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Cisplatin-induced emesis in the cat: effect of granisetron and dexamethasone

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Abstract

The emetic action of cisplatin was investigated in the cat using a closed circuit video recording system. In initial investigations, cisplatin 3 and 5 mg/kg, i.v. induced emesis over a 2-day period following a latency of 17.6 ± 9.6 and 15.6 ± 7.8 h, respectively. The anti-emetic efficacy of granisetron and dexamethasone was investigated in the cisplatin 5 mg/kg, i.v.-induced emesis model. In these experiments, cisplatin induced 47.0 ± 14.0 and 20.0 ± 9.0 retches + vomits on days 1 and 2, respectively, following a latency of 2.4 ± 0.4 h. Granisetron (1 mg/kg, i.m.) administered three times per day reduced significantly the retching + vomiting response induced by cisplatin on days 1 and 2 by 100.0% ($P < 0.05$) and 75.0% ($P < 0.05$), respectively; dexamethasone (0.01–1 mg/kg, i.m.) administered three times per day reduced significantly the retching + vomiting response by 68.8–100.0% ($P < 0.05$) and 33.3–100.0% ($P < 0.05$) on days 1 and 2, respectively. The emetic action of cisplatin 7.5 mg/kg, i.v. was also investigated. This dose of cisplatin-induced emesis following a latency of 1.2 ± 0.2 h and comprised 119.0 ± 20.8 retches + vomits over a 24-h period. Granisetron and dexamethasone antagonized the emesis occurring in the first 3-h period ($P < 0.05$) but were less effective to antagonize the subsequent emetic response ($P > 0.05$). The pharmacological sensitivity of low dose cisplatin-induced emesis in the cat is variable but unique and not representative of the clinical situation.

Keywords: Cisplatin; Anti-emesis; (Cat)

1. Introduction

Cisplatinum-based chemotherapy is well known to be associated with the side-effects of nausea and vomiting (Perez and Gandara, 1992). The emesis that occurs in man can be classified into 'acute' and 'delayed' phases (Kris et al., 1985). Acute emesis occurs during the first 24 h following chemotherapy and is highly susceptible to antagonism by 5-HT_3 receptor antagonists. Delayed emesis occurs 24–120 h post the start of chemotherapy and is less sensitive to treatment with 5-HT_3 receptor antagonists (Kris et al., 1994). Importantly, corticosteroids improve the control of both phases when used in combination with other anti-emetic drugs (Chevallier et al., 1994; Chiara et al., 1995; Latreille et al., 1995); the effect to reduce delayed emesis is more marked (Kris et al., 1994; Latreille et al., 1998). Unfortunately, however, delayed emesis remains a clinical problem and attempts have been made to develop animal models of cisplatin-induced acute and delayed emesis to facilitate an investigation of the mechanisms involved (Rudd and Naylor, 1994; Rudd et al., 1994; Milano et al., 1995; Tanihata et al., 1998).

The cat is a species that has been used to study the mechanisms involved in cisplatin-induced emesis (King, 1990). The previous studies only focused on the emesis occurring during the first 4–8 h after the administration of cisplatin. The studies revealed that the mechanism of the emesis involves the area postrema, vagal and splanchnic nerves (McCarthy and Borison, 1984; Miller and Ruggiero, 1994) and the 5HT_3 receptor (Smith et al., 1988; Lucot, 1989). A few other studies have reported the anti-emetic potential of phenothiazines (Brand et al., 1954; McCarthy and Borison, 1981), cannabinoids (London et al., 1979; McCarthy and Borison, 1981) and 5-HT_{1A} receptor agonists (Lucot and Crampton, 1988). However, an assessment of each compounds anti-emetic potential over the first 4- to 8-h period of emesis is not likely to predict

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the activity of the compound to prevent delayed emesis in man (Naylor and Rudd, 1996).

In the present studies, we have used the cat and longer observation times in an attempt to develop a new model of cisplatin-induced acute and delayed emesis. Granisetron, a selective $5HT_3$ receptor antagonist (Sanger and Nelson, 1989) and dexamethasone, a corticosteroid (Swartz and Dluhy, 1978), were used as respective anti-emetic agents to characterize the profile of the cisplatin-induced emetic response. The preliminary data are discussed in terms of the usefulness of the cat model to anti-emesis research.

