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Short communication

The actions of ondansetron and dexamethasone to antagonise cisplatin-induced emesis in the ferret

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Abstract

The ability of ondansetron and dexamethasone to antagonise cisplatin 10 mg/kg i.p. induced emesis was investigated in the ferret during a 24 h period. Ondansetron 0.5–5 mg/kg, as a single injection, effectively antagonised the response for approximately 4 h and revealed a subsequent response that was sensitive to further ondansetron treatment. The three times per day administration of dexamethasone 1 mg/kg i.p. alone or combined with ondansetron 1 mg/kg i.p. significantly reduced the vomiting response by 49 and 79%, respectively. The results are discussed in terms of their relevance to acute and delayed emesis in man.

Keywords: Cisplatin; Anti-emetic; Ondansetron; Dexamethasone; (Acute and delayed)

1. Introduction

Cancer chemotherapy using cisplatinum containing regimens is known to be associated with the development of acute and delayed phases of emesis (Kris et al., 1985). The phases of emesis have been defined by the temporal distribution of the emetic episodes and by the pharmacological sensitivity of the responses. Thus, acute emesis, which occurs on day 1 of treatment, can be markedly reduced by the use of 5-HT_3 receptor antagonists (Butcher, 1993). Delayed emesis, which occurs on subsequent days, is more resistant to the use of 5-HT_3 receptor antagonists and its successful treatment requires the use of a 5-HT_3 receptor antagonist combined with a corticosteroid regimen (Butcher, 1993; Gandara et al., 1993); corticosteroids also improve the control of acute emesis (Smyth et al., 1991). Moreover, the acute and delayed response can be further defined by the temporal increases in urinary 5-hydroxyindolacetic acid levels that occur during the acute but not the delayed phase of emesis (Cubeddu and Hoffmann, 1993).

The cisplatin-induced emesis model in the ferret has been extensively used to identify the anti-emetic potential of novel drug therapies (Andrews and Davis, 1993). The studies have used an observation period of only a few hours and an ED_{100} dose of cisplatin (10 mg/kg) to induce emesis within 2 h of administration. However, the model does not clearly identify an interaction of ondansetron and dexamethasone to control the emetic response and the observation times are inappropriate to the phenomenon of delayed emesis (Rudd et al., 1994, 1996a).

In the present study, we investigate the potential of ondansetron and dexamethasone to prevent cisplatin-induced emesis using an extended observation period of 24 h (Rudd et al., 1994). The studies were designed to assess the value of the cisplatin 10 mg/kg induced emesis model to the problem of acute and delayed emesis in man.

2. Materials and methods

Male ferrets (0.8–1.6 kg, UK bred) were individually housed at 22 ± 1°C and had free access to food (SDS Diet 'C' (E), Special Diet Services, UK) and water. At time = 0, the ferrets were injected with cisplatin 10 mg/kg i.p. Ondansetron (0.5–5 mg/kg i.p.) or vehicle was administered 30 s later. In other experiments, ferrets were injected with cisplatin 10 mg/kg i.p. at time = 0 and ondansetron (1 mg/kg i.p.) or vehicle and/or dexamethasone (1 mg/kg

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i.p.) or vehicle was administered at 30 s, 8 and 16 h post cisplatin injection.

Animal behaviour was recorded remotely using a closed circuit video recording system and analysed at the end of the experiment (Rudd et al., 1994). The significance of the difference between treatments was assessed by one-way analysis of variance (ANOVA) followed by a Bonferroni *t*-test.

Cisplatin (Lederle) was prepared in normal saline at 70–75°C followed by gradual cooling to 40–50°C and administered immediately. Ondansetron dihydrochloride (Glaxo) and dexamethasone phosphate (Sigma) were prepared in distilled water and administered in a volume of 1 ml/kg. Cisplatin was administered in a volume of 5 ml/kg. Doses, except for cisplatin, are expressed as the free base.

