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Action of glucocorticoids to antagonise cisplatin-induced acute and delayed emesis in the ferret

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Abstract

Cisplatin 5 mg/kg, i.p. induced an acute (day 1) and delayed (days 2 and 3) emetic response in the ferret that was used to investigate the potential anti-emetic activity of several glucocorticoids. Betamethasone (0.3–3 mg/kg, i.p.) reduced the emesis occurring during the initial 0–24-h period by 71.1–99.5% ($P < 0.05$). The action of methylprednisolone (1.0–10.0 mg/kg, i.p.) and hydrocortisone (1.0–30.0 mg/kg, i.p.) could not be assessed because the controls exhibited weak emetic responses and dexamethasone produced a non-significant 64.0% reduction at 0.3 mg/kg ($P > 0.05$). However, all glucocorticoids dose-dependently reduced retching + vomiting during the subsequent 24–56-h period. The rank order of anti-emetic potency was betamethasone ($ID_{80} < 0.3$ mg/kg) ≥ dexamethasone ($ID_{80} = 0.32$ mg/kg) > methylprednisolone ($ID_{80} = 0.66$ mg/kg) ≫ hydrocortisone ($ID_{80} > 30$ mg/kg). Dexamethasone was ineffective to antagonise the retching + vomiting response during the 24–56-h period when the administration was delayed until 24 h post-cisplatin injection. None of the glucocorticoids reduced the retching + vomiting response occurring during the 56–72-h period. In conclusion, the rank order of anti-emetic potency suggests that inflammation, or mediators of inflammation, contribute to the retching + vomiting response induced by cisplatin. © 2001 Published by Elsevier Science B.V.

Keywords: Emesis; Cisplatin; Glucocorticoid

1. Introduction

Cisplatin-based chemotherapy is commonly associated with severe nausea and vomiting. The acute phase comprises emetic episodes occurring during the first 24 h following the start of chemotherapy and is particularly sensitive to 5-HT_3 receptor antagonists (Martin, 1996). The delayed phase is less sensitive to 5-HT_3 receptor antagonists or conventional anti-emetics and comprises episodes occurring after the initial 24-h period; the most intense period of delayed emesis occurs during the 48–72-h period and is not satisfactorily controlled by single agent therapy (Hesketh, 1996; Kris et al., 1998).

Glucocorticoids are useful agents to combine with other anti-emetics to control both the acute and delayed phases of emesis (Gralla et al., 1996). They are also active to reduce post-operative nausea and vomiting (Baxendale et al., 1993; Fujii et al., 1999; Splinter and Roberts, 1996) and have been used to prevent hyperemesis gravidarum (Safari et al., 1998; Taylor, 1996). There is also a study detailing the action of dexamethasone to reduce motion-induced emesis (Kohl, 1986). However, there have been no clear dose-ranging studies to establish the optimal anti-emetic doses of glucocorticoids or the most effective dosing schedule to use. The mechanism of anti-emetic action of the glucocorticoids to reduce emesis is also unknown.

In our previous studies, we have shown that dexamethasone is ineffective to antagonise apomorphine-, morphine- or copper sulphate-induced emesis in the ferret (Rudd et al., 1996a). Dexamethasone also failed to antagonise the emesis induced by cisplatin 10 mg/kg (Rudd and Naylor, 1997) but was remarkably effective to antagonise emesis induced by a lower dose of cisplatin 5 mg/kg (Rudd and Naylor, 1996). The lower dose of cisplatin in the ferret may partly mimic the acute and delayed emesis seen in man and provides a model to dissect the anti-emetic mechanism of action of the glucocorticoids (Rudd and Naylor, 1996). We have demonstrated using the model that the anti-emetic action of the 5-HT_3 receptor antagonist ondansetron could be increased in combination with dexamethasone and that a more frequent administration of

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dexamethasone was associated with an improved anti-emetic control (Rudd and Naylor, 1996). Other studies have shown that dexamethasone may be a useful agent to combine with the new NK_1 receptor antagonists (Tattersall et al., 2000); such an interaction is also demonstrated in the clinic (Kris et al., 1997).

