British Journal of Pharmacology (1996) 119, 931-936

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

[1,*]J.A. Rudd, †C.C. Jordan & R.J. Naylor

Postgraduate Studies in Pharmacology, The School of Pharmacy, University of Bradford, Bradford, BD7 1DP; [1,*]Department of Pharmacology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong and †Pharmacology I, Glaxo Wellcome Research and Development Ltd., Glaxo Wellcome Medicines Research Centre, Stevenage, SG1 2NY

1 The anti-emetic effects of the NK_1 tachykinin receptor antagonist, CP 99,994 (10 mg kg^{-1}) were investigated in the ferret using a cisplatin-induced acute (day 1) and delayed (day 2 and 3) retching and vomiting model.

2 With a single cisplatin (10 mg kg^{-1}) emetogenic challenge, the i.p. administration of CP 99,994 given as a single injection immediately following the first emetic episode, promptly abolished the retching and vomiting for a 4 h period. CP 99,994 was as efficacious as ondansetron (1.0 mg kg^{-1}). The general toxicity of cisplatin 10 mg kg^{-1} precluded its use in studies of delayed emesis.

3 With a single cisplatin (5 mg kg^{-1}) emetogenic challenge, the single administration of either CP 99,994 (10 mg kg^{-1}) or ondansetron (1.0 mg kg^{-1}) immediately following the first emetic episode markedly reduced or abolished the retching and vomiting for 4 h. Such single treatments failed to modify significantly the intensity of delayed emesis appearing on the second and third day.

4 With a cisplatin (5 mg kg^{-1}) emetogenic challenge, administration of CP 99,994 (10 mg kg^{-1}) at 8 hourly intervals, the first injection being administered 30 s post cisplatin, was associated with 4 or more abolitions of emesis during both the acute and delayed phase. A 4 hourly administration of CP 99,994 for 20 h during delayed emesis completely abolished the retching and vomiting.

5 It is concluded that cisplatin 5 mg kg^{-1} provides an emetogenic challenge causing an acute and delayed phase of retching and vomiting and that CP 99,994 can abolish both phases. The results may be relevant to the understanding and treatment of chemotherapy-induced emesis in man.

Keywords: NK_1 receptor antagonist; CP 99,994; acute and delayed emesis in ferret; cisplatin

Introduction

Significant advances in the control of chemotherapy-induced emesis in man have been made by use of regimens of corticosteroids in combination with selective 5-HT_3 receptor antagonists such as ondansetron (Grunberg, 1993). Such regimens are effective in the majority of patients in controlling the acute emetic response (the emesis occurring on day one of treatment) and are also effective in reducing the development of delayed emesis (Rath *et al.*, 1993; Roila, 1993). However, there remains no effective or logical treatment of the residual emesis that occurs in patients that are unresponsive to corticosteroid and 5-HT_3 receptor antagonists (Sanger & Andrews, 1993).

Recently, the NK_1 tachykinin receptor antagonists, CP 99,994 (McLean *et al.*, 1993) and GR203040 (Beattie *et al.*, 1995) have been demonstrated to prevent the emesis induced by diverse emetic challenges including the emesis induced by apomorphine, morphine, nicotine, copper sulphate, ipecacuanha, radiation, cyclophosphamide, cisplatin and provocative motion (Bountra *et al.*, 1993; Gardner *et al.*, 1995; Tattersall *et al.*, 1993; 1994; Watson *et al.*, 1995a). This broad inhibitory profile indicates the importance of substance P in the emetic reflex and points towards the possibility that selective NK_1 tachykinin receptor antagonists may be useful in preventing emesis in man.

However, the chemotherapy-induced emesis in animal models that has been used to investigate the anti-emetic activity of CP 99,994 does not address a potential to prevent delayed emesis; the observation periods have not extended beyond 8 h. Therefore, in the present studies, we investigate the potential of CP 99,994 for antagonizing the acute and delayed emesis in the ferret, using two models (Rudd *et al.*, 1994). The first used cisplatin at a dose of 10 mg kg^{-1}, the dose normally used to induce emesis in most acute studies, but with an observation period extended to 40 h. The second used cisplatin at the lower dose of 5 mg kg^{-1} and an extended observation period of 3 days, a model that we have partially validated to reflect chemotherapy-induced acute and delayed emesis in man, having established the anti-emetic effectiveness of a combined dexamethasone/ondansetron treatment (Rudd & Naylor, 1996).

Methods

Animals

Male ferrets (0.8-1.8 kg; U.K. bred), housed individually at 22±1°C under artificial lighting with lights on between 07 h 00 min and 21 h 00 min, 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 30 min, ferrets were transferred to observation cages where they were allowed 30 min to adapt before being presented with approximately 100 g of cat food (Kitecat Supreme, Pedigree Pet Foods, Leicestershire U.K.). In some experiments, ferrets were injected with cisplatin 5 or 10 mg kg^{-1}, i.p. and allowed to develop a retching and/or vomiting response

[1] Author for correspondence.

before the administration of CP 99,994 10 mg kg^{-1}, i.p., ondansetron 1 mg kg^{-1}, i.p. or vehicle (distilled water 1.0 ml kg^{-1}, i.p.). In other experiments, ferrets were administered CP 99,994 10 mg kg^{-1}, i.p., or vehicle, 30 s after the administration of cisplatin 5 mg kg^{-1}, i.p. and then at regular 8 h intervals. A final set of experiments investigated the effect of CP 99,994 10 mg kg^{-1}, i.p. or vehicle administered at 36, 40, 44, 48, 52 and 56 h on the profile of delayed emesis induced by cisplatin 5 mg kg^{-1}. During the experiments, the animals were housed individually in observation cages for the assessment of retching and/or vomiting during the 40 and 72 h observation periods. During these time periods food (SDS Diet "C") and water was available *ad libitum*.