3. Results

The animals that received cisplatin (10 mg/kg i.p.) and a single administration of vehicle exhibited 33.3 ± 6.1 episodes of 197.3 ± 57.6 retches and 15.0 ± 3.8 vomits during the entire 24 h observation period (157.5 ± 47.2 retches + vomits occurred during the first 4 h period); the latency to the first retch or vomit was 1.2 ± 0.3 h (Fig. 1A). The single administration of ondansetron (0.5–5 mg/kg i.p.) increased significantly the latency to the first

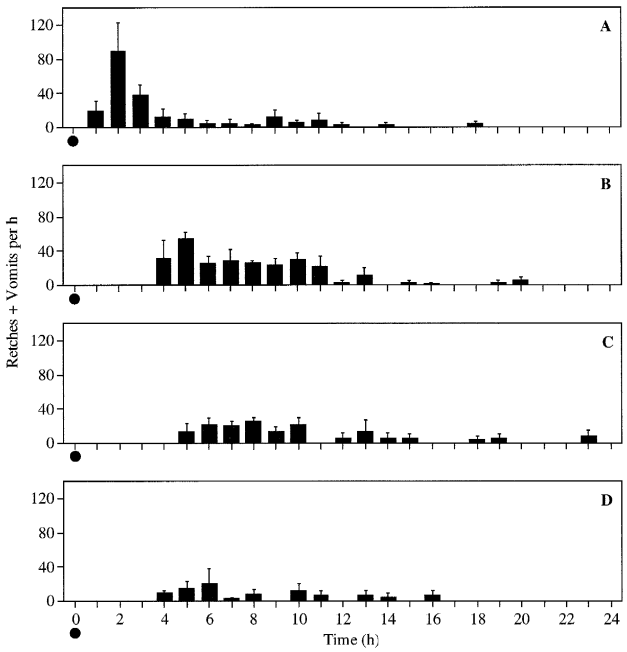

Fig. 1. The effect of a single injection of distilled water (A), ondansetron 0.5 mg/kg i.p. (B), ondansetron 1 mg/kg i.p. (C) or ondansetron 5 mg/kg i.p. (D) on cisplatin-induced retching + vomiting in the ferret. Administration of ondansetron or vehicle was at 30 s following the injection of cisplatin (10 mg/kg i.p.) and is indicated as a filled circle. Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring in 1 h time intervals post cisplatin injection at 0 h ($n = 4$).

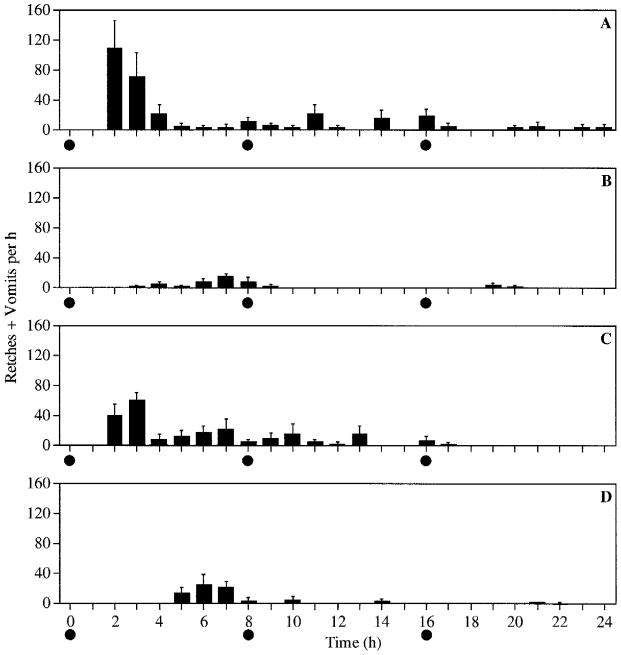

Fig. 2. The effect of an 8-hourly administration for 1 day (the first injection was 30 s after cisplatin) of distilled water 1 ml/kg i.p. (A), ondansetron 1 mg/kg i.p. (B), dexamethasone 1 mg/kg i.p. (C) or the combination treatment of ondansetron 1 mg/kg i.p. and dexamethasone 1 mg/kg i.p. (D) on the profile of retching + vomiting induced by cisplatin 10 mg/kg i.p. in the ferret. Administration of drug or vehicle is indicated as a filled circle. Results represent the mean ± S.E.M. of the total numbers of retches + vomits occurring in 1 h time intervals post cisplatin injection at 0 h ($n = 4$).