In the present studies, we have used several glucocorticoids in dose-ranging studies to establish the rank order of ant-emetic potency to antagonise cisplatin-induced acute and delayed emesis in the ferret. The studies were also designed to define the glucocorticoid-sensitive phase of emetic response in this species.

2. Methods

2.1. Animals

Castrated male or normal female ferrets (0.8–1.8 kg) were obtained from a reputable breeder in New Zealand and were housed communally at 22 ± 1°C under artificial lighting, with lights on between 0700 and 2100 h. They were fed a dry pellet diet (Laboratory Feline Diet 5003, PMI Nutrition, St. Louis, USA); water was available ad libitum.

2.2. Induction and measurement of emesis

Animals were transferred to individual observation cages and allowed at least 48 h to adapt to the new environment. On the day of the experiment (at 1430 h) they were presented with 100 g of commercially available cat food (Whiskas®, Effem Foods, Woodonga, Australia). At 1500 h, the ferrets were removed from their observation cages and injected intraperitoneally with dexamethasone (0.1–1.0 mg/kg, i.p.), betamethasone (0.3–3.0 mg/kg, i.p.), methylprednisolone (1.0–10.0 mg/kg, i.p.) or hydrocortisone (1.0–30.0 mg/kg, i.p.) or their respective vehicles, 30 s post the administration of cisplatin 5 mg/kg, i.p. ($t = 0$). Glucocorticoid or vehicle treatment was continued at regular 8-h intervals for the duration of the experiment. After treatment, the animals were returned to individual observation cages for the assessment of retching and/or vomiting during the subsequent 72-h observation period. During this time period food (Laboratory Feline Diet 5003, PMI Nutrition, USA) and water was available ad libitum. In a separate experiment, animals were injected with cisplatin 5 mg/kg, i.p. and were allowed to develop an acute emetic response. At 24 h post-cisplatin injection, the animals were administered dexamethasone 1 mg/kg, i.p. or vehicle. Drug or vehicle treatment was then continued at regular 8-h intervals for the remainder of the experiment.

Animal behaviour was recorded remotely using a closed circuit video recording system and analysed at the end of the experiment. Emesis was characterised 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 (bouts) 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.

2.3. Statistical analysis

In each animal, the latency to retch or vomit and/or and the total number of retches, vomits and episodes was calculated in each 1 h period for the duration of the experiment. The significance of difference between treatments was assessed by a one (factor = treatment)- or two-way (factor 1 = treatment, factor 2 = sex) analysis of variance (ANOVA) followed by a Fisher's Protected Least Significant Difference (PLSD) test or by an unpaired Student's *t*-test, as appropriate. Differences were considered significant when $P < 0.05$. ID_{80} values were determined on the mean data by non-linear regression analysis (Kailidagraph™, Synergy Software, USA).

2.4. Drugs used

Cisplatin was purchased as a sterile saline solution at an active concentration of 1 mg/ml (David Bull Laboratories, Victoria, Australia). Dexamethasone 21-phosphase disodium salt (Sigma-Aldrich, Saint Louis, USA), betamethasone 21-phosphate sodium salt (Sigma-Aldrich) and hydrocortisone 21-hemisuccinate sodium salt (Sigma-Aldrich) were prepared in distilled water and administered in a volume of 0.5 ml/kg. 6α-Methylprednisolone 21-hemisuccinate (Sigma-Aldrich) was prepared in distilled water and administered in a volume of 1 ml/kg. Cisplatin was administered in a volume of 5 ml/kg. Doses are expressed as the free base.

3. Results

3.1. General profile of emesis induced by cisplatin

Our investigations used castrated male and normal female animals but each experiment had a balanced design, were appropriate. The experiments were not designed to directly compare castrated male and normal female responses to cisplatin. However, pooling of the control data from the experiments utilising distilled water as the vehicle (nine male, nine female) did not reveal statistically significant differences in the total numbers of episodes (male 69.1 ± 12.5, female 82.5 ± 9.2), retches (male 345.5 ± 70.5, female 443.6 ± 65.8) or vomits (male 34.2 ± 7.3, female 40.3 ± 3.7) or the latency to onset of emesis (male 13.6 ± 5.6 h, female 10.0 ± 4.6 h) induced by cisplatin ($P > 0.05$).