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 were considered separate i.e. 'bouts' when the animal changed its location in the observation cage, or when the interval between retches and/or vomits exceeded 5 s.

Experimental design and statistical analysis

The experiments are designated as a moderately severe procedure. Ethical considerations required the use of the minimal number of animals to obtain meaningful results. Great care was also taken to ensure the constant monitoring of the animals health throughout the experiments.

In each animal, the latency to retch and/or vomit and the total number of retches, vomits and episodes of retching and/or vomiting 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 normal saline at 70–75°C followed by gradual cooling to 40–50°C and administered immediately. CP 99,994 ((+)-(2S,3S)-3-(2-methoxybenzylamino)-2-phenylpiperidine, Glaxo) and ondansetron dihydrochloride (Glaxo) were prepared in distilled water and administered in a volume of 1 ml kg^{-1}. Cisplatin was administered in a volume of 5 ml kg^{-1}. Doses, except for cisplatin, are expressed as the free base.

Results

The ability of CP 99,994 or ondansetron, administered at the first episode of retching or vomiting, to antagonize cisplatin (10 mg kg^{-1})-induced emesis in the ferret during a 40 h observation period

Cisplatin (10 mg kg^{-1}, i.p.) induced emesis within 1.7±0.1 h of administration and comprised 34.5±10.9 episodes of

