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The Antiemetic Profile of Zacopride

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Abstract—The antiemetic activity of zacopride against a variety of emetogenic agents has been determined in dogs. Zacopride was highly effective in inhibiting emesis due to a wide range of cancer chemotherapeutic agents, particularly cisplatin. It was well absorbed orally since the dose of zacopride required to inhibit cisplatin-induced emesis in dogs by 90% was 28 $\mu g\ kg^{-1}$ both by i.v. and p.o. routes. Further, zacopride (1 $mg\ kg^{-1}$ p.o.), administered after the onset of cisplatin-induced emesis, reduced the number of subsequent emetic episodes by 91%. Zacopride at 0·1, 1, or 3·16 $mg\ kg^{-1}$ p.o. or i.v., reduced the number of emetic episodes due to dacarbazine, mechlorethamine, adriamycin, actinomycin D, or peptide YY by 100, 100, 86, 96 and 79%, respectively. However, zacopride was not effective in inhibiting emesis due to either apomorphine, copper sulphate, protoveratrine A, histamine, or pilocarpine. No adverse effects attributed to zacopride were observed. Zacopride is thus a unique and potent antiemetic agent as it selectively inhibits the emetic response to cancer chemotherapy agents and peptide YY.

Few would question that nausea and vomiting cause mental and physical suffering. The complications that may arise from vomiting are many and are determined by the severity and duration of the vomiting. Electrolyte disturbances, bone fractures, and upper gastrointestinal tract tears can occur (Laszlo 1983). Particularly severe is the protracted nausea and vomiting induced by certain cancer chemotherapy agents. Before the use of metoclopramide, the prevention and treatment of nausea and vomiting due to cancer chemotherapeutic agents was less than satisfactory (Gralla 1983). Beginning with metoclopramide, the work in our laboratory over a number of years has been concentrated in discovering compounds that would effectively and safely alleviate the problems of nausea and vomiting due to cancer chemotherapy. Our first compound was dazopride, a gastric prokinetic and antiemetic agent without dopamine antagonist properties (Smith et al 1984; Alphin et al 1986a). Recently, we reported preliminary work on a more potent and more selective prokinetic and antiemetic agent, zacopride (Smith et al 1986; Alphin et al 1986b). The purpose of this communication is to present the antiemetic profile of this unique compound.

Materials and Methods

Animals

The studies were performed on dogs of either sex, 8–18 kg. The animals were fed dry dog food 60 min before the administration of the emetogenic agent. In all procedures the dogs were randomly assigned to treatment groups by the use of a table of random numbers (Moses & Oakford 1963) unless otherwise noted.

Drugs and materials

The drugs or chemicals used were: zacopride hydrochloride (A. H. Robins Research Laboratories, covered by French Patent No. 2529548 assigned to Delalande); peptide YY, apomorphine hydrochloride, histamine diphosphate, diamminedichloroplatinum (cisplatin) and protoveratrine A (Sigma Chemical Company, St. Louis, MO); cupric sulphate, anhydrous, (Mallinkrodt Chemical Company, St. Louis, MO); pilocarpine hydrochloride (Aldrich Chemical Co., Milwaukee, WI); doxorubicin Adriamycin (Adria Laboratories, Inc., Columbus, OH); dacarbazine (Miles Pharmaceuticals, Westover, CT); mechlorethamine and actinomycin D (Merck, Sharp, and Dohme, West Point, PA). Gelatin capsules (000) (Bell-Tex Lab, Little River, TX) were used to administer solutions of the compounds and emetogenic agents orally (0·05–0·1 $mL\ kg^{-1}$). When the compounds were administered subcutaneously or intravenously the volume administered was 0·1–1·0 $mL\ kg^{-1}$. Doses stated are those of the free base, and distilled water was used as the vehicle.