3.2. Antagonism of cisplatin-induced emesis by corticosteroids

The profile of cisplatin-induced acute and delayed emesis and the effect of dexamethasone (0.1–1 mg/kg, i.p.) are shown in Fig. 1. In the vehicle-treated animals, cisplatin induced emesis within 4.4 ± 1.2 h and there were 84.3 ± 32.7 retches + vomits on day 1, 182.7 ± 66.8 retches + vomits on day 2 and 142.7 ± 50.1 retches + vomits on day 3. The profile of emesis occurring on days 2 and 3 was representative of the emesis that occurred in the other experiments where the control animals received distilled water as vehicle and cisplatin. However, some of the control animals in experiments involving the use of methylprednisolone and hydrocortisone failed to develop a strong retching and vomiting response during the initial 24-h period and the effect of drug treatment could not be assessed (Fig. 2).

Dexamethasone produced a trend to reduce emesis occurring during the initial 0–24-h period but the reductions were not statistically significant ($P > 0.05$; Figs. 1 and 2). The maximum reduction observed was 64.0% at 0.3 mg/kg ($P > 0.05$). Betamethasone caused a dose-related antagonism of the retching + vomiting during the initial 24-h period and a 71.1% reduction was seen at 0.3 mg/kg ($P < 0.05$); increasing the dose to 3 mg/kg antagonised emesis by 99.5% ($P < 0.05$; Fig. 2). All drugs caused an apparent increase in the latency to onset of cisplatin-induced retching + vomiting. The increases in latency seen with dexamethasone at 0.3 mg/kg and betamethasone at 3 mg/kg were significant ($P < 0.05$; Fig. 3). The significance of the increase in the latency induced by methylprednisolone and hydrocortisone could not be statistically analysed since some of the treatment groups in the respective experiments had less than three animals responding (Fig. 3).

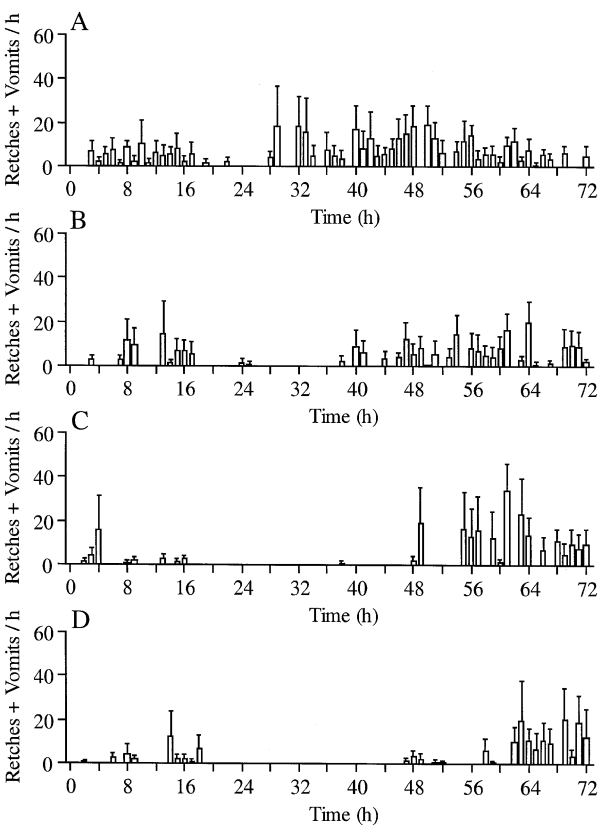

Fig. 1. The effect of (A) vehicle (distilled water) 0.5 ml/kg, (B) dexamethasone 0.1 mg/kg, (C) dexamethasone 0.3 mg/kg or (D) dexamethasone 1.0 mg/kg on the profile of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg/kg. All drugs were administered intraperitoneally. Cisplatin was injected at $t = 0$ h followed 30 s later by dexamethasone or vehicle administration. Dexamethasone or vehicle administration was repeated every 8 h for the duration of the experiment. Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring in 1-h time intervals ($n = 6$).

