting.

In this study, we found that 9 Gy of TBI, approximately LD_{50} for mice, significantly increased kaolin consumption (Fig. 1). Young reported that a single dose of 3–4 Gy, nearly LD_{50} in humans, was sufficient to elicit a 100% response to radiation-induced nausea and vomiting in humans (Young, 1986), indicating that the dose that causes radiation-induced pica in mice is comparable to that of radiation sickness in humans.

Radiation sickness is more frequently observed in patients receiving TBI or upper-abdominal irradiation than head and neck or breast irradiation (Feyer et al., 1998; Danjoux et al., 1979). The etiology of the symptom has been postulated to be that the released serotonin from enterochromaffin cells in the mucosa of the upper gastrointestinal tract activates the vomiting center, such as the area postrema and the nucleus of the solitary tract, by depolarizing the vagal afferents via 5-HT_3 receptors (Naylor and Rudd, 1996). In fact, 5-HT_3 receptor antagonists such as ondansetron, granisetron and tropisetron, are clinically effective in preventing emesis in patients undergoing highly emetic radiation therapy (Tonini et al., 2003; Prentice, 2003). Dexamethasone is also known as an effective agent for radiation sickness (Kirkbride et al., 2000; Abbott et al., 1999). It is considered that the potent anti-inflammatory action, the decrease in 5-HT turnover in the central nervous system and the reduction in permeability of the blood–brain barrier may be involved in the action of the anti-emetic efficacy of glucocorticosteroids (Kovac, 2003).

We demonstrated that a single administration of ondansetron at a dose of 2 mg/kg or dexamethasone at a dose of 2 mg/kg did inhibit radiation-induced pica in mice, although the differences were not significant (Fig. 2). Recent studies have demonstrated that the combination of 5-HT_3 receptor antagonists with glucocorticosteroids enhances the anti-emetic efficacy of 5-HT_3 receptor antagonists in human patients receiving emetic chemotherapy and radiation therapy (Antiemetic Subcommittee of the MASCC, 1998; Tonini et al., 2003; Joss et al., 1994). In this respect, we confirmed that the inhibitory effect of combination therapy of ondansetron with dexamethasone on pica in mice is superior to that of a single administration of each drug (Fig. 3). These findings suggest that the etiology of radiation-induced pica is similar to that of radiation sickness in human patients, since TBI increase kaolin consumption in mice via similar 5-HT_3 receptor antagonist and glucocorticosteroid-sensitive mechanisms.

Previous studies demonstrated that an NK_1 receptor antagonist, which was reported to have a broader spectrum of anti-emetic activity than 5-HT_3 receptor antagonists, was effective in controlling the vomiting reflex induced by X-ray irradiation in ferrets (Bountra et al., 1993; Gardner et al., 1995). In this study, we observed that both a single administration of CP-99,994 and the combination with ondansetron or dexamethasone failed to suppress the radiation-induced pica in mice (Figs. 2 and 3). Recent clinical reports revealed the administration of NK_1 receptor antagonists have been less successful in reducing acute nausea by emetogenic chemotherapy than the current standard therapy using a 5-HT_3 receptor antagonist and dexamethasone, but the triple therapy (5-HT_3 antagonist, dexamethasone and NK_1 antagonist) significantly reduced nausea compared to the standard therapy (Cocquyt et al., 2001; Van Belle et al., 2002; Campos et al., 2001). Indeed, we demonstrated that the increased kaolin consumption on the day following the TBI was significantly and completely suppressed by the combination treatment of CP-99,994 with ondansetron and dexamethasone, and that the antagonizing effect of the 5-HT_3 receptor antagonist and dexamethasone was increased by combination with an NK_1 receptor antagonist (Fig. 3). The data may be interpreted as suggesting that pica in mice may be indicative of exhibiting nausea rather than vomiting, and that the NK_1 receptor may also contribute to the development of radiation-induce pica in mice.

In summary, this study demonstrated that TBI caused pica in mice and that the combination of 5-HT_3 receptor antagonists with glucocorticosteroids and NK_1 receptor antagonists was effective to suppress the behavior, suggesting that the triple therapy is the best for preventing radiation sickness and that the radiation-induced pica in mice is a useful assessment tool for studying the anti-emetic regimens of radiation sickness, especially radiation-induced nausea.

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References

Abbott B, Ippoliti C, Bruton J, Neumann J, Whaley R, Champlin R. Antiemetic efficacy of granisetron plus dexamethasone in bone marrow transplant patients receiving chemotherapy and total body irradiation. Bone Marrow Transplant 1999;23:265–9.

AGA. Technical review on nausea and vomiting. Gastroenterology 2001;120:263–86.

Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia consensus conference. Ann Oncol 1998;9:811–9.

ASHP. Therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. Am J Health Syst Pharm 1999;56:729–64.

Barrett A. Total body irradiation (TBI) before bone marrow transplantation in leukaemia: a co-operative study from the European group for bone marrow transplantation. Br J Radiol 1982;55:562–7.

Bieri S, Helg C, Chapuis B, Miralbell R. Total body irradiation before allogeneic bone marrow transplantation: is more dose better? Int J Radiat Oncol Biol Phys 2001;49:1071–7.

Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM. Assessment of postoperative nausea using a visual analogue scale. Acta Anaesthesiol Scand 2000;44:470–4.

Bountra C, Bunce K, Dale T, Gardner C, Jordan C, Twissell D, et al. Anti-emetic profile of a non-peptide neurokinin NK_1 receptor antagonist, CP-99,994, in ferrets. Eur J Pharmacol 1993;249:R3–4.

Buchali A, Feyer P, Groll J, Massenkeil G, Arnold R, Budach V. Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation. Radiother Oncol 2000;54:157–62.