retch or vomit by at least 2.5 h ($P < 0.05$) and antagonised significantly the total numbers of retches, vomits and episodes of retching and/or vomiting during the first 4 h period by at least 80% ($P < 0.05$). However, antagonism of the early retching and vomiting induced by cisplatin affected the subsequent retching + vomiting response. During the next 4–24 h period, animals treated with ondansetron 0.5, 1 and 5 mg/kg i.p. exhibited 327 ($P < 0.05$), 162 ($P > 0.05$) and 47% ($P < 0.05$) more retching + vomiting than recorded for the vehicle treated animals (Fig. 1B–D).

A dose of ondansetron (1 mg/kg i.p.) was selected for combination studies with dexamethasone (1 mg/kg i.p.). The dose of dexamethasone was selected on the basis of previous studies which demonstrated that ondansetron (1 mg/kg i.p.) and dexamethasone (1 mg/kg i.p.) combinations, administered at 8 h intervals, are highly effective to antagonise both the acute and delayed emesis induced by cisplatin 5 mg/kg i.p. (Rudd and Naylor, 1996).

The animals that received cisplatin 10 mg/kg i.p. and three administrations of vehicle exhibited 52.0 ± 9.1 episodes of 282.3 ± 37.8 retches and 29.3 ± 4.5 vomits during the entire 24 h observation period; the latency to onset or the first retch or vomit was 1.5 ± 0.2 h (Fig. 2A). The administration of ondansetron (1 mg/kg i.p.) three times per day significantly increased the latency to the first

retch or vomit to 3.5 ± 0.5 h ($P < 0.05$) and reduced significantly the total numbers of episodes, retches and vomits induced by cisplatin during the total 24 h observation period by 78 ($P < 0.05$), 85 ($P < 0.05$) and 85% ($P < 0.05$), respectively (Fig. 2B). Dexamethasone (1 mg/kg i.p.) administered alone three times per day failed to significantly increase the latency to first retch or vomit ($P > 0.05$) and failed to reduce significantly the total numbers of episodes ($P > 0.05$) and retches ($P > 0.05$) induced by cisplatin during the total 24 h period; the number of vomits was significantly reduced by 49% ($P < 0.05$; Fig. 2C).

The combination treatment of a three times per day regimen of ondansetron (1 mg/kg i.p.) administered three times per day with dexamethasone (1 mg/kg i.p.) administered three times per day did not provide a significantly greater control of cisplatin-induced retching ($P > 0.05$) or vomiting ($P > 0.05$) than that afforded by the single treatments (Fig. 2D). However, compared to the cisplatin (10 mg/kg i.p.) and vehicle treated animals, the total numbers of episodes, retches and vomits were reduced significantly by 74 ($P < 0.05$), 77 ($P < 0.05$) and 79% ($P < 0.05$), respectively. The combination treatment also significantly increased the latency to first retch or vomit to 5.0 ± 0.4 h ($P < 0.05$). The increase in latency affected by the combination treatment was greater than an additive effect when compared to the effect of the single drug administrations ($P < 0.05$).

4. Discussion

The present study has attempted to extend the usefulness of the cisplatin 10 mg/kg induced emesis model in the ferret by using observation periods of up to 24 h. The model identifies the anti-emetic action of ondansetron to significantly reduce emesis for approximately 4 h after a single injection when administered almost immediately following cisplatin; the findings are in agreement with previous studies (Endo et al., 1990; Rudd et al., 1996a).

However, a novel finding of the study was that antagonism of the initial 2–3 h of the emetic response by ondansetron had the effect of modifying the subsequent retching and vomiting that occurred during the remainder of the observation time. Indeed, the emesis that occurred during the 4–24 h observation time was potentiated but a component of the emesis is likely to be mediated via the 5-HT_3 receptor since the three times administration of ondansetron (this study) or alosetron (Rudd and Naylor, 1994) is effective to antagonise the retching and vomiting response. It is conceivable that the control ferrets may become fatigued during the initial intense retching and vomiting that normally occurs during the first 2–3 h to seriously interfere with subsequent emesis. Additionally, there may also occur a depletion of neurotransmitter(s) or other factor(s), which would normally enable the continuation of the emetic response. It may also be possible that activation of an endogenous inhibitory pathway may protect the animals from further excessive retching and vomiting.

