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Antiemetic effect of dexamethasone on cisplatin-induced early and delayed emesis in the pigeon

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Abstract

We investigated the ability of dexamethasone to attenuate cisplatin (4 mg/kg, i.v.)-induced early and delayed emesis. These appear within the first 8-h period (early phase) and between 8 and 48 h (delayed phase), respectively, after cisplatin administration in the pigeon. Dexamethasone (0.1 and 1 mg/kg, i.m.) reduced significantly the number of emetic responses to cisplatin by 56% and 82% ($P<0.05$), respectively, in the early phase, and by 41% and 66% ($P<0.05$), respectively, in the delayed phase. Dexamethasone (1 and 10 μg/kg, i.c.v.) reduced the number of emetic responses by 66% and 91% ($P<0.05$), respectively, in the early phase, and by 56% and 87% ($P<0.05$), respectively, in the delayed phase. Indomethacin (10 mg/kg, i.m.) did not suppress cisplatin-induced early and delayed emesis. Dexamethasone (1 mg/kg, i.m.) did not affect the content of platinum in the medulla oblongata after cisplatin administration. The above results suggest that dexamethasone has antiemetic effects on both the early and delayed emetic responses to cisplatin in pigeons, partially via its central site of action, and that the antiemetic mechanism of dexamethasone is related to factors other than its inhibition of prostanoid synthesis or its membrane stabilizing effect which reduces influx of cisplatin into the medulla oblongata.

Keywords: Emesis; Cisplatin; Dexamethasone; Indomethacin; (Pigeon)

1. Introduction

Nausea and emesis are the most distressing side effects of cancer chemotherapy and cisplatin is one of the most emetogenic chemotherapeutics (Kris et al., 1985; Martin, 1996). In humans, cisplatin induces both early and delayed emesis (Kris et al., 1985), and both types have also been observed in ferrets (Rudd et al., 1994; Rudd and Naylor, 1994), piglets (Milano et al., 1995; Grélot et al., 1996) and cats (Rudd et al., 2000). We investigated whether pigeons might be suitable for studying drug-induced emetic responses using glucagon, digoxin and copper sulfate (Uchiyama et al., 1978, 1979), morphine (Saito and Tanihata, 1994), amantadine (Saitou et al., 2000) and theophylline (Tanihata et al., 2001). In our recent studies, we showed that intravenously injected cisplatin induced both types of emesis, early and delayed, which appear within the first 8-h period and between 8 and 48 h after cisplatin administration, respectively, in pigeons (Uchiyama and Suzuki, 1992; Tanihata et al., 2000, 2003).

Although corticosteroids such as dexamethasone are known to have antiemetic effects against cisplatin in humans (Aapro and Alberts, 1981; Kris et al., 1989), ferrets (Marr et al., 1991; Rudd et al., 1996; Rudd and Naylor, 1996, 1997; Sam et al., 2001) and cats (Rudd et al., 2000), the precise mechanism has not been elucidated. It has been proposed that the inhibition of prostanoid synthesis by corticosteroids may be involved (Rich et al., 1980; Rudd et al., 1996), but a role of prostanoids in the emetic response to cytotoxic drugs has not been identified. Additionally, dexamethasone is thought to stabilize membranes and affect the influx of emetogenic substances to the central nervous system (Hawthorn and Cunningham, 1990; Naylor and Rudd, 1996).

The present study was aimed at determining the antiemetic profile and antiemetic mechanism of dexamethasone on cisplatin (4 mg/kg, i.v.)-induced early and delayed emesis in the pigeon. Dexamethasone administered clinically as a single or twice daily treatment is of benefit in ameliorating both the early and delayed emesis in patients (Goedhals et al., 1998; Latreille et al., 1998;

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Tsukada et al., 2001). Furthermore, dexamethasone (1 mg/kg, i.p.) administered once per day reduced cisplatin (5 mg/kg, i.p.)-induced emesis in ferrets (Rudd and Naylor, 1996). We decided, therefore, to investigate the antiemetic activity of dexamethasone administered twice: 1 h before and 24 h after cisplatin administration. Dexamethasone was also administered intramuscularly or intracerebroventricularly, to determine whether the antiemetic activity of dexamethasone was at a central nervous system and/or a peripheral target. In addition, the antiemetic effect of indomethacin was examined to determine the role of prostanoid production in cisplatin-induced emesis. Furthermore, the platinum concentration in the medulla oblongata was determined to confirm the presence of cisplatin in the central nervous system.

2. Materials and methods

2.1. Animals

Adult domestic pigeons of either sex weighing between 400 and 550 g (Saitama Experimental Animal Supply, Saitama, Japan) were used. Pigeons were housed under a 12-h light/dark cycle, and standard pigeon chow (Daiki, Saitama, Japan) and water were available ad libitum. All

