British Journal of Pharmacology (1996) 118, 209-214

An interaction of ondansetron and dexamethasone antagonizing cisplatin-induced acute and delayed emesis in the ferret

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1 Cisplatin, 5 mg kg^{-1}, i.p., administered as a single treatment, 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 ondansetron and dexamethasone and their interaction over a three day period.

2 Ondansetron, 1 mg kg^{-1}, i.p., administered three times per day in two experiments, antagonized significantly the retching and vomiting that occurred on days 1 and 2 by 60-76 and 73-84%. On the third day of treatment there was a trend for a 38% reduction in one experiment and a 74% reduction in the other.

3 There was a trend for dexamethasone, 1 mg kg^{-1}, i.p., administered as a single daily injection for three days, to reduce by 37% the retching and vomiting response that occurred on day 1, the reduction of 77% on day 2 achieved significance and dexamethasone non-significantly increased the retching and vomiting response by 46% on day 3. However, dexamethasone 1 mg kg^{-1} i.p. administered three times per day for three days significantly reduced the retching + vomiting reponse by 85, 97 and 86% on days 1, 2 and 3 respectively.

4 The combination of dexamethasone, 1 mg kg^{-1}, i.p., as single daily injections with ondansetron, 1 mg kg^{-1}, i.p., administered three times per day improved the control of the retching and vomiting response, significantly reducing the total numbers of retches and vomits by more than 70% over a three day period. The combination of dexamethasone (1.0 mg kg^{-1}) and ondansetron (1.0 mg kg^{-1}), both administered three times daily, abolished cisplatin-induced emesis over the three day period.

5 The three times per day administration of ondansetron, 1 mg kg^{-1}, i.p., plus dexamethasone, 1 mg kg^{-1}, i.p., administered only on day 1 prevented day 1 emesis but did not modify the retching and vomiting that occurred on days 2 and 3.

6 The present results indicate that ondansetron and dexamethasone significantly reduce cisplatin-induced emesis in the ferret during both the acute and delayed phase; drug/co-treatment can exert an additive action to abolish cisplatin-induced emesis. The ferret model may be useful to detect anti-emetic drug action for treatment of chemotherapy-induced acute and delayed emesis in man.

Keywords: Emesis; cisplatin; acute and delayed; ondansetron; dexamethasone; ferret model

Introduction

The clinical success of the 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonists in antagonizing chemotherapy-induced emesis in man was originally predicted from animal models (Sanger, 1993). The models enabled a rapid evaluation of a compound's anti-emetic potential, with activity to prevent chemotherapy-induced emesis being assessed over a 4-6 h period (Andrews *et al.*, 1988). Agents such as ondansetron and granisetron were revealed as being almost completely effective (>98%) in inhibiting emesis in the 4-6 h period in the emesis models in animals (Bermudez *et al.*, 1988; Higgins *et al.*, 1989) and up to 60% effective in preventing the initial 24 h emetic response in man (Ruff *et al.*, 1994).

However, chemotherapy-induced emesis in man may last for several days and there remains a population of patients that are resistant to therapy with 5-HT_3 receptor antagonists (Gandara *et al.*, 1993; Kris *et al.*, 1992). Also, the inability of the 5-HT_3 receptor antagonists to control completely the emesis to chemotherapy in man during the later phase of the response, i.e. subsequent to the first day of treatment, was not predicted from the original animal studies. Based on the clinical studies, the 'acute' response to chemotherapy treatment with its sensitivity to antagonism by 5-HT_3 receptor antagonists may be differentiated from the subsequent or 'delayed' response showing a greater resistance to control with 5-HT_3 receptor antagonists.

Improvements in the control of both acute and delayed emesis in man have been made by use of agents such as dexamethasone in combination with other anti-emetics and the 5-HT_3 receptor antagonists (Smith *et al.*, 1991; Bishop *et al.*, 1992; Rath *et al.*, 1993; Roila, 1993; Chevallier *et al.*, 1994). However, animal models using cisplatin and 4-6 h observation periods have failed to show that the anti-emetic control by 5-HT_3 receptor antagonists can be reliably enhanced with dexamethasone (Marr *et al.*, 1992; Rudd *et al.*, 1995).

To investigate further the possibility that cisplatin-induced emesis in animals may involve an acute and delayed phase showing differing sensitivities to anti-emetic treatments, we have developed a ferret model of acute and delayed emesis to cisplatin that involves administering a low dose of cisplatin (5 mg kg^{-1}, i.p.) and continuously observing the animals for 72 h (Rudd *et al.*, 1994). Using this model we have demonstrated that ondansetron is effective in markedly antagonizing or abolising the emesis during the acute phase but also reveals a 5-HT_3 receptor antagonist-resistant component of the delayed reponse (Rudd & Naylor, 1994).