Campos D, Pereira JR, Reinhardt RR, Carracedo C, Poli S, Vogel C, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001;19:1759–67.

Cocquyt V, Van Belle S, Reinhardt RR, Decramer ML, O'Brien M, Schellens JH, et al. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. Eur J Cancer 2001;37:835–42.

Costello RT, Rey J, Fauriat C, Gastaut JA, Olive D. New approaches in the immunotherapy of haematological malignancies. Eur J Haematol 2003;70:333–45.

Danjoux CE, Rider WD, Fitzpatrick PJ. The acute radiation syndrome A memorial to William Michael Court-Brown. Clin Radiol 1979;30: 581–4.

de Wit R, Herrstedt J, Rapoport B, Carides AD, Carides G, Elmer M, et al. Addition of the oral NK_1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003;21:4105–11.

Feyer PC, Stewart AL, Titlbach OJ. Aetiology and prevention of emesis induced by radiotherapy. Support Care Cancer 1998;6:253–60.

Gardner CJ, Twissell DJ, Dale TJ, Gale JD, Jordan CC, Kilpatrick GJ, et al. The broad-spectrum anti-emetic activity of the novel non-peptide tachykinin NK_1 receptor antagonist GR203040. Br J Pharmacol 1995;116:3158–63.

Houpt K. Ingestive behavior problems of dogs and cats. Vet Clin North Am Small Anim Pract 1982;12:683–92.

Johns T, Duquette M. Detoxification and mineral supplementation as functions of geophagy. Am J Clin Nutr 1991;53:448–56.

Johnson PW, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA. Bone marrow and peripheral blood stem cell transplantation for malignancy. Health Technol Assess 1998;2:1–187.

Joss RA, Bacchi M, Buser K, Kirchner V, Neuenschwander H, Orth B, et al. Ondansetron plus dexamethasone is superior to ondansetron alone in the prevention of emesis in chemotherapy-naive and previously treated patients Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 1994;5:253–8.

King GL. Animal models in the study of vomiting. Can J Physiol Pharmacol 1990;68:260–8.

Kirkbride P, Bezjak A, Pater J, Zee B, Palmer MJ, Wong R, et al. Dexamethasone for the prophylaxis of radiation-induced emesis: a national cancer institute of Canada clinical trials group phase III study. J Clin Oncol 2000;18:1960–6.

Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. Drug Saf 2003;26:227–59.

Krishnamani R, Mahaney WC. Geophagy among primates: adaptive significance and ecological consequences. Anim Behav 2000;59: 899–915.

Kusnierczyk NM, Saunders EF, Dupuis LL. Outcomes of antiemetic prophylaxis in children undergoing bone marrow transplantation. Bone Marrow Transplant 2002;30:119–24.

Mitchell D, Wells C, Hoch N, Lind K, Wood SC, Mitchell LK. Poison induced pica in rats. Physiol Behav 1976;17:691–7.

Naylor RJ, Rudd JA. Mechanisms of chemotherapy/radiotherapy-induced emesis in animal models. Oncology 1996;53(Suppl 1):8–17.

Prentice HG. Granisetron in the control of nausea and vomiting associated with bone marrow transplantation: a review of its efficacy and tolerability. Support Care Cancer 2003;11:501–8.

Smith JE, Friedman MI, Andrews PL. Conditioned food aversion in *Suncus murinus* (house musk shrew)—a new model for the study of nausea in a species with an emetic reflex. Physiol Behav 2001;73:593–8.

Takeda N, Hasegawa S, Morita M, Matsunaga T. Pica in rats is analogous to emesis: an animal model in emesis research. Pharmacol Biochem Behav 1993;45:817–21.

Takeda N, Hasegawa S, Morita M, Horii A, Uno A, Yamatodani A, et al. Neuropharmacological mechanisms of emesis: I Effects of antiemetic drugs on motion- and apomorphine-induced pica in rats. Methods Find Exp Clin Pharmacol 1995;17:589–96.

Tonini G, Vincenzi B, Santini D, La Cesa A, Finolezzi E, Onori N, et al. Prevention of radiotherapy-induced emesis. J Exp Clin Cancer Res 2003;22:17–22.

Tramer MR, Reynolds DJ, Stoner NS, Moore RA, McQuay HJ. Efficacy of 5-HT_3 receptor antagonists in radiotherapy-induced nausea and vomiting: a quantitative systematic review. Eur J Cancer 1998;34:1836–44.

Torii Y, Shikita M, Saito H, Matsuki N. X-irradiation-induced emesis in *Suncus murinus*. J Radiat Res (Tokyo) 1993;34:164–70.

Van Belle S, Lichinitser MR, Navari RM, Garin AM, Decramer ML, Riviere A, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. Cancer 2002;94:3032–41.

Walker AR, Walker BF, Jones J, Verardi M, Walker C. Nausea and vomiting and dietary cravings and aversions during pregnancy in south African women. Br J Obstet Gynaecol 1985;92:484–9.

Welzl H, D'Adamo P, Lipp HP. Conditioned taste aversion as a learning and memory paradigm. Behav Brain Res 2001;25:205–13.

Yamamoto K, Takeda N, Yamatodani A. Establishment of an animal model for radiation-induced vomiting in rats using pica. J Radiat Res (Tokyo) 2002;43:135–41.

Yamamoto K, Matsunaga S, Matsui M, Takeda N, Yamatodani A. Pica in mice as a new model for the study of emesis. Methods Find Exp Clin Pharmacol 2002;24:135–8.

Young RW. Mechanism and treatment of radiation-induced nausea and vomiting. In: Davis CJ, Lakes-Bakaar GV, Grahame-Smith DG, editors. Nausea and vomiting: mechanisms and treatment. Berlin: Springer; 1986. p. 94–109.