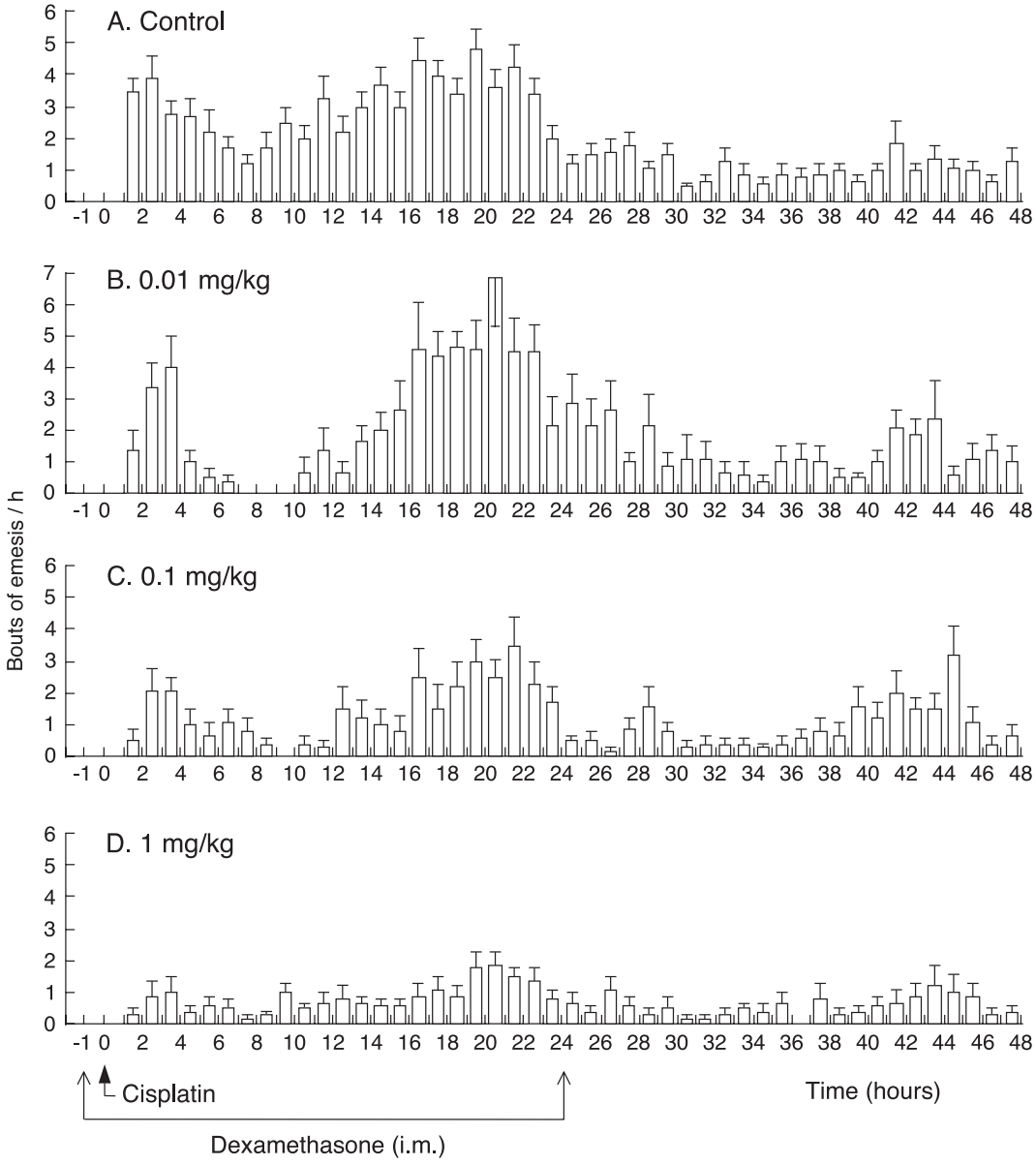

Fig. 1. The profile of the emetic response induced by cisplatin (4 mg/kg, i.v.) in pigeons during a 48-h observation period ($n = 20$), and the effect of dexamethasone (0.01–1 mg/kg, i.m., administered twice, 1 h before and 24 h after cisplatin administration) on the cisplatin-induced emetic response ($n = 8$–10). Each hourly bin with a vertical bar represents the mean ± S.E.M. of the number of bouts of emesis occurring in 1-h time intervals after cisplatin administration at time zero.

Table 1
Effect of intramuscularly injected dexamethasone on the cisplatin (4 mg/kg, i.v.)-induced emetic response during a 48-h observation period in pigeons

Dexamethasone (mg/kg, i.m.)	No. of pigeons tested	% Emetic pigeons	Onset (min)	Bouts of emesis	Total emetic behaviours
0–8 h after cisplatin administration					
– (Control)	20	100	82.8 ± 3.1	17.3 ± 2.5	131.8 ± 17.8
0.01	8	100	117.0 ± 9.7	9.9 ± 1.5	75.8 ± 19.3
0.1	10	100	176.9 ± 17.1[a]	7.6 ± 2.3[a]	61.3 ± 21.6[b]
1	10	80	215.9 ± 44.0[a]	3.2 ± 1.0[a]	30.0 ± 10.9[a]
8–48 h after cisplatin administration					
– (Control)	20	100	–	72.8 ± 7.2	443.3 ± 52.5
0.01	8	100	–	72.8 ± 15.0	606.9 ± 164.7
0.1	10	100	–	42.9 ± 7.6[b]	351.7 ± 164.3
1	10	100	–	25.0 ± 6.8[a]	180.5 ± 43.6[b]
0–48 h after cisplatin administration					
– (Control)	20	100	82.8 ± 3.1	90.0 ± 8.6	575.1 ± 61.1
0.01	8	100	117.0 ± 9.7	82.6 ± 15.2	682.6 ± 168.0
0.1	10	100	176.9 ± 17.1[a]	50.5 ± 7.3[a]	413.0 ± 81.3
1	10	100	381.5 ± 116.3[a]	28.2 ± 7.2[a]	210.5 ± 46.9[a]

Dexamethasone was administered twice, 1 h before and 24 h after cisplatin administration. The values (mean ± S.E.M.) for the bouts of emesis and the total emetic behaviours are the numbers of bouts of emesis and the total number of emetic behaviours, respectively. The values (mean ± S.E.M.) for onset are the latency times to first emesis in the pigeons which vomited after cisplatin administration.

[a] Statistically different from controls with cisplatin alone ($P < 0.01$).

[b] Statistically different from controls with cisplatin alone ($P < 0.05$).

animal experimental procedures were carried out under the Guidelines for Animal Experiments, Faculty of Medicine, Toho University.