In the present study the interaction of dexamethasone with ondansetron was investigated in the cisplatin 72 h ferret model to assess further its value as a model for investigating the mechanisms involved and the design of new treatments for acute and delayed emesis in man.

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Methods

Animals

Male ferrets (0.8–1.8 kg), obtained from Grayston, Little Lion's Farm (Hants, U.K.) were housed individually at 22±1°C under artificial lighting, with lights on between 07 h 00 min and 21 h 00 min and were routinely fed a dry pellet diet (SDS Diet 'C' (E), Special Diet Services Ltd., U.K.); water was available *ad libitum*.

Induction and measurement of emesis

At 13 h 00 min ferrets were transferred to observation cages where they were allowed 30 min to adapt before being presented with 100 g of cat food (Kitekat Supreme, Pedigree Pet Foods, Leicestershire). At 15 h 00 min the ferrets were removed from their observation cages and injected intraperitoneally with ondansetron (1 mg kg^{-1}, i.p.) and/or dexamethasone (1 mg kg^{-1}, i.p.) or vehicle (distilled water) 30 s after the administration of cisplatin (5 mg kg^{-1}, i.p.) ($t=0$). 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 (SDS Diet 'C') and water was available *ad libitum*. Drug or vehicle treatment was continued at regular 8 h intervals or at regular 24 h intervals as indicated in the Results section.

Animal behaviour was recorded remotely with a closed circuit video recording system and analysed at the end of the experiment. Emesis was characterized by rhythmic abdominal contractions which 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.

Statistical analysis

In each animal the latency to retch or vomit and/or 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 Student's unpaired t test (two way) or one-way analysis of variance (ANOVA) followed by a Fisher's PLSD test where appropriate.

Drugs used

Cisplatin (Lederle) was prepared in saline (0.9% w/v) at 70–75°C followed by gradual cooling to 40–50°C and administered immediately. Ondansetron dihydrochloride (Glaxo) and dexamethasone sodium phosphate (Sigma) were prepared in distilled water. Cisplatin was administered in a volume of 5 ml kg^{-1}. All other drugs were administered in a volume of 1 ml kg^{-1}. Doses are expressed as the free base.