2. Materials and methods

2.1. Animals

The experiments were performed on male (3.4–5.6 kg) and female (1.7–3.4 kg) cats bred at the Chinese University of Hong Kong. Prior to the experiments, they were housed communally at 22 ± 2°C and had free access to food (Feline Diet® 5003, PMI® Feeds, USA) and water. On the day of the experiment, each cat was presented with approximately 200 g of commercially available tinned cat food (Whiskas® Effen Foods, Australia) 30 min before being transferred to the laboratory. All experiments were conducted in accordance with the Animal Research Ethics Committee, The Chinese University of Hong Kong.

2.2. Administration of drugs

To facilitate the intravenous administration of drugs, the animals were lightly anaesthetized with 5% halothane (carrier: N_2 80%, O_2 20%) and a temporary cannula was inserted into the cephalic vein. Cisplatin (3–7.5 mg/kg) was infused intravenously over a 4-min period (time = 0 min) followed immediately by an intramuscular injection of granisetron (1 mg/kg), dexamethasone (0.01–1 mg/kg) or their respective vehicles. The cannula was removed and the animals transferred to individual observation cages for the assessment of emesis. All animals were conscious within 1–5 min of discontinuation of the anaesthetic. During the experiments, the animals received further intramuscular drug/vehicle injections at regular 8-h intervals. Cat food (Feline Diet® 5003, PMI® Feeds, USA) and water was available ad libitum.

2.3. Measurement of emesis

Animal behavior was recorded remotely using a closed circuit video recording system and analyzed at the end of the experiment. Emesis was characterized by rhythmic abdominal contractions that were either associated with the oral expulsion of solid or liquid material from the gastrointestinal tract (i.e., vomiting) or not associated with the passage of material (i.e., retching movements). Episodes of retching and/or vomiting were considered separate when the animal changed its location in the observation cage or when the interval between retches and/or vomits exceeded 5 s.

2.4. Data analysis

In each animal, the latency to retch or vomit following the administration of the respective emetogen and the total number episodes of retching and/or vomiting were calculated for the duration of the experiment. Latency data is expressed as the mean time (min) of only the animals that retched or vomited; all other data is expressed as the mean $\pm$ S.E.M. The significance of differences between treatments was assessed by a one- or two-way analysis of variance (ANOVA) followed by a Fisher's Protracted Least Significant Difference (PLSD) test (Statview®, Abacus Concepts, USA) and is indicated as $P < 0.05$.

2.5. Drugs

Cisplatin (David Bull Laboratories, Australia), granisetron hydrochloride (SmithKline Beecham Pharmaceuticals, England) and dexamethasone sodium phosphate (Sigma, USA) were formulated in saline (0.9% w/v). Cisplatin was administered in a volume of 5 ml/kg. All other drugs were administered in a volume of 0.05 ml/kg. Doses, except for cisplatin, are expressed as the free base.

3. Results

3.1. Profile of cisplatin (3 and 5 mg/kg)-induced emesis during a 48-h observation period

We conducted a preliminary study to ascertain the optimal observation times to use in the subsequent antagonism of emesis studies. We initially determined that 48 h was an acceptable observation time since the cats condition would rapidly deteriorate after this period. In the preliminary experiments, cisplatin 3 mg/kg, i.v. induced a retching and vomiting response in three out of four cats following a latency of 17.6 ± 9.6 h (the cats responding had individual latencies of 35.7, 14.5 and 2.7 h). The emesis that occurred during the 48-h observation period comprised 25.3 ± 21.4 and 73.6 ± 64.0 retches + vomits that occurred on days 1 and 2, respectively (Fig. 1). The higher dose of cisplatin 5 mg/kg, i.v.-induced emesis in four out of four cats following a latency of 15.6 ± 7.8 h (individual latencies: 2.8, 1.6, 31.2 and 26.9 h) and comprised 29.5 ± 17.3 and 46.0 ± 10.6 retches + vomits that occurred on days 1 and 2, respectively (Fig. 1). There were no significant differences between the magnitude of retching + vomiting responses induced by cisplatin 3 and 5 mg/kg, i.v. during the 0–24-, 24–48-, or 0–48-h periods ($P > 0.05$).