2.2. Cisplatin-induced emesis

Details of this procedure have been described in previous publications (Tanihata et al., 2000, 2003). Briefly, pigeons were placed in individual cages and cisplatin (4 mg/kg) was administered intravenously (i.v.) via the brachial wing vein. The behaviour of the pigeons was observed with a video-monitoring system for up to 48 h. During the observation period, food and water were available ad libitum. Each pigeon was used once. Vomiting and retching associated with and without oral expulsion, respectively, were considered as the emetic response (Preziosi et al., 1992). The

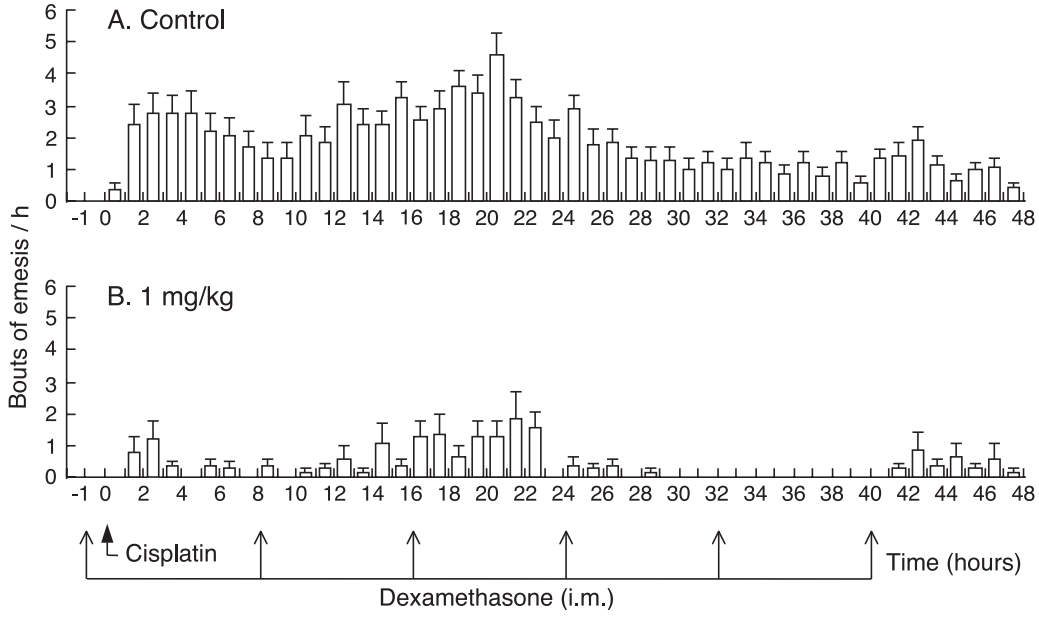

Fig. 2. The effect of dexamethasone (1 mg/kg, i.m., administered six times, 1 h before and 8, 16, 24, 32 and 40 h after cisplatin administration) on the cisplatin (4 mg/kg, i.v.)-induced emetic response during a 48-h observation period in pigeons ($n = 10–12$). Each hourly bin with a vertical bar represents the mean ± S.E.M. of the number of bouts of emesis occurring in 1-h time intervals after cisplatin administration at time zero.

emetic responses were characterized by a bout of emesis and more than one emetic behaviour occurring within one bout. The latency time to first emesis, the number of bouts of emesis and the total number of emetic behaviours were recorded.

The antiemetic effect of dexamethasone was studied by intramuscular injections (0.01–1 mg/kg, i.m.) into the greater pectoral muscle or by intracerebroventricular administration (0.1–10 μg/kg, i.c.v.) through an implanted cannula. Dexamethasone was administered twice: 1 h before and 24 h after cisplatin administration. The antiemetic effect of intramuscular dexamethasone at a dose of 1 mg/kg was also studied by more frequent administration with an interval of 8 h: 1 h before and every 8 h after cisplatin administration. The antiemetic effect of indomethacin was also studied by intramuscular administration at 8- or 24-h intervals.

Experiments were usually performed with 10 pigeons at a time, and several control pigeons were always included in each experiment. Therefore, the sizes were unequal for the control and the experimental (dexamethasone or indomethacin treatment) groups.

2.3. Surgical preparation for i.c.v. administration

The animal preparation procedure was in accord with that described in a previous study (Tanihata et al., 2003).