Emetogenic agents

Cancer chemotherapy

Cisplatin. The test procedure used was a modification of the method of Gylys et al (1979) whereby the compounds were administered p.o. or i.v. after cisplatin instead of before and after the administration of the emetic agent. On the day of study, cisplatin (3 $mg\ kg^{-1}$) was injected into a cephalic vein. Approximately 60 min later in the oral study or 75 min later in the i.v. study, the vehicle or zacopride was administered. The dogs were then observed for emesis for 5 h, from the time the cisplatin was administered.

To determine the ability of zacopride to suppress the emetic response subsequent to its onset, zacopride was administered orally immediately following the first emetic episode; and the animals observed for emesis for 5 h. Analysis for significant differences from control responses was determined with Dunnett's *t*-test (Dunnett 1955). ID50 and ID90 values were determined by linear regression analysis, and interval estimates were computed by using Fieller's theorem (Zerbe 1978). To stabilize the variance, the data were converted to the square root. The Behrens-Fischer *t*-test was used for analysis of the data in the therapeutic study (Bolt Beranek & Newman Inc. 1983).

Dacarbazine. A randomized crossover design was used to

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determine the treatment regimen for any particular dog on a given day. On the day of study, dacarbazine, 30·0 mg kg^{-1}, was injected into a cephalic vein of each of 8 dogs. Approximately 60 min later zacopride or the vehicle was given orally. The dogs were then observed continuously for 5 h for emetic episodes. The results were compared by a randomization test for paired data (Siegel 1956a).

Mechlorethamine. Groups of 4 dogs each were used in a two-period, two-treatment crossover test design. Each dog received mechlorethamine, 0·4 mg kg^{-1}, injected into a cephalic vein. Approximately 60 min later each dog received the vehicle or zacopride orally. The dogs were observed continuously for 5 h for emetic episodes. The results were analysed by using a randomization test for paired data (Siegel 1956a).

Doxorubicin. Groups of four dogs each were used in a parallel test design. On the day of study, zacopride or the vehicle was administered to each dog. Fifteen min later, each dog was administered 2·0 mg kg^{-1} of doxorubicin by intravenous injection in a cephalic vein. The dogs were then observed continuously for 2 h for emetic episodes. Analysis for differences from control emetic episodes was performed by using Student's *t*-test with a one-sided alternative (Bolt Beranek & Newman Inc. 1983).

Actinomycin D. Groups of four dogs each were used in a parallel test design. On the day of study, actinomycin D (150 $\mu g\ kg^{-1}$) was injected into a cephalic vein. Sixty min after receiving actinomycin D, zacopride or the vehicle was given orally. The dogs were then observed continuously for 5 h, and the number of emetic episodes was recorded. The data was analysed for statistical significance by Steel's many-to-one Rank Test (Miller 1981) after analysis by the Kruskal-Wallis Analysis of Variance by ranks (Siegel 1956b).

Non-cancer chemotherapy

Apomorphine. The method used was that of Chen & Ensor (1950). A randomized block design employing seven dogs was used to determine the treatment regimen for any particular dog on a given day. Each dog was given the emetic agent, apomorphine (0·1 mg kg^{-1}), subcutaneously on three separate days to determine its control emetic response. Subsequently, each dog received zacopride 30 min before receiving apomorphine. Different doses of zacopride were given to the same dogs, but a minimum of seven days elapsed between trials. The dogs were observed for 1 h after the administration of apomorphine, and the number of emetic episodes experienced by each dog was recorded. To stabilize the variance the data were converted to the square root. Comparison of differences in the emetic response among the 5 dose groups was made by using a randomized block analysis of variance (Cochran & Cox 1957).

Copper sulphate. The procedure used was a modification of that of Wang & Borison (1951). A balanced Latin Square design for treatment was used to determine the treatment for each dog on each dosing day. In this 4-period design, each dog received the vehicle or zacopride orally 30 min before receiving 20 mg kg^{-1} of copper sulphate orally. There was a minimum of 7 days between trials. The dogs were observed for 1 h after receiving copper sulphate. To stabilize the variance, the data were converted to the square root. Comparisons of differences in the numbers of emetic episodes among the four dose groups were made by using an analysis of variance appropriate for a 4-period crossover design (Cochran & Cox 1957).