The treatment of the animals with the single injection of ondansetron may protect the animals from the initial phase of the response but as the bioavailability of the ondansetron declines (the plasma half-life is reported to be 2.3 ± 0.2 h in the ferret; Endo et al., 1990), vomiting is able to return. This may imply that the emetic signal(s) generated by cisplatin treatment is present in vivo to cause severe retching and vomiting for at least 8 h. However, this interpretation must be viewed with caution when considering the actions of cisplatin to induce emesis in man since the dose of cisplatin used in the present study may be inappropriately high. Thus, cisplatin 5 mg/kg i.p. induced emesis in the ferret is not potentiated following a single administration of ondansetron and the lower dose of cisplatin more accurately reflects acute and delayed emesis in man (Rudd et al., 1996b; Rudd and Naylor, 1996).

The present studies have also investigated the anti-emetic potential of dexamethasone 1 mg/kg i.p., administered three times per day, when used alone or in combination with ondansetron. In a previous study, we demonstrated that dexamethasone 1 mg/kg i.p. as a three times per day treatment was effective to markedly antagonise the acute (day 1) and delayed (days 2 and 3) retching and vomiting induced by cisplatin 5 mg/kg i.p. We also demonstrated that dexamethasone was also highly effective when combined with ondansetron 1 mg/kg i.p. to control the response (Rudd and Naylor, 1996). However, in the present study, dexamethasone was essentially ineffective to reduce the retching and vomiting induced by cisplatin 10 mg/kg and also failed to markedly improve the anti-emetic action of ondansetron when used as a combined regimen. The failure of dexamethasone to control the retching and vomiting during the present studies may suggest that arachidonic acid products are not likely to be involved in the mediation of the response. However, it could be equally possible that the higher dose of cisplatin may activate additional mechanisms that make a predominant contribution to the overall response, thus concealing any potential involvement of prostanoids or leukotrienes.

Clearly, the ferret cisplatin 10 mg/kg model is not ideally representative of the acute and delayed emesis that is experienced by man in response to cisplatin chemotherapy (see Section 1). There is no apparent temporal separation of the retching and vomiting episodes into ‘acute’ and ‘delayed’ emetic phases and in any event, the time period of 24 h is probably inappropriate to study delayed emesis. Further, the results of the present study indicate that the pharmacological sensitivity of the response may be different from the pharmacological sensitivity of delayed emesis in man.

We have previously highlighted the limitations of the

ferret cisplatin 10 mg/kg induced emesis model when measurements are made over a period of only a few hours (Rudd et al., 1996a). The present studies have also indicated further limitations of the cisplatin 10 mg/kg induced emesis model when the observation period is extended to 24 h (i.e. the potentiation of emesis following a single dose of ondansetron). Indeed, in a separate study we extended the observation period of the cisplatin 10 mg/kg induced emesis model up to 40 h but were unable to observe a temporal separation of emesis that could be considered to represent acute and delayed emesis (Rudd et al., 1996b).

Whilst the present studies have been critical of the value of the ferret cisplatin 10 mg/kg induced emesis model with respect to delayed emesis, the studies do not necessarily imply that the model has no benefits. Certainly, ondansetron appeared to be effective when administered three times per day and dexamethasone did have some effect to increase the latency to the first retch or vomit, particularly when used in combination with ondansetron.

In conclusion, the ferret cisplatin 10 mg/kg induced emesis model may have limitations to predict the anti-emetic effectiveness of drugs to prevent delayed emesis in man. However, the model does appear to retain characteristics of the acute emetic response that may be relevant to drug administration in man. Moreover, the extended observation period used in the present studies may be useful to conduct preliminary investigations into the duration of action of drugs to prevent the emetic response and to further investigate the residual emetic response induced by cisplatin 10 mg/kg. However, the interpretation of the possible potentiating effects of a single injection of an anti-emetic drug should be carefully assessed.

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