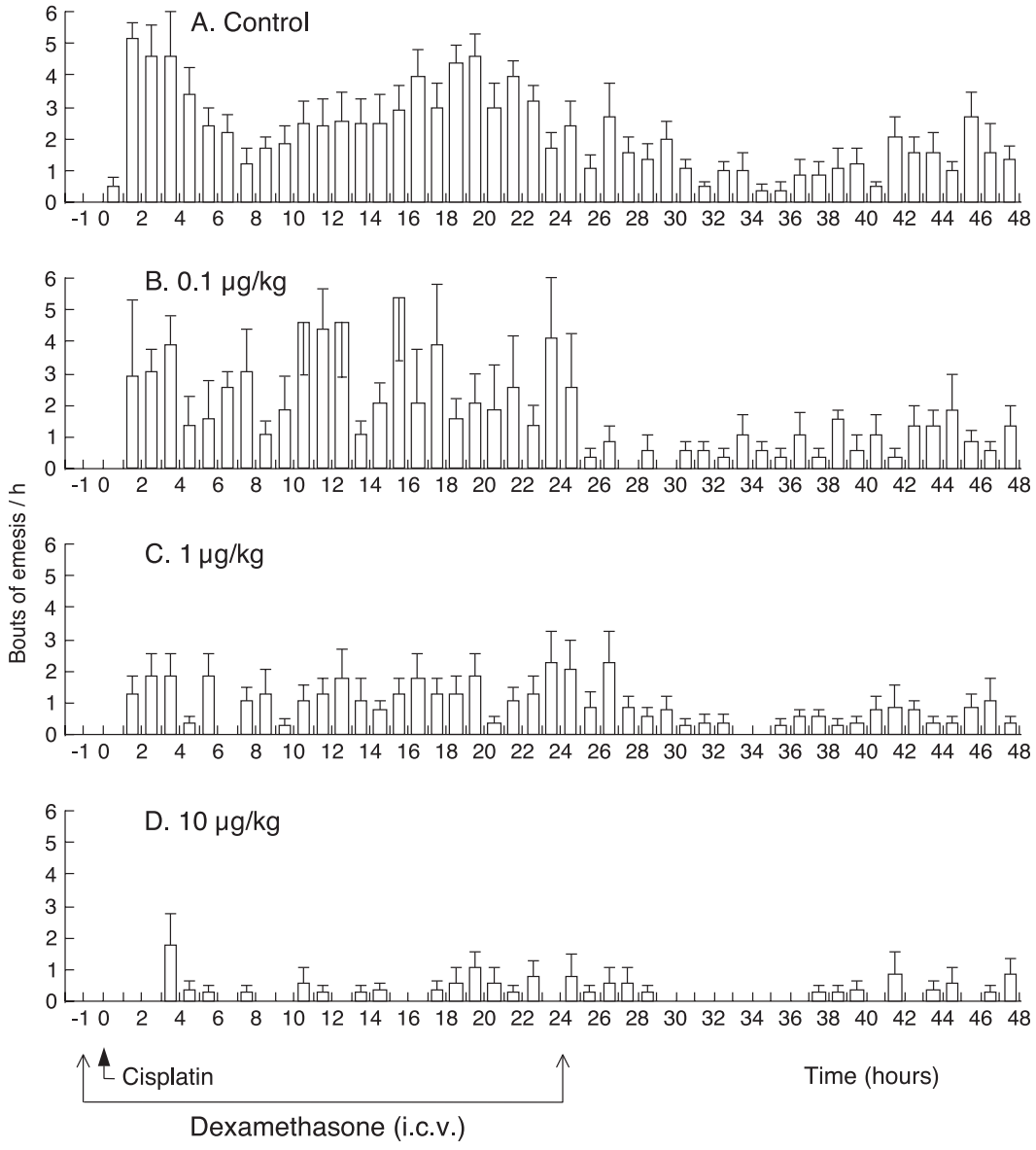

Fig. 3. The effect of intracerebroventricularly injected dexamethasone (0.1–10 μg/kg, administered twice, 1 h before and 24 h after cisplatin administration) on the cisplatin (4 mg/kg, i.v.)-induced emetic response during a 48-h observation period in pigeons ($n = 4–8$). Each hourly bin with a vertical bar represents the mean ± S.E.M. of the number of bouts of emesis occurring in 1-h time intervals after cisplatin administration at time zero.

Pigeons were anaesthetized with pentobarbital sodium (35 mg/kg, i.m., Sigma, St. Louis, MO, USA), and a stainless-steel guide cannula (G-14, Eicom, Kyoto, Japan) was surgically implanted into the fourth ventricle using a stereotaxic apparatus (SR-6N, Narishige Scientific Instrument Lab., Tokyo, Japan) with a Revzin pigeon adaptor (Karten and Hodos, 1967). The stereotaxic coordinates were 0.50 mm posterior from the interaural line in the midline, and 9.30 mm below the surface of the calvaria according to our adjustment from the atlas of Karten and Hodos (1967). The cannula was fixed with dental cement and screwed to the skull, and a dummy cannula (D-14, Eicom) was inserted into the guide cannula. The animals were allowed 5 days to recover from surgery.

2.4. Determination of platinum concentration

The blood and brain were collected at 2 and 20 h after injection of cisplatin (4 mg/kg, i.v.), when the cisplatin-induced early and delayed emesis reached the peak, respectively, after cisplatin administration.

Pigeons were anaesthetized with pentobarbital sodium (35 mg/kg, i.m., Sigma). Blood samples of 2 ml were collected by cardiocentesis and placed in a test tube containing heparin (Nipro, Osaka, Japan). The blood sample was centrifuged at $1500 \times g$ for 15 min and the plasma was stored at -20 °C until analysis. After blood sampling, pigeons were perfused through the ascending aorta with 500 ml of heparin solution diluted in distilled water. The brain was removed and the medulla oblongata was excised. Following measurement of wet weight, the medulla oblongata was stored at -20 °C until analysis.

The medulla oblongata and plasma samples were digested with nitric acid–H_2O_2 and the platinum levels in the residue were measured by an inductively coupled plasma-mass spectrometer (ICP-MS: ELAN 5000, Perkin Elmer, Norwalk, CT, USA) after appropriate dilutions of the samples with distilled water. The platinum level was taken as the number of counts per second under the peak at mass number 195. The absolute detection limit for platinum was 0.03 ng/ml.

2.5. Drugs

Cisplatin [*cis*-platinum (II) diamine dichloride] was dissolved in 0.9% saline solution at 65–70 °C, followed by cooling to 45–50 °C and administered immediately. Dexamethasone 21-phosphate disodium salt was dissolved in 0.9% saline solution and doses are expressed as the free base. Indomethacin was dissolved in 0.05 M Na_2CO_3 (pH 9.6). All these drugs were purchased from Sigma and drug solutions were prepared just before use.

2.6. Data analysis

The values presented are the mean ± S.E.M. The differences among means were evaluated for statistical significance using one-way analysis of variance followed by either Dunnett's test or Tukey's multiple comparison test. Fisher's exact test was used for the statistical

Table 2
Effect of intracerebroventricularly injected dexamethasone on the cisplatin (4 mg/kg, i.v.)-induced emetic response during a 48-h observation period in pigeons

Dexamethasone (μg/kg, i.c.v.)	No. of pigeons tested	% Emetic pigeons	Onset (min)	Bouts of emesis	Total emetic behaviours
0–8 h after cisplatin administration					
– (Control)	8	100	73.3 ± 5.1	23.3 ± 4.0	301.9 ± 76.1
0.1	4	100	101.8 ± 22.3	17.8 ± 4.0	229.3 ± 78.2
1	6	100	121.3 ± 21.5	8.0 ± 1.4[a]	68.3 ± 12.6[a]
10	6	50	187.7 ± 13.3	2.3 ± 1.1[a]	17.5 ± 8.5[a]
8–48 h after cisplatin administration					
– (Control)	8	100	–	74.4 ± 7.4	488.9 ± 37.7
0.1	4	100	–	61.3 ± 14.9	360.5 ± 111.0
1	6	100	–	33.0 ± 7.6[a]	225.5 ± 56.3[a]
10	6	66.7	–	9.7 ± 5.0[a]	89.2 ± 55.5[a]
0–48 h after cisplatin administration					
– (Control)	8	100	73.3 ± 5.1	97.6 ± 8.3	790.8 ± 103.1
0.1	4	100	101.8 ± 22.3	79.0 ± 16.3	589.8 ± 84.5
1	6	100	121.3 ± 21.5	41.0 ± 8.7[a]	294.0 ± 65.4[a]
10	6	66.7	362.0 ± 174.4[a]	12.0 ± 5.4[a]	106.7 ± 61.8[a]