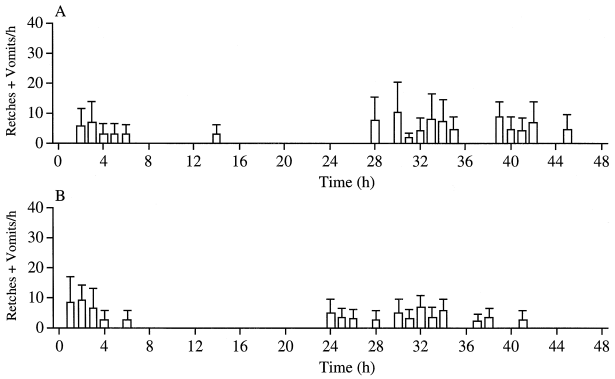

Fig. 1. The profile of cisplatin-induced retching + vomiting in the cat during a 48-h observation period. Cisplatin 3 mg/kg (A) and 5 mg/kg (B) was administered intravenously at $t = 0$. Results represent the mean ± S.E.M of the total numbers of retches + vomits occurring in 1-h time intervals ($n = 4$).

3.2. The ability of granisetron and dexamethasone to antagonize cisplatin (5 mg / kg)-induced emesis

Cisplatin 5 mg/kg was selected as the most reliable dose causing emesis in all cats during the preliminary studies. However, in the subsequent series of experiments, emesis occurred following a shorter latency of 2.4 ± 0.4 h and comprised 47.0 ± 14.0 and 20.0 ± 9.0 retches + vomits on days 1 and 2, respectively (Fig. 2). The administration of granisetron 1 mg/kg administered intramuscularly three times per day reduced respectively the retching + vomiting response induced by cisplatin on day 1 and day 2 by 100.0% ($P < 0.05$) and 75.0% ($P < 0.05$), respectively; retching and vomiting was prevented completely in two out of three cats and the latency to onset of retching or vomiting in the unprotected cat was 24.8 h. Dexamethasone at 0.01, 0.1 and 1.0 mg/kg administered intramuscularly three times per day reduced respectively the retching + vomiting response induced by cisplatin by 68.8% ($P < 0.05$), 100.0% ($P < 0.05$), and 89.4% ($P < 0.05$) on day 1 and by 55.0% ($P < 0.05$), 100.0% ($P < 0.05$), and 38.3% ($P < 0.05$) on day 2.

3.3. The ability of granisetron and dexamethasone to antagonize cisplatin (7.5 mg / kg)-induced emesis

In the initial experiments we found that the emesis induced by cisplatin 5 mg/kg, i.v. was variable but highly susceptible to antagonism by granisetron and dexamethasone (Sections 3.1 and 3.2). We decided, therefore, to investigate the anti-emetic activity of granisetron and dexamethasone against a higher dose of cisplatin 7.5 mg/kg, i.v. In these experiments, cisplatin 7.5 mg/kg, i.v. induced retching + vomiting in three out of three cats following a latency of 1.2 ± 0.21 h. However, the cat's condition rapidly deteriorated after 24 h to restrict the use of longer observation times. Granisetron 1 mg/kg was most effective ($P < 0.05$) to antagonise retching + vomiting during the first 3 h of the observation period (controls: 62.3 ± 14.5 retches + vomits; granisetron treated animals: 0.0 ± 0.0 retches + vomits; see Fig. 3). Dexamethasone at the doses of 0.01, 0.1 and 1.0 mg/kg reduced the retching + vomiting response during the initial 3 h observation time by 28.9% ($P > 0.05$), 100.0% ($P < 0.05$) and 9.6% ($P > 0.05$), respectively; some of the reductions were statistically significant. None of the drug treatments affected significantly the retching + vomiting response that occurred during the subsequent 4–24 h observation period ($P > 0.05$).

Analysis of data collected during the entire 0–24-h period revealed a 26.3% non-significant ($P > 0.05$) reduction of retching + vomiting by granisetron 1 mg/kg administered intraperitoneally three times per day. Dexamethasone 1 mg/kg administered intraperitoneally three times per day produced 46.5%, 80.5% and 27.2% reduc-