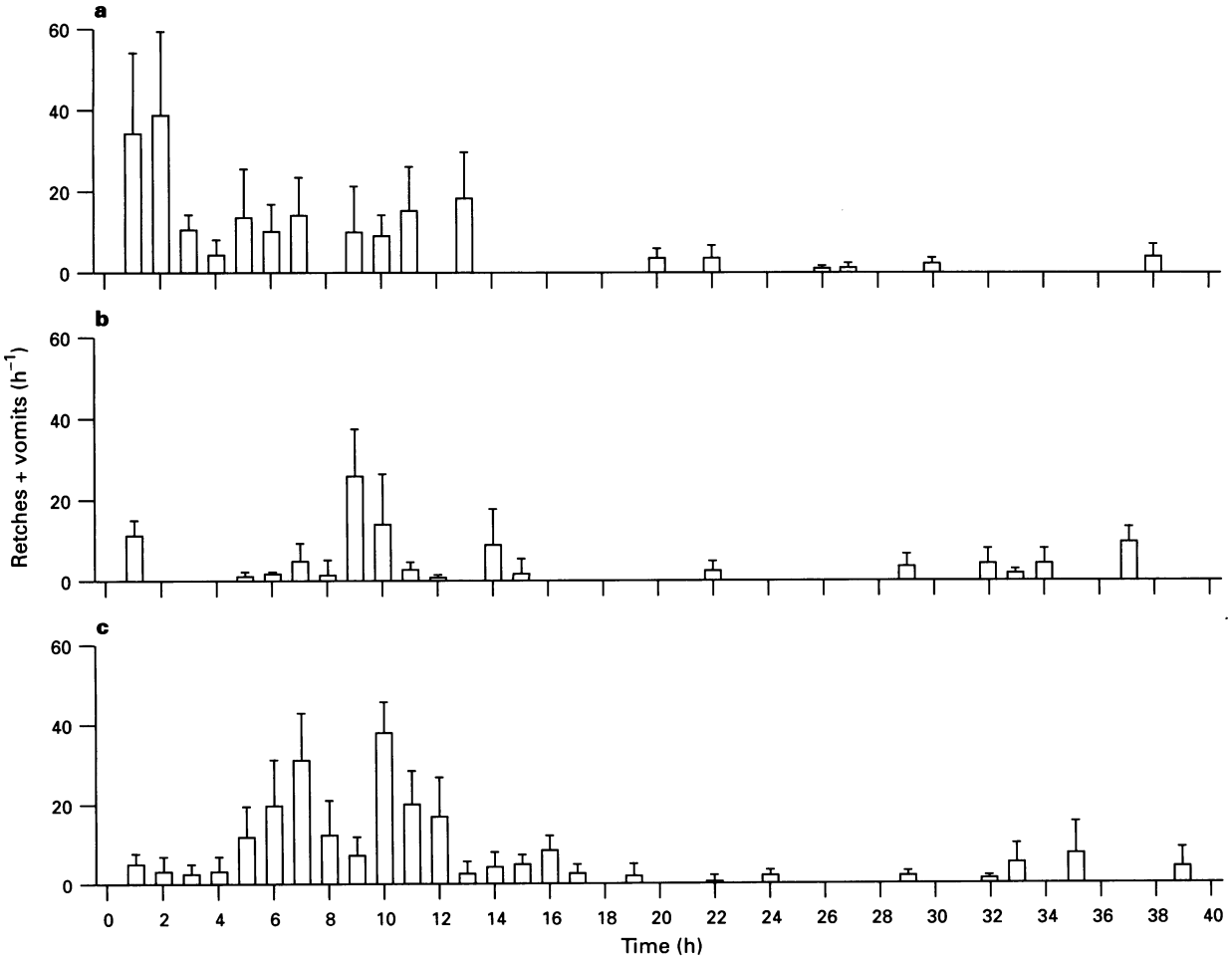

Figure 1 The effect of distilled water 1 ml kg^{-1}, i.p. (a), CP 99,994 10 mg kg^{-1}, i.p. (b) or ondansetron 1 mg kg^{-1}, i.p. (c) administered at the first emetic episode on the subsequent development of retching + vomiting induced by cisplatin (10 mg kg^{-1}, i.p.) in the ferret. Results represent the mean±s.e.mean of the total numbers of retches + vomits occurring in 1 h time intervals after cisplatin injection at 0 h (n=4).

173.5±67.9 retches and 12.8±3.4 vomits during the total 40 h observation period. The response consisted of 84.3±37.0 retches+vomits that occurred during the first 4 h after cisplatin administration and 98.0±45.9 retches+vomits during the next 20 h period. There were 5.8±4.1 retches+vomits recorded during the subsequent 24–40 h period. CP 99,994 (10 mg kg^{-1}, i.p.) and ondansetron (1 mg kg^{-1}, i.p.) administered at the first retching or vomiting episode reduced significantly the retching+vomiting induced by cisplatin by 100% ($P<0.05$) and 96% ($P<0.05$) respectively during the initial 4 h observation. During the next 20 h period, when emesis in control treated animals was at a lower intensity, animals that had received prior treatment with CP 99,994 or ondansetron showed non-significant changes in retching or vomiting ($P>0.05$). During the remaining 16 h observation period, the initial treatment with either CP 99,994 or ondansetron failed to modify the sporadic and low intensity retching and vomiting response induced by cisplatin ($P>0.05$) as compared to the control treated animals (Figure 1).

It should be noted that cisplatin (10 mg kg^{-1}) is a severely cytotoxic challenge in the ferret and, whilst the initial intensity and duration of retching and vomiting is generally comparable to that induced by the lower dose of cisplatin (5 mg kg^{-1}, see below), the systemic toxicity, lethargy and lassitude gradually presents as a debilitating appearance requiring a termination of the experiments at 40 h. The generally low level of retching or vomiting observed 20 to 30 or 40 h after cisplatin injection may reflect the initially intense and persistent retching observed over a 12 h period followed by exhaustive disruption and general debilitation. In any event, the use of the higher dose of cisplatin (10 mg kg^{-1}) is inappropriate to a study of delayed emesis.

The ability of CP 99,994, ondansetron or vehicle, administered as a single treatment at the first episode of retching or vomiting induced by cisplatin (5 mg kg^{-1}, i.p.) to modify the development of acute and delayed emesis during a 72 h observation period

The experiment used 22 ferrets that were originally intended to receive randomized treatments of CP 99,994, ondansetron or vehicle immediately following the development of the first retching and/or vomiting episode induced by cisplatin 5 mg kg^{-1}, i.p. However, during the course of the experiment, 7 ferrets failed to retch or vomit to cisplatin during the initial 8 h period (latency to onset: 29.2±7.2 h) and consequently did not receive the scheduled treatment. The group of animals that did not receive treatment were not included in the data analysis at the end of the experiment but were observed to experience a delayed emetic response that comprised 181.1±66.8 retches+vomits that occurred over days 2 and 3. The latency to the onset of emesis induced by cisplatin for the vehicle, CP 99,994 and ondansetron treatment groups was 2.4±0.7, 2.5±0.9, and 2.6±0.9 h.

In vehicle-treated cisplatin animals, the emetic response consisted of 68.0±10.0 episodes of 295.3±50.8 retches and