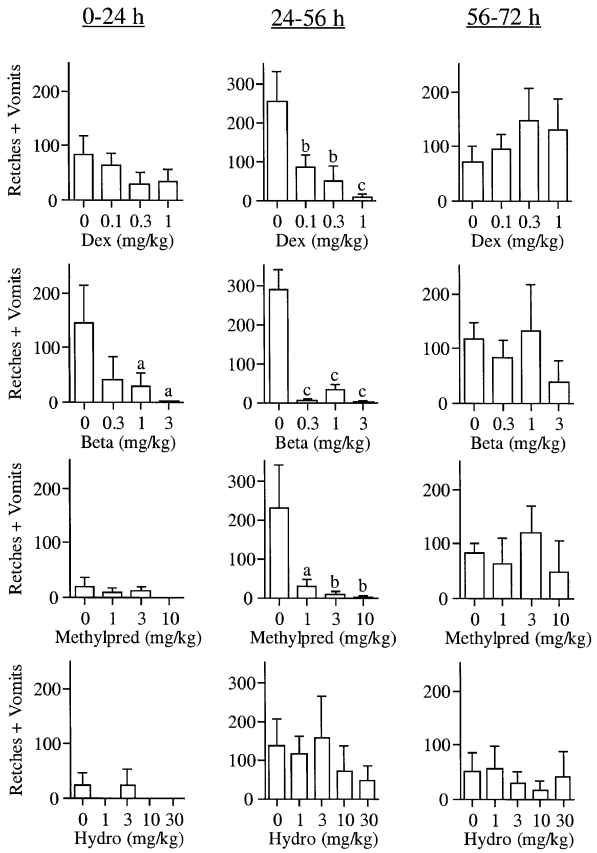

Fig. 2. The effect of dexamethasone (Dex), betamethasone (Beta), methylprednisolone (Methylpred) or hydrocortisone (Hydro) or their respective vehicles, on the profile of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg/kg. All drugs were administered intraperitoneally. Cisplatin was injected at $t = 0$ h followed 30 s later by corticosteroid or vehicle administration. Glucocorticoid or vehicle administration was repeated every 8 h for the duration of the experiment. Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring in 0–24-, 24–56- and 56–72-h time intervals ($n = 4$–6). Significant differences in retching + vomiting in cisplatin vehicle-treated animals and the respective cisplatin glucocorticoid-treated animals are indicated as $^{a}P < 0.05$, $^{b}P < 0.01$ or $^{c}P < 0.005$ (one- or two-way ANOVA followed by Fisher's PLSD tests).