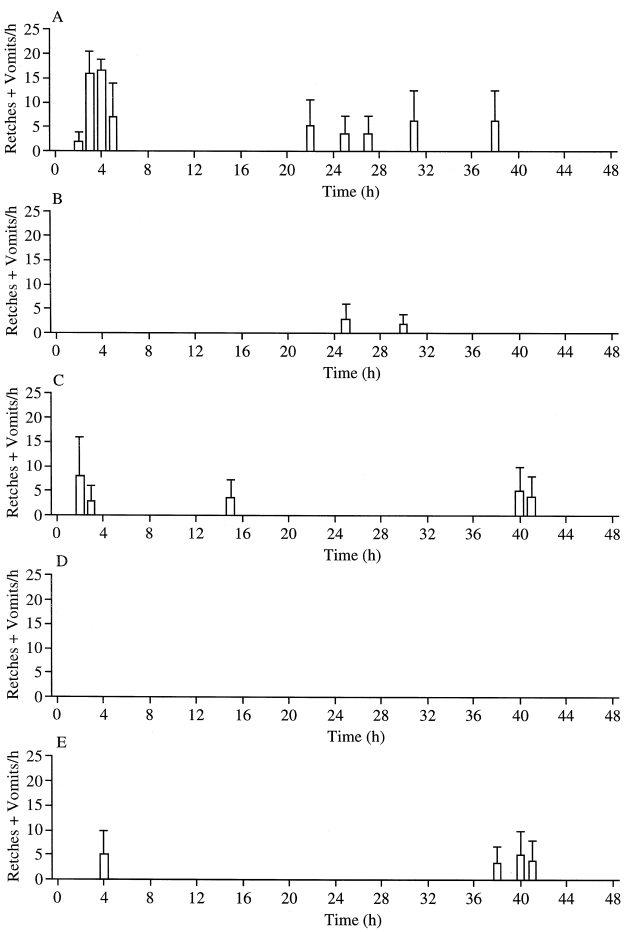

Fig. 2. The effect of a three times per day administration of (A) saline 0.05 ml/kg, i.m., (B) granisetron 1 mg/kg, i.m., (C) dexamethasone 0.01 mg/kg, i.m., (D) dexamethasone 0. 1 mg/kg, i.m. or (E) dexamethasone 1.0 mg/kg, i.m. on the profile of retching + vomiting in the cat induced by a single dose of cisplatin 5 mg/kg, i.v. Results represent the mean ± S.E.M of the total numbers of retches + vomits occurring in 1-h time intervals ($n = 3$).

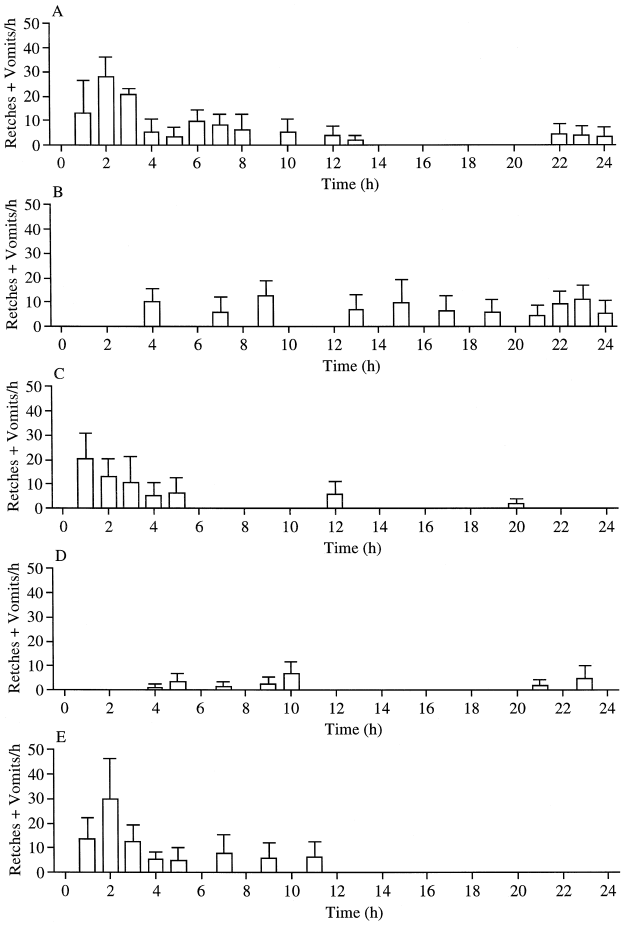

Fig. 3. The effect of a three times per day administration of (A) saline 0.05 ml/kg, i.m., (B) granisetron 1 mg/kg, i.m., (C) dexamethasone 0.01 mg/kg, i.m., (D) dexamethasone 0.1 mg/kg, i.m. or (E) dexamethasone 1.0 mg/kg, i.m. on the profile of retching + vomiting in the cat induced by a single dose of cisplatin 7.5 mg/kg, i.v. Results represent the mean ± S.E.M of the total numbers of retches + vomits occurring in 1-h time intervals ($n = 3$–4).

tions, respectively in retching + vomiting but the reductions were not statistically significant ($P > 0.05$).