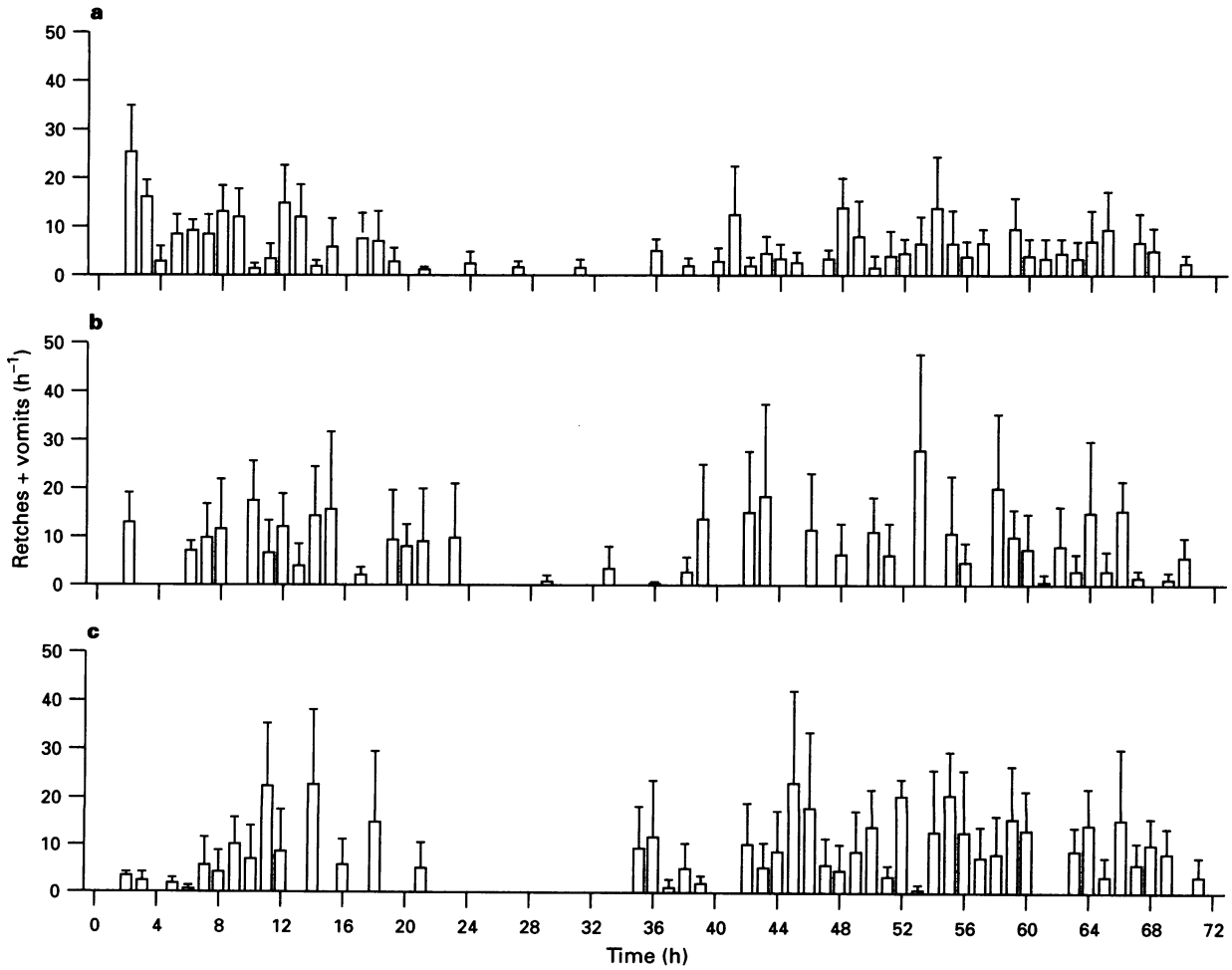

Figure 2 The effect of distilled water 1 ml kg^{-1}, i.p. (a), CP 99,994 10 mg kg^{-1}, i.p. (b) or ondansetron 1 mg kg^{-1}, i.p. (c) administered at the first emetic episode on the subsequent development of retching+vomiting induced by cisplatin (5 mg kg^{-1}, i.p.) in the ferret. Results represent the mean±s.e.mean of the total numbers of retches+vomits occurring in 1 h time intervals after cisplatin injection at 0 h ($n=4-7$).

28.0±3.7 vomits during the total 72 h observation period. The response was divided into 43.8±12.5, 109.5±19.8, 55.2±11.1 and 114.5±35.9 retches+vomits during the initial 4 h period, during the 4–24 h period and on days 2 and 3 respectively. The injection of CP 99,994 (10 mg kg^{-1}, i.p.) administered at the first episode of retching or vomiting reduced significantly the retching and vomiting response induced by vehicle-treated cisplatin animals by 82.3% ($P<0.05$) during the initial 4 h period and caused a non-significant trend to increase the retching+vomiting response by 27.0 ($P>0.05$) 34.0 ($P>0.05$) and 35.8% ($P>0.05$) during the 4–24 h period and on days 2 and 3 respectively. Ondansetron (1 mg kg^{-1}, i.p.) administered at the first episode of retching or vomiting also reduced significantly the retching+vomiting by 99% ($P<0.01$) during the initial 4 h period but did not significantly modify retching and vomiting (a 3% decrease, $P>0.05$) during the subsequent 4–24 h period. The consequence of the ondansetron treatment on day 1 was to produce a non-significant trend to increase the retching+vomiting response on days 2 and 3 by 90.2 ($P>0.05$) and 80.0% ($P>0.05$) respectively (Figure 2).

Data analysis of the entire 72 h period revealed that the injection of CP 99,994 or ondansetron, as a single treatment, failed to affect significantly the total retching and vomiting response ($P>0.05$).