Protoveratrine A. The procedure used was a modification of that of Swiss (1952). A balanced Latin Square design for treatment was used to determine the treatment for each dog. In this 4-period design, each dog received the vehicle or zacopride (0·1, 1·0, or 10·0 mg kg^{-1} p.o.) 30 min before receiving 100 $\mu g\ kg^{-1}$ p.o., of protoveratrine A. The dogs were then observed for 1 h for emetic episodes. Different doses of zacopride were evaluated in the same dogs, but there was a minimum of 7 days between trials. To stabilize the variance, the data were converted to the square root. Comparison of differences in the numbers of emetic episodes among the four dose groups was made by using an analysis of variance appropriate for a 4-period crossover design (Cochran & Cox 1957).

Histamine, pilocarpine, or peptide YY. Groups of 4–8 dogs each were used in a parallel test design. Each dog received either the vehicle or zacopride, 0·1 mg kg^{-1} i.v. or 1·0 mg kg^{-1} p.o. Fifteen min later each dog was given either 3 mg kg^{-1} of histamine diphosphate, 3 mg kg^{-1} of pilocarpine hydrochloride, or 2 $\mu g\ kg^{-1}$ of peptide YY, i.v. Each animal was then observed continuously for 2 h, and the number of emetic episodes recorded. The data were analysed for difference from control by use of Student's *t*-test (Bolt Beranek & Newman Inc. 1983).

Results

Antiemetic activity (cancer chemotherapy)

Cisplatin. Against the emetic activity of 3 mg kg^{-1} i.v. of cisplatin, zacopride at oral or intravenous doses, ranging from 1 to 316 $\mu g\ kg^{-1}$, reduced in a dose-dependent manner the number of emetic episodes occurring during the following 4 h (Table 1). The data in the i.v. study represent the

Table 1. Effect of zacopride on cisplatin-induced emesis in dogs.

Treatment	Route	Dose (mg kg^{-1})	n	Emetic episodes (mean ± s.d.)
Vehicle	i.v.	0·1 mL kg^{-1}	34	14·8 ± 6·1
Zacopride	i.v.	0·001	6	9·5 ± 3·7[b]
		0·00316	6	7·2 ± 3·0[a,b]
		0·010	6	1·0 ± 1·5[a,b]
Vehicle	p.o.	0·1 mL kg^{-1}	10	12·9 ± 12·3
Zacopride	p.o.	0·001	6	11·0 ± 5·2[b]
		0·00316	6	8·5 ± 4·5[b]
		0·01	6	2·0 ± 2·6[a,b]
		0·0316	6	1·5 ± 2·1[a]
		0·100	6	0·3 ± 0·8[a]
		0·316	4	0·0 ± 0·0[a]

[a] $P < 0·05$.
[b] Used to determine the ID50, ID90 dose and 95% confidence limits.

pooling of several experiments since the data for the control animals did not appear to be different from test to test. The data in the p.o. study represent the pooling of two experiments. The ID90 dose, determined from the regression line (the dose that reduced the number of emetic episodes by 90%) was 28 $\mu g\ kg^{-1}$ by both oral and intravenous routes of administration. The ID50 oral and i.v. doses were also similar (Table 2). Further, zacopride at 1 mg kg^{-1} p.o., administered after the onset of cisplatin-induced emesis, inhibited further emesis by 91% (Table 3).

Dacarbazine, mechlorethamine, adriamycin, or actinomycin D. Zacopride orally was effective in suppressing emesis induced by these drugs as shown in Table 4.