4. Discussion

4.1. Cisplatin 3 and 5 mg / kg emesis models

In the present studies, we have attempted to use a minimum number of animals to provide meaningful data on the suitability of the cat to model cisplatin-induced acute and delayed emesis. In our initial studies, cisplatin 3–5 mg/kg was found to be capable of inducing emesis that occurred over a 2-day period. Only three out of four cats vomited to the lower dose of cisplatin 3 mg/kg. Therefore, our studies primarily focused on the emesis induced by cisplatin 5 mg/kg as the more reliable dose to induce a retching and vomiting response. Unfortunately, the latency data obtained between experiments with cisplatin 5 mg/kg was variable and may be a reflection of the small number of animals used. However, variation in latency data and other parameters is also apparent at higher doses of cisplatin (7.5–10 mg/kg) in this species (McCarthy and Borison, 1984; Lucot, 1989; Lucot and Crampton, 1988; Smith et al., 1988; King, 1990; Milano et al., 1991). Such variation has also been reported in the ferret and is presumed to occur because of using close to threshold doses of cisplatin to induce emesis (Rudd et al., 1996b). However, while the latency data may be considered variable, the variation of the magnitude of retching and vomiting during the 0–48-h period was reasonably consistent.

Cisplatin at both 3 and 5 mg/kg induced generalised toxicity that limited the observation period to 48 h. Nevertheless, during this period, the temporal profile of emesis appeared similar to that seen in man since there were distinct phases of emesis separated by a period of relative inactivity (between 8 and 20 h). However, both granisetron and dexamethasone were highly effective to prevent the emesis occurring on both days 1 and 2 and this is not consistent with their action in the clinic (see Introduction) suggesting that the pharmacological sensitivity is unique. The emesis occurring in the cat to cisplatin 5 mg/kg is therefore not ideally representative of the acute and delayed emesis experienced in the clinic and may not be reliable to use to detect novel anti-emetic drugs to prevent delayed emesis in man. The potential large variation in the emetic sensitivity of the cat to cisplatin poses an additional problem to future investigations into acute and delayed emesis in this species.

In our experience, the toxicity of cisplatin in the cat was much greater than seen in the ferret (Rudd et al., 1996b) or reported in the piglet (Milano et al., 1995) or pigeon (Tanihata et al., 1998) and may be due to a species-specific primary pulmonary toxicity (Knapp et al., 1987).

4.2. Cisplatin 7.5 mg / kg emesis model

In order to develop a more reliable model of chemotherapy-induced emesis, that may have a more useful pharmacological sensitivity to anti-emetic drugs, we increased the dose of cisplatin to 7.5 mg/kg. This dose has been extensively used to investigate the mechanisms of cisplatin-induced emesis in this species (see Introduction), but in our studies, the severe toxicity of the higher dose of cisplatin restricted the observations to 24 h. The present studies confirmed that the early emesis is induced by cisplatin 7.5 mg/kg is susceptible to 5-HT_3 receptor antagonism by the activity of granisetron to inhibit emesis for at least 3 h. However, granisetron was not effective to reduce the emesis occurring during the subsequent 4–24-h period. The limited activity of granisetron in this model contrast its activity seen in man, where an excellent control

of emesis is observed during the acute phase (Chevallier, 1993).

It is perhaps pertinent that dexamethasone was highly effective to prevent days 1 and 2 emesis induced by the lower dose of cisplatin 5 mg/kg in the cat but was less consistent to inhibit emesis when the dose of cisplatin was increased to 7.5 mg/kg. Indeed we did not observe a clear dose-related inhibition of retching + vomiting with dexamethasone against the higher dose of cisplatin and our data must therefore be viewed with caution. Only dexamethasone at 0.1 mg/kg was active to reduce significantly the numbers of emetic episodes and the antagonism was also apparent during the initial 5-HT_3 sensitive phase of the response (all cats were completely protected for at least 4 h). In the ferret, dexamethasone has no action to modify the initial 5-HT_3 receptor antagonist sensitive emetic response when cisplatin is used at 10 mg/kg (Rudd et al., 1996a) but it is effective to antagonize emesis when cisplatin is administered at 5 mg/kg (Rudd and Naylor, 1996).