The ability of CP 99,994 (10 mg kg^{-1}, i.p.) administered three times per day for 3 days to antagonize the acute and delayed emetic response induced by cisplatin (5 mg kg^{-1}) during a 72 h observation period

Cisplatin (5 mg kg^{-1}, i.p.) induced emesis within 6.3±4.6 h of administration and comprised 52.7±9.2 episodes of 316.5±56.1 retches and 27.8±5.4 vomits (one animal did not develop emesis until 29.3 h after cisplatin administration and exhibited 13 episodes of 57 retches and 3 vomits) during the entire 72 h observation period. The response was divided into 112.5±37.5, 140.3±39.3 and 91.5±26.9 retches+vomits that occurred on days 1, 2 and 3 respectively. The administration of CP 99,994 (10 mg kg^{-1}, i.p.) three times per day at 8 h intervals for 3 days, with the first injection 30 s after cisplatin injection, produced an initial 1.7 h delay in the onset of the first episode and abolished the retching and vomiting response for at least 3–4 h following each subsequent injection, up to the seventh administration at 56 h. Overall, CP 99,994 produced a trend to antagonize the retching+vomiting response that occurred on day 1 by 33.8% ($P>0.05$) and reduced significantly the retching+vomiting response that occurred on days 2 and 3 by 87.4 ($P<0.05$) and 87.7% ($P<0.05$) respectively (Figure 3).

Further analysis of the data revealed that CP 99,994 (10 mg kg^{-1}, i.p.) administered three times per day for 3 days antagonized significantly the total numbers of episodes, retches and vomits that was induced by cisplatin during the entire 72 h observation period by 62.5 ($P<0.05$), 70.1 ($P<0.05$) and 67.7% ($P<0.05$) respectively.

The ability of CP 99,994 (10 mg kg^{-1}, i.p.) administered as an intervention treatment of six injections to antagonize an established delayed retching and vomiting response induced by cisplatin (5 mg kg^{-1})

Ferrets received vehicle or CP 99,994 (10 mg kg^{-1}, i.p.) at 36, 40, 44, 48, 52 and 56 h after cisplatin (5 mg kg^{-1}, i.p.) injection. The vehicle and CP 99,994 treatment groups developed retching and vomiting within 4.6±1.9 and 5.1±2.0 h respectively ($P>0.05$). The total number of retches+vomits recorded for the vehicle-treatment group on days 1 (141.3±52.0) and 2 (118.8±50.6) were not significantly different from the retching+vomiting response recorded for the CP 99,994-treated animals ($P>0.05$). The vehicle-treated cisplatin animals exhibited 74.3±5.4 episodes of 411.3±18.2 retches and 35.3±4.5 vomits during the entire 72 h observation period.

During the 36–72 h period, vehicle-treated cisplatin animals exhibited 277.3±41.9 retches+vomits. The administra-