Dexamethasone was administered twice, 1 h before and 24 h after cisplatin administration. The values (mean ± S.E.M.) for the bouts of emesis and the total emetic behaviours are the numbers of bouts of emesis and the total number of emetic behaviours, respectively. The values (mean ± S.E.M.) for onset are the latency times to first emesis in the pigeons which vomited after cisplatin administration.

[a] Statistically different from controls with cisplatin alone ($P < 0.01$).

Table 3
Effect of indomethacin (i.m., administered twice, 1 h before and 24 h after cisplatin administration) on the cisplatin (4 mg/kg, i.v.)-induced emetic response during a 48-h observation period in pigeons

Indomethacin (mg/kg, i.m.)	No. of pigeons tested	% Emetic pigeons	Onset (min)	Bouts of emesis	Total emetic behaviours
0–8 h after cisplatin administration					
– (Control)	10	100	117.3 ± 10.6	18.5 ± 3.6	139.1 ± 33.2
10	3	100	85.7 ± 7.9	16.3 ± 5.9	128.7 ± 51.5
20	3	100	131.7 ± 35.5	15.0 ± 7.0	110.0 ± 49.2
8–24 h after cisplatin administration					
– (Control)	10	100	–	45.7 ± 5.7	395.7 ± 56.1
10	3	100	–	42.7 ± 13.7	426.0 ± 192.1
20[a]	2	100	–	51.0 ± 15.0	395.0 ± 167.0
24–48 h after cisplatin administration					
– (Control)	10	100	–	22.4 ± 6.3	159.8 ± 45.9
10[b]	2	100	–	17.0 ± 2.0	111.5 ± 30.5
20[a]	1	100	–	25	275

Indomethacin was administered twice, 1 h before and 24 h after cisplatin administration. Indomethacin was dissolved in 0.05 M Na_2CO_3, and controls were injected with the same volume of the solvent adjusted to pH 9.6. The values (mean ± S.E.M.) for the bouts of emesis and the total emetic behaviours are the numbers of bouts of emesis and the total number of emetic behaviours, respectively. The values (mean ± S.E.M.) for onset are the latency times to first emesis after cisplatin administration.

[a] Two of three pigeons administered indomethacin (20 mg/kg, i.m.) died 22 and 26 h after cisplatin administration.

[b] One of three pigeons administered indomethacin (10 mg/kg, i.m.) died 38 h after cisplatin injection.

evaluation of the incidence of emesis. $P<0.05$ was considered statistically significant.

3. Results

3.1. Effect of dexamethasone on cisplatin-induced emesis

Intravenously injected cisplatin at a dose of 4 mg/kg induced early emesis with a latency of 82.8 ± 3.1 min ($n=20$). The early emetic response reached a peak between 1 and 3 h, and decreased gradually within 8 h after injection. Then the delayed phase-emetic response, whose peak was found at 16–22 h, lasted up to 48 h (Fig. 1). The pattern of the emetic response induced by cisplatin was much the same as in previous studies (Tanihata et al., 2000, 2003).

Intramuscularly injected dexamethasone at doses of 0.01, 0.1 and 1 mg/kg dose-dependently reduced the number of bouts of cisplatin-induced early emesis by 42.8% ($P>0.05$), 56.1% ($P<0.05$) and 81.5% ($P<0.05$), respectively. Dexamethasone at a dose of 0.01 mg/kg did not affect the delayed emetic response, but at 0.1 and 1 mg/kg significantly reduced the number of bouts of cisplatin-induced emesis by 41.1% ($P<0.05$) and 65.7% ($P<0.05$), respectively, in the delayed phase. The latency time to first emesis was also significantly prolonged to more than twofold by dexamethasone at 0.1 and

Table 4
Effect of indomethacin (10 mg/kg, i.m., administered three times, 1 h before, and 8 and 16 h after cisplatin administration) on the cisplatin (4 mg/kg, i.v.)-induced emetic response during a 24-h observation period in pigeons

Indomethacin (mg/kg, i.m.)	No. of pigeons tested	% Emetic pigeons	Onset (min)	Bouts of emesis	Total emetic behaviours
0–8 h after cisplatin administration					
– (Control)	10	100	117.3 ± 10.6	18.5 ± 3.6	139.1 ± 33.2
10	5	100	62.4 ± 9.5[a]	17.0 ± 2.7	141.0 ± 29.5
8–24 h after cisplatin administration					
– (Control)	10	100	–	45.7 ± 5.7	395.7 ± 56.1
10	3[b]	100	–	28.3 ± 7.3	236.0 ± 71.8

Indomethacin was dissolved in 0.05 M Na_2CO_3, and controls were injected with the same volume of the solvent adjusted to pH 9.6. The values (mean ± S.E.M.) for the bouts of emesis and the total emetic behaviours are the numbers of bouts of emesis and the total number of emetic behaviours, respectively. The values (mean ± S.E.M.) for onset are the latency times to first emesis after cisplatin administration.

[a] Statistically different from controls with cisplatin alone ($P<0.05$).

[b] Two of five pigeons died between 17 and 19 h after cisplatin injection.

1 mg/kg (Fig. 1; Table 1). The frequent administration of dexamethasone at a dose of 1 mg/kg decreased the number of bouts of cisplatin-induced emesis by 85.2% ($P<0.05$) in the early phase and 78.7% ($P<0.05$) in the delayed phase (Fig. 2). The reduction of the delayed emetic response to cisplatin by dexamethasone (1 mg/kg, i.m.) administered at 8-h intervals was not statistically different ($P>0.05$) from that by dexamethasone administered twice, 1 h before and 24 h after cisplatin administration.