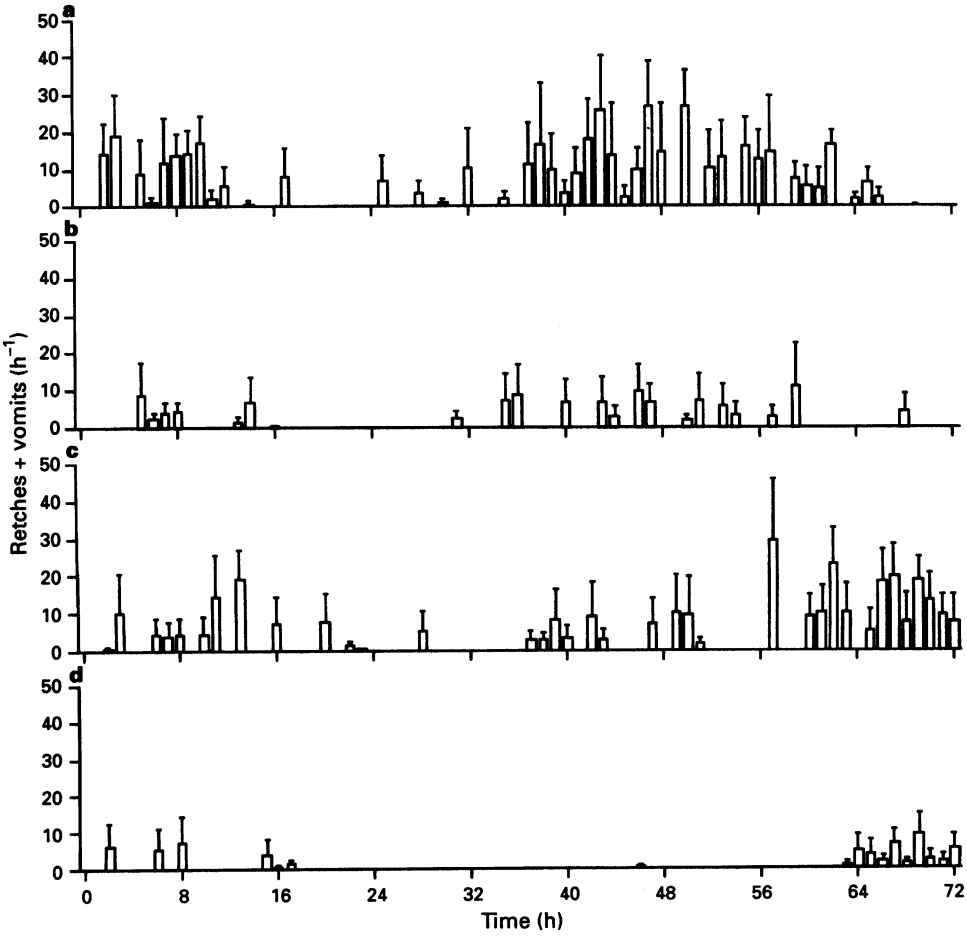

Figure 1 The effect of (a) vehicle (distilled water) 1 ml kg^{-1}, i.p., three times per day, (b) ondansetron 1 mg kg^{-1}, i.p., three times per day, (c) dexamethasone 1 mg kg^{-1}, i.p., once per day or (d) the combination of ondansetron (1 mg kg^{-1}, i.p., three times per day) and dexamethasone (1 mg kg^{-1}, i.p., once per day) all administrations being for 3 days, on the profile of retching + vomiting in the ferret induced by a single injection of cisplatin, 5 mg kg^{-1}, i.p., on day 1. Results represent the mean±s.e.mean of the total numbers of retches + vomits occurring in 1 h time intervals ($n=4$).

Results

The ability of ondansetron administered three times per day and/or dexamethasone administered once per day to antagonize cisplatin (5mg kg^{-1} i.p.)-induced retching and vomiting in the ferret during a 72 h observation period

Cisplatin (5 mg kg^{-1}, i.p.) induced emesis within 2.6±0.7 h of administration and comprised 79.3±5.1 episodes of 390.5±17.8 retches and 49.5±4.1 vomits during the total 72 h observation period (Figure 1). The response was divided into 116.8±18.9, 184.3±28.0 and 139.0±32.8 retches+vomits that occurred on days 1, 2 and 3 respectively. The administration of ondansetron (1 mg kg^{-1}, i.p.) three times per day, the administration of dexamethasone (1 mg kg^{-1}, i.p.) once per day and the combination treatment of ondanestron (1 mg kg^{-1}, i.p.) three times per day and dexamethasone (1 mg kg^{-1}, i.p.) once per day reduced respectively the retching+vomiting response induced cisplatin by 76% ($P<0.05$), 37% ($P<0.05$) and 78% ($P<0.05$) on day 1 and by 73% ($P<0.001$), 77% ($P<0.001$) and 99% ($P<0.001$) on day 2. On day 3, ondansetron (1 mg kg^{-1}, i.p.) administered three times per day ($P<0.001$) reduced significantly the retching+vomiting response by 74% ($P<0.05$) but dexamethasone non-significantly increased the retching and vomiting response by 46% ($P>0.05$); the combination treatment of ondanestron and dexamethasone reduced the retching+vomiting response by 72% ($P<0.05$).

Overall, ondanestron (1 mg kg^{-1}) administered three times per day significantly antagonized the total numbers of episodes, retches or vomits that were induced by cisplatin during the entire 72 h observation period by 69% ($P<0.001$), 73% ($P<0.001$) and 82% ($P<0.001$) respectivley. Conversely, dexamethasone (1 mg kg^{-1}, i.p.) administered once per day as a single pretreatment reduced non-significantly ($P>0.05$) the total numbers of episodes (18%) and retches (23%) but did antagonize significantly ($P<0.05$) the number of vomits (54%). However, the combination treatment of ondansetron (1 mg kg^{-1}, i.p.) three times per day and dexamethasone (1 mg kg^{-1}, i.p.) once per day antagonized significantly the total numbers of episodes, retches and vomits recorded during the entire 72 h observation period by 79% ($P<0.001$), 73% ($P<0.001$) and 87% ($P<0.001$) respectively (Figure 1).

The ability of ondansetron administered three times per day and/or dexamethasone administered three times per day to antagonize cisplatin (5 mg kg^{-1}, i.p.)-induced retching and vomiting in the ferret during a 72 h observation period

Cisplatin (5 mg kg^{-1}, i.p.) induced emesis within 2.0±0.2 h of administration and comprised 81.2±10.8 episodes of 462.0±81.6 retches and 28.8±5.8 vomits; 193.2±55.1, 112.4±13.7 and 185.2±34.3 of the number of retches+vomits occurred on days 1, 2 and 3 respectively during the total 72 observation period.