Apomorphine, copper sulphate, protoveratrine A, or peptide YY. Zacopride at doses up to 10 mg kg^{-1} p.o., was ineffective against emesis induced by apomorphine, copper sulphate, or protoveratrine A (Tables 5, 6). Pilocarpine- or histamine-induced emesis was not inhibited by zacopride at 1 mg kg^{-1} p.o., while emesis induced by Peptide YY was suppressed by 0·1 mg kg^{-1} i.v. of zacopride (Table 7).

Table 2. Inhibitory doses of zacopride versus cisplatin-induced emesis in dogs.

Zacopride dose (mg kg^{-1})	Route	% Inhibition	95% Confidence Limits
0·004	i.v.	50	0·002–0·008
0·007	p.o.	50	0·0034–0·0435
0·028	i.v.	90	0·014–0·088
0·028	p.o.	90	0·016–1·561

Table 3. Therapeutic effect of zacopride versus cisplatin-induced emesis in dogs (zacopride administered *after* the onset of emesis).

Treatment	Dose (mg kg^{-1} p.o.)	n	Emetic episodes after onset (mean ± s.d.)
Vehicle	0·1 mL kg^{-1}	4	10·0 ± 7·9
Zacopride	1·0	4	0·3 ± 0·5[a]

[a] $P < 0·05$.

Table 4. Effect of zacopride against emesis induced by various cancer chemotherapy agents in dogs.

Agent	Treatment	Dose (mg kg^{-1} p.o.)	n	Emetic episodes (mean ± s.d.)
Dacarbazine	Vehicle	0·1 mL kg^{-1}	8	8·0 ± 3·7
	Zacopride	1·0	8	0·0 ± 0·0[a]
Mechlorethamine	Vehicle	0·1 mL kg^{-1}	8	7·0 ± 4·7
	Zacopride	1·0	8	0·0 ± 0·0[a]
Doxirubicin	Vehicle	0·1 mL kg^{-1}	4	3·5 ± 2·4
	Zacopride	1·0	4	0·5 ± 1·0[a]
Actinomycin D	Vehicle	0·1 mL kg^{-1}	6	8·3 ± 4·2
	Zacopride	1·0	6	3·3 ± 5·5[a]
		3·16	6	0·3 ± 0·8[a]

[a] Significantly different ($P < 0·05$) from the respective vehicle treated group.

Table 5. Effect of zacopride on apomorphine-induced emesis in dogs.

Treatment[a]	Dose (mg kg^{-1} p.o.)	No. Trials	Emetic episodes (mean ± s.d.)
Vehicle	0·1 mL kg^{-1}	21	3·9 ± 2·5
Zacopride	0·01	7	3·9 ± 1·2
	0·1	7	4·9 ± 2·3
	1·0	7	3·9 ± 1·9
	10·0	7	4·3 ± 1·7

[a] Zacopride given 30 min before apomorphine (0·1 mg kg^{-1} s.c.).

Table 6. Effect of zacopride on oral copper sulphate or protoveratrine A-induced emesis.

Treatment[a]	Dose (mg kg^{-1} p.o.)	Emetic Agent	n	Emetic episodes (mean ± s.d.)
Vehicle	0·1 mL kg^{-1}	Copper Sulphate	8	5·5 ± 4·0
Zacopride	0·1	Copper	8	4·1 ± 3·0
	1·0	Sulphate	8	4·4 ± 2·7
	10·0		8	4·4 ± 2·6
Vehicle	0·1 mL kg^{-1}	Proto-veratrine A	8	5·6 ± 5·6
Zacopride	0·1	Proto-	8	12·0 ± 10·1
	1·0	veratrine A	8	12·0 ± 12·3
	10·0		8	10·8 ± 7·8

[a] Zacopride given 30 min before copper sulphate (20 mg kg^{-1} of 400 mg mL^{-1} solution orally) or protoveratrine A (100 $\mu g\ kg^{-1}$ p.o.).

Table 7. Effect of zacopride on histamine, pilocarpine, or peptide YY-induced emesis in dogs.