Intracerebroventricularly injected dexamethasone at a dose of 0.1 μg/kg did not affect cisplatin-induced emesis, but at 1 and 10 μg/kg dose-dependently reduced the number of bouts of cisplatin-induced emesis by 65.7% ($P<0.05$) and 90.1% ($P<0.05$), respectively, in the early phase, and by 55.6% ($P<0.05$) and 87.0% ($P<0.05$), respectively, in the delayed phase. The latency time to first emesis was significantly prolonged by dexamethasone at a dose of only 10 μg/kg (Fig. 3; Table 2). Two of six pigeons treated with 10 μg/kg of dexamethasone had no emetic responses to cisplatin during a 48-h observation period (Table 2).

3.2. Effect of indomethacin on cisplatin-induced emesis

In preliminary experiments, indomethacin (10 and 20 mg/kg) administered intramuscularly twice, 1 h before and 24 h after cisplatin administration, did attenuate cisplatin-induced emesis (Table 3). Therefore, indomethacin (10 mg/kg) was administered intramuscularly three times at 8 hourly intervals, 1 h before and 8 and 16 h after cisplatin administration. In indomethacin-treated pigeons, latency time to the first emetic response to cisplatin was significantly shortened (by half). Two of five pigeons died following the third dose of indomethacin (total dose of 30 mg/kg), and that limited the observation period to 24 h. Indomethacin reduced neither the early, nor the delayed emetic response to cisplatin occurring in the 24-h observation period (Table 4). Lack of an antiemetic effect of indomethacin (10 mg/kg, i.m.) on the delayed emetic response between 8 and 24 h was confirmed by indomethacin treatments at 8 and 16 h after cisplatin administration (Table 5).

Table 5
Effect of indomethacin (10 mg/kg, i.m., administered twice, 8 and 16 h after cisplatin administration) on the delayed phase (8–24 h) of cisplatin (4 mg/kg, i.v.)-induced emesis in pigeons

Indomethacin (mg/kg, i.m.)	No. of pigeons tested	% Emetic pigeons	Bouts of emesis	Total emetic behaviours
– (Control)	5	100	55.8 ± 7.1	472.4 ± 78.0
10	5	100	59.4 ± 4.8	575.2 ± 89.7

Indomethacin was dissolved in 0.05 M Na_2CO_3, and controls were injected with the same volume (1 ml/kg) of the solvent adjusted to pH 9.6. The values (mean ± S.E.M.) for the bouts of emesis and the total emetic behaviours are the numbers of bouts of emesis and the total number of emetic behaviours, respectively.

Table 6
Effect of dexamethasone (1 mg/kg, i.m.) on the platinum concentrations in plasma and medulla oblongata 2 and 20 h after cisplatin (4 mg/kg, i.v.) administration in pigeons

Dexamethasone (mg/kg, i.m.)	Time after cisplatin i.v. (h)	Platinum concentrations	
		Plasma (μg/ml)	Medulla oblongata (μg/g tissue)
– (Control)	2	0.81 ± 0.11	0.26 ± 0.02
1	2	0.98 ± 0.12	0.29 ± 0.03
– (Control)	20	0.46 ± 0.06[a]	0.32 ± 0.04
1	20	0.65 ± 0.03[b]	0.35 ± 0.04

Dexamethasone was administered 1 h before cisplatin administration. The values are the mean ± S.E.M. ($n=5$).

[a] Statistically different from controls 2 h after cisplatin administration ($P<0.05$).

[b] Statistically different from controls with cisplatin alone ($P<0.05$).

3.3. Platinum concentration

The platinum detection limit of the tissue was about 0.08 μg/g of dry weight, and platinum was not detected in plasma and medulla oblongata of non-cisplatin-treated pigeons ($n=3$). The platinum concentration in the plasma was significantly lower at 20 h compared to 2 h after cisplatin administration. Platinum was detected in the medulla oblongata at 2 and 20 h after cisplatin administration, although there was no statistical difference in the platinum levels at these two times.

Dexamethasone (1 mg/kg, i.m.) pretreatment did not influence the platinum content of the medulla oblongata 2 and 20 h after cisplatin administration. In contrast, the platinum level in plasma 20 h after cisplatin administration was significantly higher in the dexamethasone-treated group than in the nontreated control group. No difference was found in the platinum level in plasma between dexamethasone-treated and nontreated groups 2 h after cisplatin administration (Table 6).

4. Discussion

4.1. Antiemetic profile of dexamethasone against cisplatin-induced emesis

The present study confirmed that dexamethasone has an antiemetic effect against cisplatin (4 mg/kg, i.v.)-induced early and delayed emesis that appear within the first 8-h period and between 8 and 48 h after cisplatin administration, respectively, in the pigeon. Dexamethasone is a useful antiemetic for moderately emetogenic chemotherapy-induced emesis in humans (Cassileth et al., 1983; Jones et al., 1991), and it has been used for cisplatin-induced acute (Aapro and Alberts, 1981) and delayed emesis (Kris et al., 1989). The antiemetic effect of dexamethasone when used alone against cisplatin-induced early and delayed emesis

was also observed in ferrets (Marr et al., 1991; Rudd and Naylor, 1996) and cats (Rudd et al., 2000).