4.3. Anti-emetic mechanism of action

Our studies with granisetron may indicate that low doses of cisplatin in the cat may induce emesis primarily via a mechanism involving an activation of the 5-HT_3 receptor and the anti-emetic action of dexamethasone indicates an involvement of eicosanoids (Sanger, 1993). This may seem reasonable as it has previously been suggested that cisplatin can induce a release of 5-HT (Cubeddu et al., 1990; Milano et al., 1991; Schworer et al., 1991) which could activate 5-HT_3 receptors located peripherally on vagal afferents and centrally in the area postrema and nucleus tractus solitarius (Naylor and Rudd, 1994) and some eicosanoids are emetic (Eiler and Paddleford, 1979; De Saedeleer et al., 1992). However, as the dose of cisplatin is increased, it is likely that other factors or pathways predominate, particularly during the later part of the response and the mechanisms operating in the cat are similar to those in the ferret (Rudd et al., 1998). Indeed, a similar profile of anti-emetic activity has been reported with granisetron to antagonise low and high doses of radiation-induced emesis in the ferret but the effect of corticosteroids on the 5-HT_3 sensitive and resistant phases of the response was not studied (Andrews et al., 1992).

Not much is known about the mechanisms involved in cisplatin-induced delayed emesis. A study in the pigeon reveals that the delayed phase of cisplatin-induced emesis is mediated centrally and is unaffected by bilateral vagotomy or the 5-HT synthesis inhibitor *para*-chlorophenylalanine (Tanihata et al., 1998). In this species, the delayed phase is antagonised by dexamethasone and reserpine to suggest a role for eicosanoids and possibly monoamines other than 5-HT (Tanihata et al., 1998); such a situation is partly consistent with the clinical experience (Wilder-Smith et al., 1993; Janes et al., 1998). Clearly, more research is required to elucidate the mechanisms involved.

At present, it is not clear how dexamethasone could affect the emetic mechanism of action of cisplatin. Dexamethasone is not active to prevent apomorphine, morphine or copper sulphate-induced emesis in the ferret suggesting that the anti-emetic potential is not mediated by a generalized action on the emetic reflex (Rudd et al., 1996a). However, there is some evidence that dexamethasone can reduce cisplatin-induced vagal neurotoxicity and this action may be relevant to the anti-emetic effects observed in the present study and possibly the clinic (Woods and Andrews, 1995).

5. Conclusion

The results of the present studies have revealed the marked toxicity of cisplatin in the cat when used over a narrow dose range. The emesis data was also variable and interpreting drug effects must be made with caution. Nevertheless, the emesis induced by cisplatin 5 mg/kg, i.v. had a unique sensitivity to both granisetron and dexamethasone. The emesis induced by cisplatin 7.5 mg/kg, i.v. was less susceptible to granisetron over a 24-h period but dexamethasone had anti-emetic activity at 0.1 mg/kg, administered three times per day. It is not known why dexamethasone fails to inhibit emesis in a dose-dependent manner but we were unable to extend our findings due to ethical considerations. In any event, neither doses of cisplatin provide robust or convincing models of emesis in the cat to mimic the acute and delayed emesis in man.

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References

Andrews, P.L.R., Bhandari, P., Davis, C.J., 1992. Plasticity and modulation of the emetic reflex. In: Bianchi, A.L., Grélot, L., Miller, A.D., King, G.L. (Eds.), Mechanisms and Control of Emesis. Inserm/John Libbey Eurotext, Paris, France, pp. 275–284.

Brand, E.D., Harris, T.D., Borison, H.L., Goodman, L.S., 1954. The antiemetic activity of 10-(alpha-dimethylaminopropyl)-2-chlorophenothiazine (chlopromazine) in dog and cat. J. Pharmacol. Exp. Ther. 100, 86–92.

Chevallier, B., 1993. The control of acute cisplatin-induced emesis — a comparative study of granisetron and a combination regimen of high-dose metoclopramide and dexamethasone. Br. J. Cancer 68, 176–180, Granisetron Study Group.