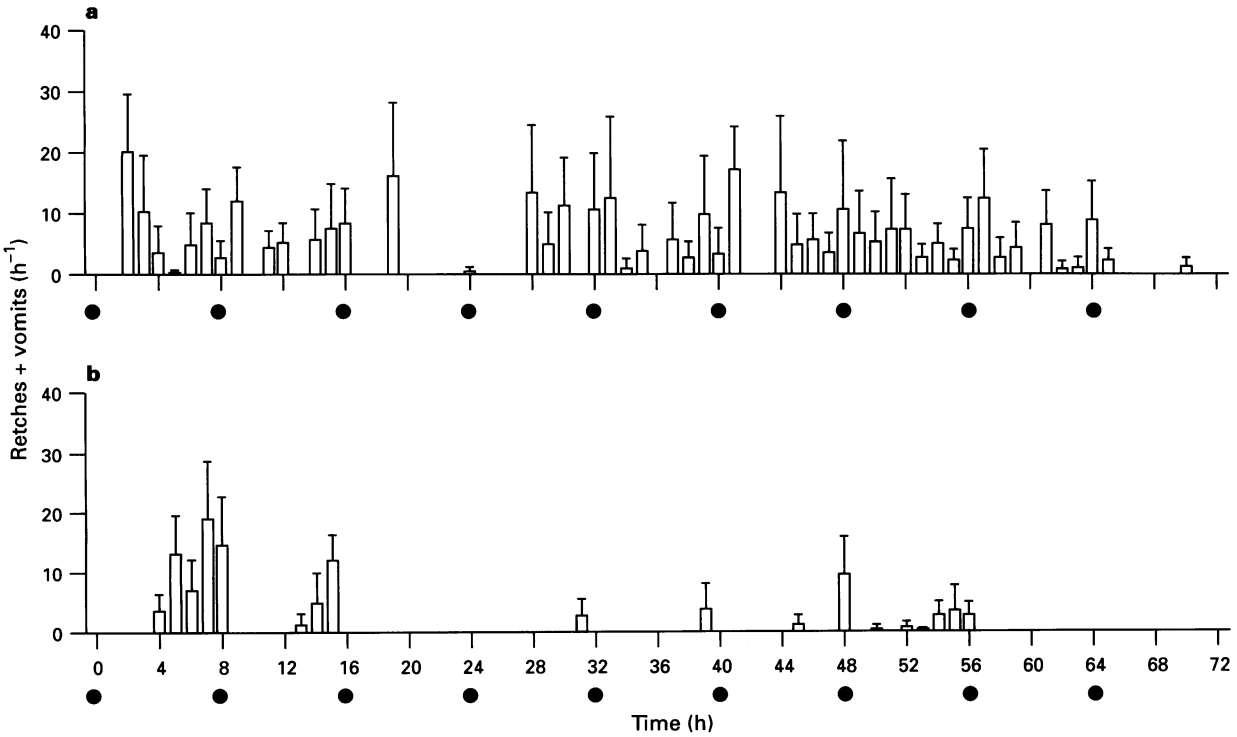

Figure 3 The effect of an injection of distilled water 1 ml kg^{-1}, i.p. (a) or CP 99,994 10 mg kg^{-1}, i.p. (b), at 8 hourly intervals for 3 days (the first injection was 30 s after cisplatin) on the profile of retching+vomiting induced by cisplatin (5 mg kg^{-1}, i.p.) in the ferret. Administration of drug or vehicle is indicated as (●). Results represent the mean±s.e.mean of the total numbers of retches+vomits occurring in 1 h time intervals after cisplatin injection at 0 h ($n=4-6$).

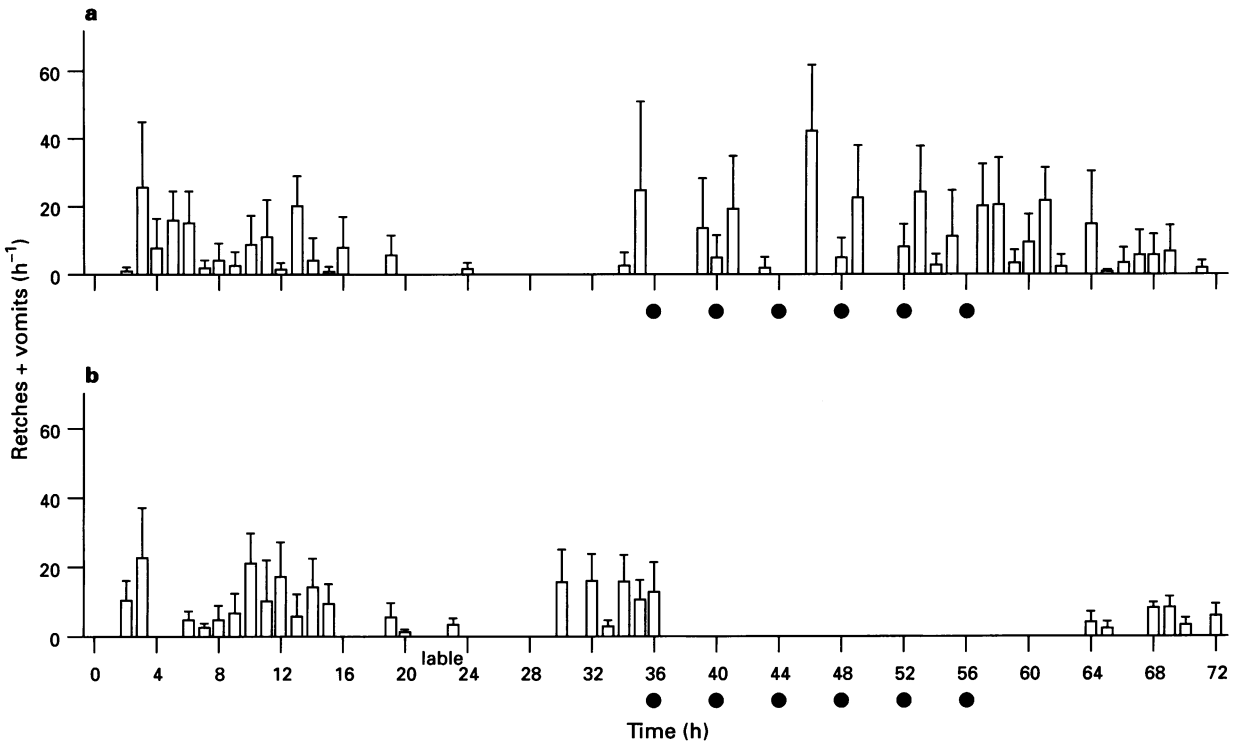

Figure 4 The effect of repeated injections of distilled water 1 ml kg^{-1}, i.p. (a) or CP 99,994 10 mg kg^{-1}, i.p. (b) on the profile of retching + vomiting induced by cisplatin (5 mg kg^{-1}, i.p.) in the ferret. Administration of drug or vehicle is indicated as (●). Results represent the mean ± s.e.mean of the total numbers of retches + vomits occurring at 1 h time intervals after cisplatin injection at 0 h ($n=4$).

tion of CP 99,994 (10 mg kg^{-1}, i.p.) during this period completely prevented retching and vomiting until 7.9 ± 0.2 h after the last injection and significantly antagonized by 89% ($P<0.01$) the retching and vomiting response that occurred during the 36–72 h period (Figure 4).