In the present study, dexamethasone revealed antiemetic action against cisplatin-induced emesis dose-dependently by both the peripheral (i.m.) and central (i.c.v.) administrations. Direct injection of dexamethasone into the fourth ventricle induced a dose-related antiemetic actin at low doses (1 and 10 μg/kg). These low doses of dexamethasone when administered intramuscularly did not show any antiemetic effect on cisplatin-induced emesis. The antiemetic effect of dexamethasone when administered intracerebroventricularly was more potent than when administered intramuscularly, suggesting a central site of antiemetic action of dexamethasone against cisplatin-induced emesis in pigeons. Additionally, the antiemetic effect of dexamethasone still occurred 24 h after its administration by either the intramuscular or intracerebroventricular route. In the clinic, once or twice daily treatment of dexamethasone ameliorates both acute and delayed cisplatin-induced emesis (Goedhals et al., 1998; Latreille et al., 1998; Tsukada et al., 2001). In the ferret, dexamethasone (1 mg/kg, i.p.) administered once per day showed a tendency to reduce cisplatin (5 mg/kg, i.p.)-induced emesis (Rudd and Naylor, 1996). In humans (Kris et al., 1985) and ferrets (Rudd et al., 1994), the early phase is presumed to last for 1 day, whereas in pigeons we classified the emetic response within the first 8-h period as early, and the emetic response between 8 and 48 h as delayed emesis. Although there may be species differences in the time course of the early and delayed phases of cisplatin-induced emesis, the antiemetic effect of dexamethasone on both cisplatin-induced early and delayed emesis was present in the pigeon.

4.2. Role of prostanoids in cisplatin-induced emesis

The mechanism for the antiemetic action of dexamethasone is not well understood. It has been proposed that dexamethasone acts by inhibiting prostanoid synthesis (Rudd et al., 1996), but a role of prostanoids in the emetic response to cytotoxic drugs has not been identified. Prostanoid levels increase in tissue after irradiation (Pausescu et al., 1976; Steel et al., 1983), and ibuprofen can control nausea and emesis induced by radiotherapy in cancer patients (Stryker et al., 1979). Furthermore, indomethacin has been reported to reduce radiation-induced emesis in dogs (Carpenter et al., 1986) and cisplatin-induced both early and delayed emesis in piglets (Girod et al., 2002). On the contrary, prostanoids have not been shown to increase in the plasma of cancer patients during early cisplatin-induced emesis (Curry et al., 1981). It might be suggested that increase of prostanoid levels occurs at the tissue level in the cisplatin-induced emesis.

In the present study, the role of prostanoid production in cisplatin-induced emesis in pigeons was studied by treatment with indomethacin. It was reported that indomethacin inhibited cerebral prostaglandin synthesis by approximately 80% at an intravenous dose of 10 mg/kg (Zatz and Roth, 1975) or subcutaneous doses of 3–10 mg/kg (Abdel-Halim et al., 1978) in rats. In a preliminary experiment, intramuscularly administered indomethacin at 20 mg/kg induced lethality within a 24-h observation period in pigeons. Thus, we investigated the antiemetic efficacy of indomethacin at a dose of 10 mg/kg against cisplatin-induced emesis. At a dose of 10 mg/kg (i.m.), indomethacin reduced neither the early, nor the delayed emetic response to cisplatin. Although we have not determined prostanoid levels in plasma and brain, these results with indomethacin suggest that prostanoid production does not play a role in the intensity of both early and delayed emetic responses induced by cisplatin in the pigeon. However, further studies using other specific cyclooxygenase inhibitors for cyclooxygenase-2 enzyme are required to resolve a role of prostanoids in the emetic response to cisplatin.

Girod et al. (2002) reported that indomethacin had a potent antiemetic activity against both the early and delayed emetic response to cisplatin, but indomethacin also had intrinsic emetic activity in piglets. Furthermore, other nonspecific cyclooxygenase inhibitors, diclofenac and naproxen, also exhibited emetogenic activity, and did not show antiemetic effect on cisplatin-induced emesis. In their study, the relatively specific inhibitor of cyclooxygenase-2 enzyme, meloxicam did not exhibit emetic effect, and showed antiemetic effect on cisplatin-induced emesis in piglets. It is well known that nonspecific cyclooxygenase inhibitors including indomethacin inhibit cyclooxygenase-1 enzyme in the gastric mucosa, resulting in gastric damage. Consequently, it is likely that the emetic effect of cyclooxygenase-1 inhibitors may partly mask their antiemetic activity (Girod et al., 2002). In the pigeon, unlike in the piglet, indomethacin did not exhibit emetogenic activity, but shortened the latency time to the onset of the emetic response to cisplatin. Furthermore, indomethacin exhibited a high toxicity with severe mortality in pigeons. The toxicity of indomethacin may be responsible for the decrease in latency time to the onset of emesis, but the role of prostanoids in the cisplatin-induced emesis in pigeons remains to be elucidated with specific cyclooxygenase-2 inhibitors. Recently, it was hypothesized that cisplatin-induced emesis is mediated partly by other inflammatory mediators, in particular cytokines, which are also regulated by glucocorticoids (Sam et al., 2001). Further studies are required to substantiate a role for inflammatory mediators in the emetic action of cisplatin.

4.3. Transport of cisplatin into the central nervous system

Our previous study revealed that direct injection of a low dose of cisplatin (10 μg/kg) into the fourth ventricle produced emesis, suggesting a central site of the emetic response to cisplatin in pigeons (Tanihata et al., 2003). Emetogenic activity of centrally administered cisplatin was also observed in cats (Smith et al., 1988). The central mechanism of emetic response to cisplatin in pigeons is supported by the result of our previous study in which the