Chevallier, B., Marty, M., Paillarse, J.M., 1994. Methylprednisolone enhances the efficacy of ondansetron in acute and delayed cisplatin-induced emesis over at least three cycles. Br. J. Cancer 70, 1171–1175, Ondansetron Study Group.

Chiara, S., Campora, E., Simoni, C., Confalonieri, M., Psilogenis, M.,

Rosso, R., 1995. Prevention of delayed emesis with metoclopramide and dexamethasone in patients receiving moderately emetogenic cytotoxic treatment. Anticancer Res. 15, 1597–1599.

Cubeddu, L.X., Hoffmann, I.S., Fuenmayor, Finn, A.L., 1990. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N. Engl. J. Med. 322, 810–816.

De Saedeleer, V., Wechsung, E., Houvenaghel, A., 1992. Effect of infusion of a diarrheogenic dose of PGE_2 on gastrointestinal electrical activity in the conscious piglet. Prostaglandins, Leukotrienes Essent. Fatty Acids 45, 67–70.

Eiler, H., Paddleford, R., 1979. Induction of intestinal evacuation or vomition (or both) in the dog by prostaglandin F2alpha injection: clinical potential. Am. J. Vet. Res. 40, 1731–1732.

Janes, R.J., Muhonen, T., Karjalainen, U.P., Wiklund, T., 1998. Urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion during multiple-day high-dose chemotherapy. Eur. J. Cancer 34, 196–198.

King, G.L., 1990. Animal models in the study of vomiting. Can. J. Physiol. Pharmacol. 68, 260–268.

Knapp, D.W., Richardson, R.C., DeNicola, D.B., Long, G.G., Blevins, W.E., 1987. Cisplatin toxicity in cats. J. Vet. Int. Med. 1, 29–35.

Kris, M.G., Gralla, R.J., Clark, R.A., Tyson, L.B., O'Connell, J.P., Wertheim, M.S., Kelsen, D.P., 1985. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. J. Clin. Oncol. 3, 1379–1384.

Kris, M.G., Pisters, K.M., Hinkley, L., 1994. Delayed emesis following anticancer chemotherapy. Support. Care Cancer 2, 297–300.

Latreille, J., Pater, J., Johnston, D., Laberge, F., Stewart, D., Rusthoven, J., Hoskins, P., Findlay, B., McMurtrie, E., Yelle, L., Williams, C., Walde, D., Ernst, S., Dhaliwal, H., Warr, D., Shepherd, F., Mee, D., Nishimura, L., Osoba, D., Zee, B., 1998. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. J. Clin. Oncol. 16, 1174–1178, National Cancer Institute of Canada Clinical Trials Group.

Latreille, J., Stewart, D., Laberge, F., Hoskins, P., Rusthoven, J., McMurtrie, E., Warr, D., Yelle, L., Walde, D., Shepherd, F., 1995. Dexamethasone improves the efficacy of granisetron in the first 24 h following high-dose cisplatin chemotherapy. Support. Care Cancer 3, 307–312.

London, S.W., McCarthy, L.E., Borison, H.L., 1979. Suppression of cancer chemotherapy-induced vomiting in the cat by nabilone, a synthetic cannabinoid. Proc. Soc. Exp. Biol. Med. 160, 437–440.

Lucot, J.B., 1989. Blockade of 5-hydroytryptamine$_3$ receptors prevents cisplatin-induced but not motion- or xylazine-induced emesis in the cat. Pharmacol. Biochem. Behav. 32, 207–210.

Lucot, J.B., Crampton, E.H., 1988. 8-OH-DPAT suppresses vomiting in the cat elicited by motion, cisplatin or xylazine. Pharmacol. Biochem. Behav. 33, 627–631.

McCarthy, L.E., Borison, H.L., 1981. Antiemetic activity of *N*-methyllevonantradol and nabilone in cisplatin-treated cats. J. Clin. Pharmacol. 21, 30S–37S.

McCarthy, L.E., Borison, H.L., 1984. Cisplatin-induced vomiting eliminated by ablation of the area postrema in cats. Cancer Treat. Rep. 68, 401–404.

Milano, S., Blower, P., Romain, D., Grélot, L., 1995. The piglet as a suitable animal model for studying the delayed phase of cisplatin-induced emesis. J. Pharmacol. Exp. Ther. 274, 951–961.