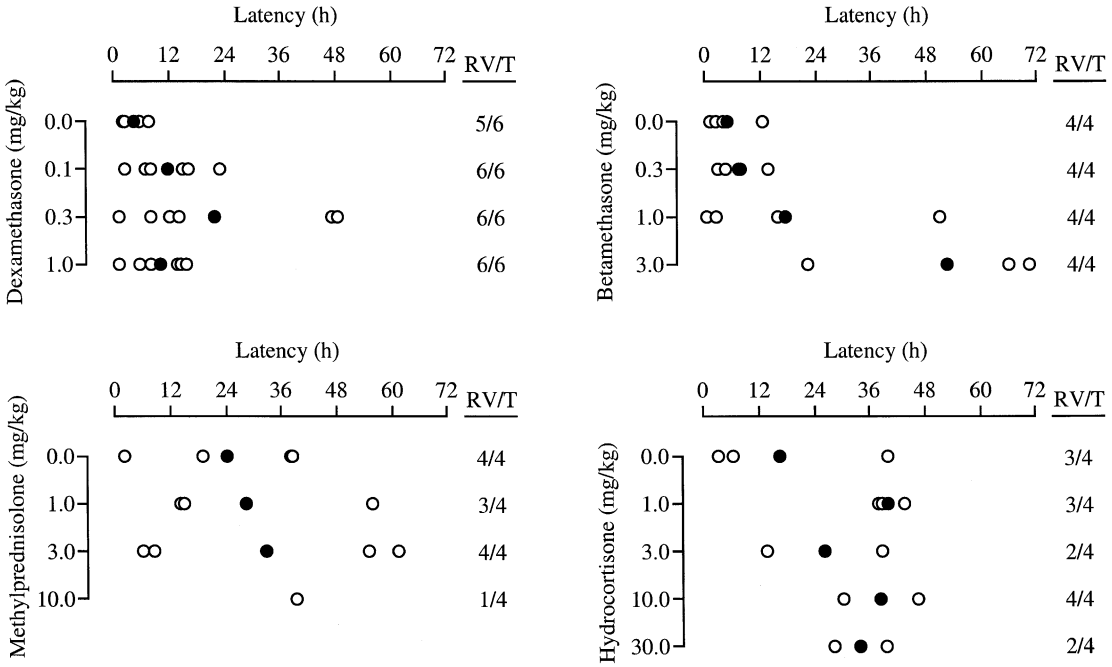

Fig. 3. The effect of dexamethasone, betamethasone, methylprednisolone or hydrocortisone or their respective vehicles, on the latency to onset of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg/kg. All drugs were administered intraperitoneally. Cisplatin was injected at $t = 0$ h followed 30 s later by corticosteroid or vehicle administration. Glucocorticoid or vehicle administration was repeated every 8 h for the duration of the experiment. Open circles represent the individual latencies. Filled circles represent the mean latencies of the respective treatment groups. The numbers of animals retching and/or vomiting out of the number of animals tested (RV/T) is indicated as a 'fraction' for each treatment group.

Examining the effect of dexamethasone on the profile of cisplatin-induced emesis occurring during the remaining 2-day period revealed that emesis could be practically abolished ($P < 0.05$) in a dose-related manner up to 56 h following cisplatin administration (maximum reduction in the 24–56 h period was 96.7% at 1 mg/kg; see Figs. 1 and 2). The protective effect during the 24–56-h period was shared by betamethasone (maximum reduction was 99.0% at 3 mg/kg; $P < 0.05$) and methylprednisolone (maximum reduction was 98.9% at 10 mg/kg; $P < 0.05$). Hydrocortisone produced a non-significant trend to antagonise retching + vomiting (maximum reduction was 66.6% at 30 mg/kg; $P > 0.05$) (see Fig. 2; profiles not shown). Analysis of the data revealed the following rank order of anti-emetic potency to reduce the 24–56 h retching + vomiting response: betamethasone ($ID_{80} < 0.3$ mg/kg) ≥ dexamethasone ($ID_{80} = 0.32$ mg/kg) > methylprednisolone ($ID_{80} = 0.66$ mg/kg) > hydrocortisone ($ID_{80} > 30.0$ mg/kg). None of the glucocorticoids antagonised significantly the retching + vomiting response occurring during the 56–72-h period ($P > 0.05$; Fig. 2)

3.3. The action of dexamethasone (1 mg / kg, i.p.) administered as an intervention treatment on an established delayed retching and vomiting response induced by cisplatin

Ferrets were randomised to receive 8-h administrations of dexamethasone (1 mg/kg, i.p.) or distilled water (0.5 ml/kg, i.p.) starting 24 h post-cisplatin injection. In the groups receiving cisplatin and distilled water, there were 70.8 ± 47.1, 353.3 ± 144.1 and 88.5 ± 16.7 retches + vomits during the 0–24-, 24–56- and 56–72-h periods, respectively (Fig. 4). The latency of cisplatin to induce emesis and the numbers of retches + vomits occurring in the 0–24-h period of the dexamethasone group (latency = 7.2 ± 1.7 h, retches + vomits = 70.8 ± 47.1) was not sta-