The administration of ondansetron (1 mg kg^{-1}, i.p.) three times per day reduced the total numbers of retches+vomits

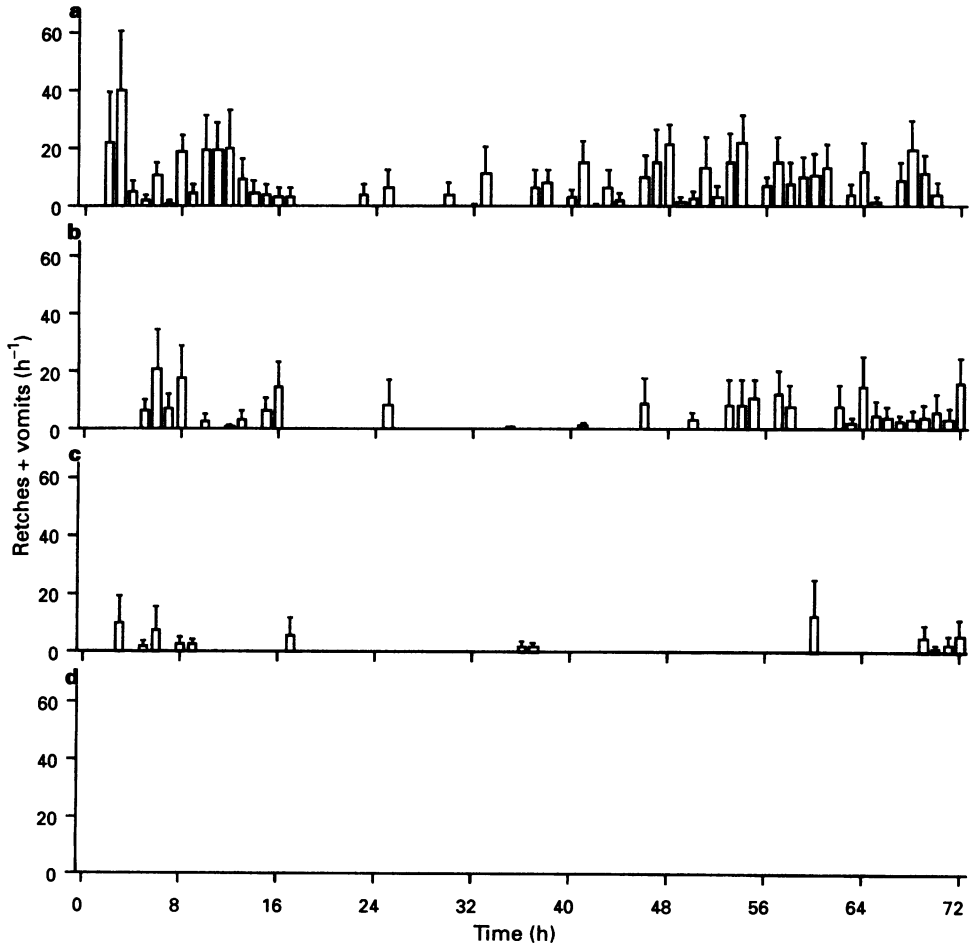

Figure 2 The effect of (a) vehicle (distilled water) 1 ml kg^{-1}, i.p., three times per day, (b) ondansetron, 1 mg kg^{-1}, i.p., three times per day, (c) dexamethasone, 1 mg kg^{-1}, i.p., three times per day or (d) the combination of ondansetron (1 mg kg^{-1}, i.p., three times per day) and dexamethasone (1 mg kg^{-1}, i.p., three times per day) all treatments being for 3 days, on the profile of retching+vomiting in the ferret induced by a single dose of cisplatin 5 mg kg^{-1}, i.p., on day 1. Results represent the mean±s.e.mean of the total numbers of retches+vomits occurring in 1 h time intervals ($n=5$).