Milano, S., Simon, C., Grélot, L., 1991. In vitro release and tissue levels of ileal serotonin after cisplatin-induced emesis in the cat. Clin. Auton. Res. 1, 275–280.

Miller, A.D., Ruggiero, D.A., 1994. Emetic reflex arc revealed by expression of the immediate-early gene C-Fos in the cat. J. Neurosci. 14, 871–888.

Naylor, R.J., Rudd, J.A., 1994. Emesis and anti-emesis. In: Sidesbottom, E., Franks, L.M. (Eds.), Cancer Surveys, Advances and Prospects in Clinical, Epidemiological and Laboratory Oncology. Cold Spring Harbour Laboratory Press, New York, USA, pp. 177–194.

Naylor, R.J., Rudd, J.A., 1996. Mechanisms of chemotherapy/radiotherapy-induced emesis in animal models. Oncology 53 (Suppl. 1), 8–17.

Perez, E.A., Gandara, D.R., 1992. Advances in the control of chemotherapy-induced emesis. Ann. Oncol. 3 (Suppl. 3), 47–50.

Rudd, J.A., Bunce, K.T., Naylor, R.J., 1996a. The interaction of dexamethasone with ondansetron on drug-induced emesis in the ferret. Neuropharmacology 35, 91–97.

Rudd, J.A., Cheng, C.H.K., Naylor, R.J., 1998. Serotonin-independent model of cisplatin-induced emesis in the ferret. Jpn. J. Pharmacol. 78, 253–260.

Rudd, J.A., Jordan, C.C., Naylor, R.J., 1994. Profiles of emetic action of cisplatin in the ferret: a potential model of acute and delayed emesis. Eur. J. Pharmacol. 262, R1–R2.

Rudd, J.A., Jordan, C.C., Naylor, R.J., 1996b. The action of the NK_1 tachykinin receptor antagonist, CP 99,994, in antagonizing the acute and delayed emesis induced by cisplatin in the ferret. Br. J. Pharmacol. 119, 931–936.

Rudd, J.A., Naylor, R.J., 1994. Effects of 5-HT_3 receptor antagonists on models of acute and delayed emesis induced by cisplatin in the ferret. Neuropharmacology 33, 1607–1608.

Rudd, J.A., Naylor, R.J., 1996. An interaction of ondansetron and dexamethasone antagonizing cisplatin-induced acute and delayed emesis in the ferret. Br. J. Pharmacol. 118, 209–214.

Sanger, G.J., Nelson, D.R., 1989. Selective and functional 5-hydroxytryptamine3 receptor antagonism by BRL 43694 (granisetron). Eur. J. Pharmacol. 159, 113–124.

Sanger, G.S., 1993. The pharmacology of antiemetic agents. In: Andrews, P.L.R., Sanger, G.J. (Eds.), Emesis in Anti-cancer Chemotherapy. Chapman & Hall, London, UK, pp. 179–210.

Schworer, H., Racke, K., Kilbinger, H., 1991. Cisplatin increases the release of 5-hydroxytryptamine (5-HT) from the isolated vascularly perfused small intestine of the guinea-pig — involvement of 5-HT_3 receptors. Naunyn-Schmiedeberg's Arch. Pharmacol. 344, 143–149.

Smith, W.L., Callaham, E.M., Alphin, R.S., 1988. The emetic activity of centrally administered cisplatin in cats and its antagonism by zacopride. J. Pharm. Pharmacol. 40, 142–143.

Swartz, S.L., Dluhy, R.G., 1978. Corticosteroids: clinical pharmacology and therapeutic use. Drugs 16, 238–255.

Tanihata, S., Suzuki, M., Ohata, S., Uchiyama, T., 1998. Cisplatin-induced delayed emesis in pigeons. Naunyn-Schmiedeberg's Arch. Pharmacol. 358 (Suppl. 1), R435.

Wilder-Smith, O.H., Borgeat, A., Chappuis, P., Fathi, M., Forni, M., 1993. Urinary serotonin metabolite excretion during cisplatin chemotherapy. Cancer 72, 2239–2241.

Woods, A.J., Andrews, P.L.R., 1995. Cisplatin acutely reduces 5-hydroxytryptamine-induced vagal depolarization in the rat: protective action of dexamethasone. Eur. J. Pharmacol. 278, 275–278.