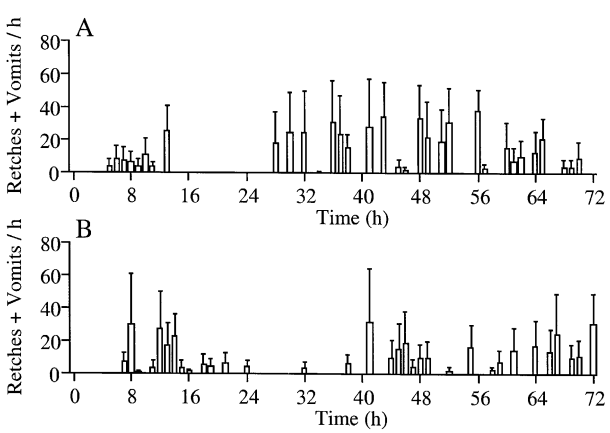

Fig. 4. The effect of (A) vehicle (distilled water) or (B) dexamethasone 1.0 mg/kg on the profile of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg/kg. All drugs were administered intraperitoneally. Cisplatin was injected at $t = 0$ h followed 24 h later by dexamethasone or vehicle administration. Dexamethasone or vehicle administration was repeated every 8 h for the remainder of the experiment. Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring in 1-h time intervals ($n = 4$).

tistically different ($P > 0.05$) from the control animals (latency = 8.8 ± 2.5 h, retches + vomits = 136.5 ± 57.6). In the 24–56-h period, dexamethasone produced a 63.1% reduction in retching + vomiting but potentiated the retching + vomiting response by 47.5% in the 56–72-h period. However, the changes did not achieve statistical significance ($P > 0.05$).

4. Conclusions

The present studies have partially confirmed the anti-emetic action of dexamethasone 1 mg/kg, i.p., administered three times per day to reduce significantly the retching and vomiting response induced by a single administration of cisplatin (Rudd and Naylor, 1996). The antagonism of emesis observed in the present studies was particularly apparent during the 24–56-h period following cisplatin injection but less effective to control emesis occurring after the 56-h period. Importantly, the other glucocorticoids were also highly active to reduce emesis during the 24–56-h period and the reductions seen were dose-related. Based on ID_{80} values, the rank order of potency of the glucocorticoids to antagonise emesis during the 24–56-h period was betamethasone ($ID_{80} < 0.3$ mg/kg) ≥ dexamethasone ($ID_{80} = 0.32$ mg/kg) > methylprednisolone ($ID_{80} = 0.66$ mg/kg) > hydrocortisone ($ID_{80} > 30.0$ mg/kg).

The rank order of anti-emetic activity of the glucocorticoids is remarkably similar to their known rank order of anti-inflammatory potency, where dexamethasone and betamethasone are approximately equipotent but more potent than methylprednisolone and hydrocortisone, respectively (Dollery, 1991; Marble et al., 1980). Hydrocortisone may have been expected to be more potent but the difference may be due to the compounds relatively short plasma half life and/or its additional mineralocorticoid activity (reported in man; Begg et al., 1987). Nevertheless, the data suggests that inflammation, or inflammatory mediators/products, contribute to the emesis seen during 24–56-h period following cisplatin treatment. At present, we do not know the site of proposed inflammation or if cisplatin induces local inflammation following intraperitoneal injection in the ferret.

Based on the anti-emetic activity of dexamethasone (present studies; Fukunaka et al., 1998; Rudd and Naylor, 1996; Tattersall et al., 2000) and betamethasone, an inflammatory response and/or involvement of inflammatory mediators/products may also contribute to the initial phase (0–24 h) of emesis induced by cisplatin (we do not know if a pretreatment of the glucocorticoids would result in a enhanced control of emesis). Unfortunately, a stronger argument cannot be made from the experiments involving methylprednisolone and hydrocortisone since some of the animals in the control groups failed to develop a strong emetic response during this period. Such variation in the emetic responsiveness of the ferret to cisplatin has been previously reported (Rudd et al., 1996b). Only betamethasone significantly antagonised the early emetic response by up to 99.5% and dexamethasone produced a non-significant trend for a 25.7–64.0% reduction. In our previous study, dexamethasone at 1 mg/kg, i.p., administered three times per day, reduced the initial phase of emesis by approximately 85% (Rudd and Naylor, 1996). The variation in anti-emetic potency may relate to the different strains of ferrets used in the studies.