induced by cisplatin by 60% ($P>0.05$) on day 1, by 84% ($P<0.001$) on day 2 and by 38% ($P>0.05$) on day 3. Dexamethasone (1 mg kg^{-1}, i.p.) administered three times per day antagonized significantly the total numbers of retches + vomits on day 1, 2 and 3 by 85% ($P<0.01$), 97% ($P<0.001$) and 86% ($P<0.001$) respectively. Indeed, four out of five ferrets were completely protected from retching or vomiting on days 1 and 2 and three out of five ferrets were protected on day 3. The combination treatment of ondansetron and dexamethasone completely prevented the retching + vomiting response on all days in 5 out of 5 ferrets ($P<0.001$). Further, the total numbers of episodes and retches recorded during the entire 72 h observation period for cisplatin vehicle-treated animals were significantly reduced by 53% ($P<0.01$) and 58% respectively ($P<0.01$) by the treatment of ondansetron 1 mg kg^{-1}, i.p. three times per day; the total number of vomits was reduced by 36% ($P>0.05$). Dexamethasone (1 mg kg^{-1}, i.p.) administered three times per day significantly antagonized the total numbers of episodes, retches and vomits recorded during the entire 72 h observation period by 87% ($P<0.001$), 88% ($P<0.001$) and 80% ($P<0.01$) respectively. The combination treatment of ondansetron and dexamethasone reduced the numbers of episodes, retches and vomits by 100% during the 72 h observation period ($P<0.001$) (Figure 2).

The failure of the combination of ondansetron and dexamethasone plus cisplatin (5 mg kg^{-1}, i.p.) administered on day 1 to prevent the development of retching and vomiting on days 2 and 3

Cisplatin (5 mg kg^{-1}, i.p.) induced emesis within 15.3 ± 7.8 h of administration and comprised 76.6 ± 19.6 episodes of 376.8 ± 115.4 retches and 37.0 ± 10.9 vomits during the total 72 h observation period. The number of retching + vomiting responses occurring on days 1, 2 and 3 was 103.8 ± 56.4, 83.0 ± 29.0 and 227.0 ± 60.3 respectively. The combination of ondansetron (1 mg kg^{-1}, i.p.) and dexamethasone (1 mg kg^{-1}, i.p.) administered every 8 h on day 1 reduced significantly the retching + vomiting response by 99% during the first 24 h period ($P<0.05$); 1 out of 4 ferrets had 2 episodes of 2 and 3 retches 7.1 h post administration of cisplatin. There was a trend for the animals that had received the ondanestron and dexamethasone treatment to exhibit 73% more retches + vomits on day 2 ($P>0.05$) and exhibit 20% less retches + vomits on day 3 than those animals treated with vehicle ($P>0.05$). The antagonism of day 1 retching + vomiting by the ondansetron plus dexamethasone regimen did not significantly affect the total numbers of episodes, retches or vomits and that occurred during the entire 72 h observation period ($P>0.05$) (Figure 3).

Discussion

The present study has confirmed that administration of ondansetron three times a day can reduce significantly the retching and vomiting induced by a single dose of cisplatin on day one (the 'acute phase') of treatment (Rudd & Naylor, 1994). More variable reductions were recorded on the second and third days of treatment (the 'delayed response'); ethical considerations precluded an extension of the studies beyond this period. The importance of the study has been to establish that dexamethasone administered once or three times daily both during the acute and delayed phases can also reduce cisplatin-induced emesis in the ferret model and can enhance the effect of ondansetron in preventing cisplatin-induced retching and vomiting. The anti-emetic effects of ondanestron are reasonably attributed to a 5-HT_3 receptor blockade during both the acute and delayed phase, the receptor antagonism being probably afforded at central sites in the area postrema and nucleus tractus solitarius and peripherally on afferent vagus nerve fibres in the gastointestinal tract (Naylor & Rudd, 1994). The anti-emetic action of dexamethasone and the nature of its interaction with ondansetron remains essentially unknown. Plasma cortisol levels may be inversely related to the development of nausea induced by chemotherapy in man (Fredrikson *et al.*, 1992; Hirsti *et al.*, 1993) and the anti-emetic effects of dexamethasone may be related to an ability to reduce prostaglandin synthesis (Sanger, 1993). Certainly, dexamethasone has been reported to reduce postoperative nausea and vomiting (Mataruski *et al.*, 1990) and this may be related to an ability to control pain following surgical procedures (Baxendale *et al.*, 1993); prostaglandins may be involved in such mechanisms.