Zacopride Dose (mg kg^{-1})	Route	Emetogenic[a] agent	Treatment	n	Emetic episodes (mean ± s.d.)
		Histamine	Vehicle	4	4·3 ± 0·5
1·0	p.o.		Zacopride	4	3·8 ± 1·7
		Pilocarpine	Vehicle	4	8·5 ± 4·8
1·0	p.o.		Zacopride	4	6·8 ± 5·9
		Peptide YY	Vehicle	4	2·3 ± 0·5
0·1	i.v.		Zacopride	4	0·5 ± 0·6[b]

[a] Administered 15 min following dosing with zacopride.
[b] $P < 0·05$.

Discussion

The dog has been used as a model for emesis caused by numerous emetogenic agents (Barnes 1984). This species is particularly suited for studying cisplatin-induced emesis since high-dose cisplatin leads to the same sequence of events in the dog as it does in man (Gylys et al 1979; Barnes 1984). Numerous agents have been used to ameliorate the nausea and vomiting due to cancer chemotherapy agents (Wampler 1983). However, to-date, metoclopramide is the only agent to meet with sufficient success to be considered of real value in treating the nausea and vomiting due to cancer chemotherapy, particularly cisplatin (Harrington et al 1983). The usefulness of metoclopramide in treating nausea and vomiting may be limited due to extrapyramidal reactions, which may be attributed to its dopamine-receptor blocking properties. In 452 patients receiving high doses of metoclopramide, 14 (3·1%) produced acute dystonic reactions indicative of

extrapyramidal symptoms and manifested by torticollis or trismus (Kris et al 1983).

The results described here clearly demonstrate that zacopride is highly effective against the emesis due to cancer chemotherapy (Tables 1–4). The similarity of the ID50 and ID90 values by the p.o. and i.v. routes suggests that zacopride is well absorbed by the oral route. The wide 95% confidence limits at the ID90 are not surprising because it is at the upper end of the range of the data. Indeed, zacopride is even active in inhibiting emesis after the onset of emesis due to cisplatin (Table 3). The lack of effect of zacopride in inhibiting apomorphine-induced emesis is indicative of the lack of dopamine-receptor antagonism (Table 5). This affords zacopride a much higher therapeutic index than metoclopramide since zacopride lacks the potential for producing extrapyramidal side effects.

Zacopride was also effective in suppressing the emesis induced by peptide YY (Table 7). However, it did not affect emesis caused by protoveratrine A, oral copper sulphate, histamine, or pilocarpine (Tables 5–7). More recently, zacopride was reported to suppress emesis induced by radiation in rhesus monkeys and in ferrets (Dubois et al 1987; King et al 1988). In the monkey study zacopride further reduced the decreased gastric emptying effect due to the radiation. This may be attributed to its potent gastrokinetic property (Alphin et al 1986a; Smith et al 1986) and not due to its antiemetic activity since domperidone suppressed radiation-induced emesis in dogs without reducing the decreased gastric emptying (Dubois et al 1984).

The antiemetic effect of zacopride may be centrally mediated since zacopride administered i.c.v. immediately following the onset of emesis due to cisplatin given i.c.v. completely blocked subsequent emesis (Smith et al 1988a).

Zacopride and other inhibitors of cytotoxic-induced emesis, while differing chemically, possess 5-HT_3-blocking properties (Bradley et al 1986; Costall et al 1986; Miner & Sanger 1986; Andrews & Hawthorn 1987; Miner et al 1987; Smith et al 1988b). Since the methods employed to demonstrate $5HT_3$-blocking activity are peripheral, the relationship between emesis and $5HT_3$-receptor antagonism are associated and not causative (Gylys et al 1988). It has long been known that 5-HT is present near the area postrema (Fuxe & Owman 1965); however, it remains to be seen whether 5-HT_3 receptors are present in that area of the brain and what role they play in emesis induced by cytotoxic agents, radiation, or peptide YY. Nevertheless, zacopride is a potent and selective antiemetic agent.

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