Inflammation involves components of the immune response and many different mediators (Leirisalo-Repo, 1994; Levy, 1996), some of which are known to activate the emetic reflex. The classical mediators that are emetic include histamine (e.g. dog, Bhargava and Dixit, 1968), 5-hydroxytryptamine (5-HT) (e.g. *Suncus murinus*, Torii et al., 1991), prostaglandins (e.g. dog, Eiler and Paddleford, 1979), substance P (e.g. ferret, Gardner et al., 1994) and possibly leukotrienes (e.g. monkey, Jett et al., 1990). It is well known that glucocorticoids decrease histamine production and/or release from mast cells (Hirasawa et al., 1990) and prevent the synthesis of prostaglandins, thromboxane and leukotrienes (Vane and Botting, 1996). Less information is available about the emetic potential of other inflammatory mediators such as nitric oxide, bradykinin, cytokines and oxygen derived free radicals, which are also involved in inflammation and regulated by glucocorticoids (Barnes and Adcock, 1993; Dray and Bevan, 1993; Moncada and Palmer, 1991). Other unknown mechanisms may also be involved.

If inflammation is involved in the model, a critical question arising is how can cisplatin activate the inflammatory response or elevate levels of inflammatory mediators? Perhaps the trigger for cisplatin to induce inflammation or the production of inflammatory mediators could relate to its cytotoxic and neurotoxic action (Scott et al., 1994) and/or the ability to modulate cytokine levels (Coulon et al., 1993; Preziosi et al., 1992; Rabinowitz et al., 1993). Recent studies suggest that interleukins, (e.g. interleukin-1β, interleukin-6, interleukin-8), macrophage colony-stimulating factor or even tumour necrosis factor-α may be key players in triggering the mechanism as they are elevated following cisplatin treatment (Pogrebniak et al., 1991; Rabinowitz et al., 1993; Shi et al., 1998) and during 'sickness' behaviour (Kent et al., 1992). Cisplatin also indirectly activates the inflammatory mechanism by reducing the levels of the natural 'decoy receptor' for interleukin-1β (Arenberg et al., 1995). The corticosteroids are well known to prevent the production of the cytokines (Barnes and Adcock, 1993) and this could presumably prevent the involvement of many of the mediators involved in inflammation and possibly emesis.

We would like to hypothesise that the involvement of cytokines and other pro-inflammatory mediators may occur early in response to cisplatin treatment since dexamethasone was more effective to antagonise delayed eme-

sis (i.e. during the 24–56-h period) if administration was started on the first day. The data are partially consistent with the clinical experience where a poor control of acute emesis impacts on the control of delayed emesis (Hesketh, 1996). However, the mechanism(s) contributing to the emesis occurring after 56 h is currently unknown.

In conclusion, cisplatin-induced emesis, particularly the emesis occurring during the 24–56-h phase, is sensitive to glucocorticoids and the rank order of inhibitory potency suggests an involvement of inflammation and/or inflammatory mediators. The identification of a specific glucocorticoid sensitive phase may be important to the rational use of glucocorticoids as anti-emetics in the clinic. However, the involvement of the mediators probably begins on the first day of cisplatin treatment and may affect the development of delayed emesis. Importantly, the studies have also identified that betamethasone may be a suitable glucocorticoid to use to reduce emesis in the clinic.

Unfortunately, there may be a dilemma with the use of glucocorticoids as anti-emetics since there could be suppression of useful cytokines that normally combat malignancy in addition to the suppression of cytokines that may be involved in emesis (Powell et al., 1990). There are also other limiting side effects associated with glucocorticoid therapy (Truhan and Ahmed, 1989). Understanding how corticosteroids antagonise retching and vomiting may facilitate the development of a new range of anti-emetic drugs that have an improved selectivity in their mechanism of action. Further studies are required to confirm an involvement of pro-inflammatory mediators in the emetic action of cisplatin.

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