Discussion

The present studies have revealed the anti-emetic potential of CP 99,994 in preventing both the acute delayed phase of emesis induced by cisplatin in the ferret. In both the high and low dose cisplatin (10 and 5 mg kg^{-1})-induced emesis models, CP 99,994 was rapidly effective in reducing or abolishing the retching and vomiting. The antagonism of the acute response was evident in two ways. Early treatment with CP 99,994 (administered at the same time as cisplatin) prevented cisplatin-induced emesis; CP 99,994 was also shown to antagonize cisplatin-induced emesis when administered during an established response. The antagonism confirms previous observations (Tattersall *et al.*, 1993; Bountra *et al.*, 1993) and shows that CP 99,994 is as efficacious as ondansetron. The novel finding of the study was the antagonism by CP 99,994 of the delayed phase (day two and three) of emesis induced by the low dose of cisplatin. Thus, an 8 hourly administration of CP 99,994, for 3 days, markedly reduced the delayed phase and is consistent with the recent data obtain by Watson and co-workers (1995b). During the present study, a 4 hourly administration of CP 99,994 during the second and third days also abolished an established delayed emetic response. Compared to previous studies in these laboratories (Rudd & Naylor, 1994; 1996), CP 99,994 has been shown to be more effective than ondansetron in antagonizing the delayed phase of emesis as a 3 times per day administration.

The pathways activated by cisplatin to induce acute and delayed emesis in the ferret and man are essentially unknown and multiple drug therapy is at present required to provide a reasonable control of chemotherapy-induced emesis in man. Thus, the regimen of a 5-HT_3 receptor antagonist plus a corticosteroid such as dexamethasone represents the optimal therapy to reduce both phases of the emetic response (see introduction). The efficacy of the regimen, although not maximal, indicates that 5-hydroxytryptaminergic and perhaps eicosanoid pathways may be involved in both the acute phase (Cubeddu *et al.*, 1990) and in part during the delayed phase (Cubeddu & Hoffmann, 1993; Wilder-Smith *et al.*, 1993). However, a residual emesis has remained that is resistant to treatment and of unknown aetiology.

Whilst the mechanisms mediating the residual emesis in man are not known, it is logical to consider that the mechanisms are those unaffected by 5-HT_3 receptor blockade or treatment with corticosteroids in the ferret emesis model. Such mechanisms may be evoked in models of drug-induced emesis that are also resistant to ondansetron or dexamethasone-treatment e.g. the emesis induced by apomorphine or intragastric copper sulphate (Rudd *et al.*, 1996). However, it has been shown unequivocally that CP 99,994 is effective in preventing the emesis induced by all these emetogens (see introduction) and to which the present studies extend to delayed emesis in the ferret.

The anatomical site(s) of action of CP 99,994 are likely to be at NK_1 tachykinin receptors located in the dorsal vagal complex (Watson *et al.*, 1995a) since the injection of NK_1 tachykinin receptor antagonists into this brain area has been demonstrated to antagonize the early emesis induced by cisplatin and substance P (Gardner *et al.*, 1994). However, NK_1 tachykinin receptor antagonists also have anti-inflammatory properties (Walsh *et al.*, 1995) and such an action might contribute to the control of delayed emesis and the trauma associated with persistent retching and vomiting over so many hours during the present studies.

The present studies also revealed a variation in the sensitivity of the ferret to the emetic action of cisplatin (5 mg kg^{-1}, i.p.). Some of the animals did not develop an acute emetic response or developed emesis after a latency in excess of 8 h to indicate that the dose of cisplatin (5 mg kg^{-1}, i.p.) may be a

threshold dose to induce emesis. Such variation in the emetic action of cisplatin 5 mg kg^{-1}, i.p. has not been observed previously in our laboratories within a 2 year period and there is no obvious explanation of the present findings. Moreover, the animals did develop a delayed emetic response to cisplatin.

In summary, the NK_1 tachykinin receptor antagonist, CP 99,994 (10 mg kg^{-1}), administered 3 times per day, was revealed as being effective in antagonizing the acute and delayed emesis induced by cisplatin in the ferret. When administered as an intervention therapy as 6 injections at 4 h intervals CP 99,994 completely prevented the delayed retching and vomiting response. The studies provide a strong rationale for assessing the action of NK_1 tachykinin receptor antagonists in controlling acute and delayed emesis in man. The studies also indicate the NK_1 tachykinin receptor antagonists may be useful in preventing an established emetic response and reveal the importance of substance P to the different phases of emesis induced by cisplatin. The potential of NK_1 tachykinin receptor antagonists for reduction of nausea awaits clinical assessment.

References

BEATTIE, D.T., BERESFORD, I.J.M., CONNOR, H.E., MARSHALL, F.H., HAWCOCK, A.B., HAGAN, R.M., BOWERS, J., BIRCH, P.J. & WARD, P. (1995). The pharmacology of GR203040, a novel, potent and selective non-peptide tachykinin NK_1 receptor antagonist, *Br. J. Pharmacol.*, **116,** 3149–3157.

BOUNTRA, C., BUNCE, K., DALE, T., GARDNER, C., JORDAN, C., TWISSELL, D. & WARD, P. (1993). Anti-emetic profile of a non-peptide neurokinin-NK_1 receptor antagonist, CP-99,994, in ferrets. *Eur. J. Pharmacol.*, **249,** R3–R4.

CUBEDDU, L.X. & HOFFMANN, I.S. (1993). Participation of serotonin on early and delayed emesis induced by initial and subsequent cyclies of cisplatinum-based chemotherapy–effects of antiemetics. *J. Clin. Pharmacol.*, **33,** 691–697.

CUBEDDU, L.X., HOFFMANN, I.S., FUENMAYOR, N.T. & FINN, A.L. (1990). Efficacy of ondansetron (GR38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *New Engl. J. Med.*, **322,** 810–816.