cisplatin-induced emetic response persisted after bilateral cervical vagotomy (Tanihata et al., 2000). It is known that the chemoreceptor trigger zone located in the area postrema at the base of the fourth ventricle plays a role in the emetic reaction induced by various stimuli. The emetic stimulus is transmitted to the emetic center by way of the chemoreceptor trigger zone (Borison and Wang, 1953; Borison et al., 1981). The area postrema has been identified anatomically at the base of the fourth ventricle in pigeons (Weindl and Sofroniew, 1982). While we could not show direct evidence for a role of the area postrema in cisplatin-induced emesis in pigeons, it is possible that cisplatin-induced emesis is due to stimulation of this area. In the present study, the platinum concentration in the medulla oblongata confirmed the transport of cisplatin into the central nervous system. Although at a relatively low level, platinum was detected in the medulla oblongata 2 and 20 h after cisplatin administration. These were the peak time points of early and delayed emesis, respectively. The low platinum level measured in the brain was possibly due to the blood–brain barrier as it has been reported that cisplatin, a hydrophilic drug, does not easily cross the blood–brain barrier (Gormley et al., 1981; Gregg et al., 1992; Minami et al., 1996). Dexamethasone is thought to stabilize membranes and reduce the influx of emetogenic substances into the central nervous system (Hawthorn and Cunningham, 1990; Naylor and Rudd, 1996). However, in the present study, dexamethasone (1 mg/kg, i.m.) did not affect the platinum content in the medulla oblongata 2 and 20 h after cisplatin administration. Such a lack of effect of dexamethasone on the passage of cisplatin through the blood–brain barrier into the brain has been reported in rats (Straathof et al., 1998). The mechanism of the antiemetic action for dexamethasone thus remains unclear, but it may not involve the inhibition of prostanoid synthesis or effects that maintain the blood–brain barrier and prevent cisplatin from entering the central nervous system in the pigeon.

In the present study, the emetic response to cisplatin in pigeons was significantly reduced but not abolished by dexamethasone. The role of 5-hydroxytryptamine (5-HT) in cisplatin-induced early emesis has been documented in humans and animals, and it has been shown that dexamethasone acts synergistically with 5-HT_3 receptor antagonists, but alone it is a poor antiemetic in ferrets (Hawthorn and Cunningham, 1990; Marr et al., 1991; Naylor and Rudd, 1996), and in piglets (Grélot et al., 1996). The combination of corticosteroids and 5-HT_3 receptor antagonists are highly effective in preventing acute and delayed cisplatin-induced emesis in humans (Smith et al., 1991; Smyth et al., 1991; Chevallier et al., 1994), and in ferrets (Rudd and Naylor, 1996). In our previous study, cisplatin (4 mg/kg, i.v.)-induced early emesis in pigeons was significantly reduced by pretreatment with *para*-chlorophenylalanine, an inhibitor of 5-HT synthesis, suggesting a role for serotonergic mechanisms in the emetic response to cisplatin in pigeons (Tanihata et al., 2000). However, in pigeons, we cannot study the antiemetic effect of the combination of dexamethasone and 5-HT_3 receptor antagonists since indolic 5-HT_3 receptor antagonists such as granisetron and ondansetron have intrinsic emetic activity in pigeons (Preziosi et al., 1992).

Recently, it was shown that the combination of dexamethasone and tachykinin NK_1 receptor antagonists is effective in preventing acute and delayed cisplatin-induced emesis in humans (Kris et al., 1997; Campos et al., 2001) and in ferrets (Tattersall et al., 2000). We have shown that GR205171 ([(2*S*-cis)-*N*-((2-methoxy-5 (5-(trifluoromethyl)-1*H*-tetrazol-1-yl)-phenyl)methyl)-2-phenyl-3-piperidinamine dihydrochloride]), a tachykinin NK_1 receptor antagonist, reduced both early and delayed emesis induced by cisplatin (4 mg/kg, i.v.) in pigeons (Tanihata et al., 2003). Thus, further studies are needed to confirm the synergistic antiemetic activity of dexamethasone in combination with other antiemetics, in particular the tachykinin NK_1 receptor antagonists.

We investigate whether pigeons might be suitable for studying the drug-induced emetic response. Animal studies on cisplatin-induced delayed-phase emesis have been performed in ferrets (Rudd et al., 1994, 1996; Rudd and Naylor, 1994), piglets (Milano et al., 1995; Grélot et al., 1996; Girod et al., 2002) and cats (Rudd et al., 2000). There may be species differences in the mechanisms of cisplatin-induced emesis, and time course of both the early and delayed phases of cisplatin-induced emesis in pigeons seems shorter than those observed in other species. In humans (Kris et al., 1985), ferrets (Rudd et al., 1994) and cats (Rudd et al., 2000), the early phase is presumed to last for 1 day, and in piglets for the first 16 h (Milano et al., 1995). In addition, the role of the vagus nerve differs among animal studies. Cisplatin-induced early emesis is potently inhibited by bilateral vagotomy in ferrets (Hawthorn et al., 1988) and piglets (Diemunsch and Grélot, 2000). However, bilateral vagotomy has little effect on cisplatin-induced emesis other than a small prolongation in the latency time of the first emetic episode in cats (Miller and Nonaka, 1992) and pigeons (Tanihata et al., 2000). Furthermore, sensitivity to various emetics or antiemetic drugs differs among animal species (Borison et al., 1981; King, 1990). 5-HT_3 receptor antagonists have intrinsic emetic activity in pigeons (Preziosi et al., 1992). Indomethacin has a potent antiemetic activity against cisplatin-induced emesis and also has intrinsic emetic activity in piglets (Girod et al., 2002). As there are discrepancies among pigeons and other animal species in the experimental results of cisplatin-induced emesis, more research is required to elucidate the usefulness and suitability of the pigeon for research on the cisplatin-induced delayed-phase emetic response.

4.4. General conclusions

Dexamethasone has antiemetic effects on both cisplatin (4 mg/kg, i.v.)-induced early and delayed emesis, which appear within the first 8-h period and between 8 and 48 h after cisplatin administration, respectively, in the pigeon. Dexamethasone administered via either the intramuscular or

the intracerebroventricular route reduced both types of emesis and prolonged the latency time to first emesis. The antiemetic effect of centrally administered dexamethasone was more potent than when it was peripherally administered. Indomethacin was unable to antagonize cisplatin-induced emesis, and dexamethasone (1 mg/kg, i.m.) did not influence the content of platinum in the medulla oblongata after cisplatin administration. These results suggest that dexamethasone has antiemetic effects on both the early and delayed emetic responses to cisplatin in pigeons, partially via its central site of action, and its antiemetic mechanism is related to other factors other than its inhibition of prostanoid synthesis and its membrane stabilizing effect and reduction of the influx of cisplatin into the central nervous system.

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