The anti-emetic effect of dexamethasone appears to be selective to chemotherapy in the ferret since it does not affect the emesis caused by an activation of central mechanisms induced by apomorphine or morphine or those induced by gastric irritation caused by treatment with oral copper sulphate solution (Rudd *et al.*, 1995). Indeed, the acute and delayed emesis

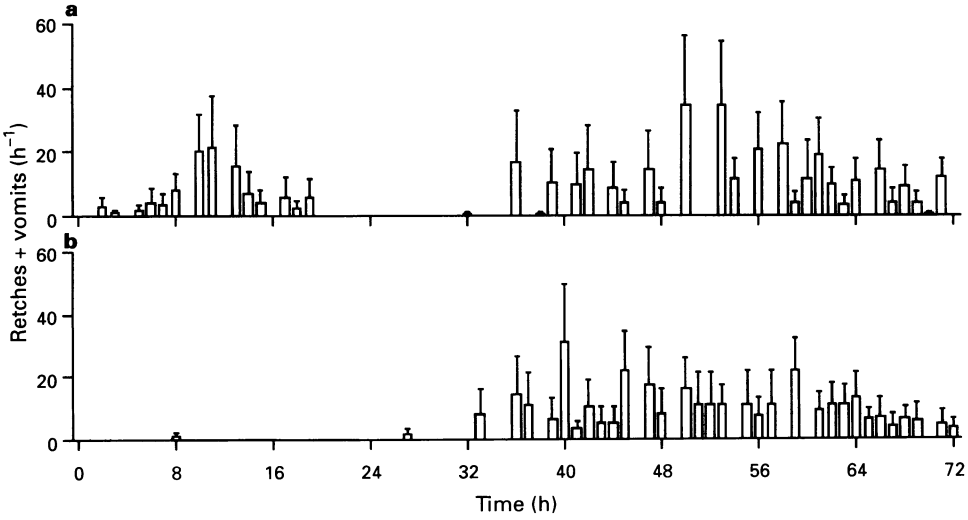

Figure 3 The effect of (a) vehicle (distilled water) 1 ml kg^{-1}, i.p., three times per day for one day only or (b) ondansetron (1 mg kg^{-1}, i.p., three times per day) plus dexamethasone (1 mg kg^{-1}, i.p., three times per day) for one day only on the profile of retching + vomiting in the ferret over a 3 day period induced by a single injection of cisplatin, 5 mg kg^{-1}, i.p., on day 1. Results represent the mean ± s.e.mean of the total numbers of retches + vomits occurring in 1 h time intervals ($n=4$).

model in the ferret is the first to reveal an unequivocal anti-emetic action of dexamethasone in its own right. In a previous study, a single injection of 2 or 5 mg kg^{-1} dexamethasone failed to reduce cyclophosphamide-induced emesis in the ferret when measured over a 4 h period. Moreover, when combined with ondansetron, dexamethasone hastened the onset of emesis although finally reducing the phase of emesis resistant to ondansetron treatment (Hawthorn & Cunningham, 1990).

The ability of the acute and delayed emesis model in the ferret to demonstrate the anti-emetic potential of dexamethasone and its interaction with ondansetron supports its value in an understanding of the mechanisms of chemotherapy-induced emesis and its treatment in man. Dexamethasone administered as a single daily treatment improves the control of both acute and delayed chemotherapy-induced emesis in man (see introduction). The anti-emetic dose of dexamethasone in the present study is some five to ten times higher than that used in the clinic (Cerosimo & Karp, 1986) and was required in a three times per day administration to maximize its effects. The requirement in a three times per day administration may be related to its relatively short half life which is estimated to be 2 to 3.5 h, at least in man (Tsuei *et al.*, 1979; Ridgeway *et al.*, 1984). Such observations may have important implications for the clinical use of dexamethasone. Future studies are necessary to establish the minimum effective doses of dexamethasone and the use of other corticosteroids are required to establish the importance of the anti-inflammatory actions to an anti-emetic potential.

The model also provides an opportunity to assess the relevance of the acute response and its control, to the development of the delayed response: there are reports that a good control of the acute response in man can predispose to an improved control of the delayed response (Aapro, 1992). In the present experiments, cisplatin-induced emesis on day one was virtually abolished by a combined regimen of ondansetron and dexamethasone administered three times per day on day one only: the emesis occurring on days 2 and 3 was not significantly different from that occurring in the absence of ondansetron and dexamethasone. Clearly, the development of the delayed response can occur independently of the acute responses in the ferret model.

In summary, the ability of dexamethasone to improve the control of emesis afforded by ondansetron in the ferret is consistent with the clinical profile of these agents in the treatment of chemotherapy-induced emesis. The use of the ferret model may increase an understanding of the mechanisms involved in acute and delayed emesis and further the detection of improved treatments.

The financial support of Glaxo Research and Development is gratefully acknowledged.

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(Received November 27, 1995
Accepted January 22, 1996)