GARDNER, C.J., BOUNTRA, C., BUNCE, K.T., DALE, T.J., JORDAN, C.C., TWISSELL, D.J. & WARD, P. (1994). Anti-emetic activity of neurokinin NK_1 receptor antagonists is mediated centrally in the ferret. *Br. J. Pharmacol.*, **112,** 516P.

GARDNER, C.J., TWISSELL, D.J., DALE, T.J., GALE, J.D., JORDAN, C.C., KILPATRICK, G.J., BOUNTRA, C. & WARD, P. (1995). The broad-spectrum anti-emetic activity of the novel non-peptide tachykinin NK_1 receptor antagonist GR203040. *Br. J. Pharmacol.*, **116,** 3158–3163.

GRUNBERG, S.M. (1993). Potential for combination therapy with the new antiserotonergic agents. *Eur. J. Cancer*, **29A** S39–S41.

MCLEAN, S., GANONG, A., SEYMOUR, P.A., SNIDER, R.M., DESAI, M.C., ROSEN, T., BRYCE, D.K., LONGO, K.P., REYNOLDS, L.S., ROBINSON, G., SCHMIDT, A.W., SIOK, C. & HEYM, J. (1993). Pharmacology of CP-99,994: a non-peptide antagonist of the tachykinin NK-1 receptor. *J. Pharmacol. Exp. Ther.*, **267,** 472–479.

RATH, U., UPADHYAYA, B.K., ARECHAVALA, E., BOCKMANN, H., DEARNALEY, D., DROZ, J.P., FOSSA, S.D., HENRIKSSON, R., AULITZKY, W.E., JONES, W.G., WEISSBACH, L., PASKA, W. & FREEMAN, A. (1993). Role of ondansetron plus dexamethasone in fractionated chemotherapy. *Oncology*, **50,** 168–172.

ROILA, F. (1993). Ondansetron plus dexamethasone compared to the 'Standard' metoclopramide combination. *Oncology*, **50,** 163–167.

RUDD, J.A., BUNCE, K.T. & NAYLOR, R.J. (1996). The interaction of dexamethasone with ondansetron on drug-induced emesis in the ferret. *Neuropharmacology*, **35,** 91–97.

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. & NAYLOR, R.J. (1994). Effects of 5-HT_3 receptor antagonists on models of acute and delayed emesis induced by cisplatin in the ferret. *Eur. J. Pharmacol.*, **262,** R1–R2.

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.S. & ANDREWS, P.L.R. (1993). Afterword: Unresolved issues and future prospects. In *Emesis in Anti-Cancer Therapy Mechanisms and Treatment*. ed. Andrews, P.L.R. & Sanger, G.S. pp. 247–249. London: Chapman & Hall Medical.

TATTERSALL, F.D., RYCROFT, W., HARGREAVES, R.J. & HILL, R.G. (1993). The tachykinin NK_1 receptor antagonist CP-99,994 attenuates cisplatin induced emesis in the ferret. *Eur. J. Pharmacol.*, **250,** R5–R6.

TATTERSALL, F.D., RYCROFT, W., HILL, R.G. & HARGREAVES, R.J. (1994). Enantioselective inhibition of apomorphine-induced emesis in the ferret by the neurokinin$_1$ receptor antagonist CP-99,994. *Neuropharmacology*, **33,** 259–260.

TATTERSALL, F.D., RYCROFT, W., MARMONT, N., CASCIERI, M., HILL, R.G. & HARGREAVES, R.J. (1995). Enantiospecific inhibition of emesis induced by nicotine in the house musk shrew (*Suncus murinus*) by the neurokinin$_1$ (NK_1) receptor antagonist CP-99,994. *Neuropharmacology*, **34,** 1697–1699.

WALSH, D.T., WEG, V.B., WILLIAMS, T.J. & NOURSHARGH, S. (1995). Substance P-induced inflammatory responses in guinea-pig skin: The effect of specific NK_1 receptor antagonists and the role of endogenous mediators. *Br. J. Pharmacol.*, **114,** 1343–1350.

WATSON, J.W., GONSALVES, S.F., FOSSA, A.A., MCLEAN, S., SEEGER, T., OBACH, S. & ANDREWS, P.L.R. (1995a). The anti-emetic effects of CP-99,994 in the ferret and the dog: role of the NK_1 receptor. *Br. J. Pharmacol.*, **115,** 84–94.

WATSON, J.W., NAGAHISA, A., LUCOT, J.B. & ANDREWS, P.L.R. (1995b). The tachykinins and emesis: towards complete control? In *Serotonin and the Scientific Basis of Anti-Emetic Therapy*. ed. Reynolds, D.J.M., Andrews, P.L.R. & Davis, C.J. pp. 233–238. Oxford: Oxford Clinical Communications.

WILDER-SMITH, O.H.G., BORGEAT, A., CHAPPUIS, P., FATHI, M. & FORNI, M. (1993). Urinary serotonin metabolite excretion during cisplatin chemotherapy. *Cancer*, **72,** 2239–2241.

(Received April 9, 1996
Revised July 5, 1996
Accepted August 2, 1996)