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The emetic activity of centrally administered cisplatin in cats and its antagonism by zacopride

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Abstract—Cisplatin administered by either the intravenous (i.v.) or intra-cerebroventricular (i.c.v.) route produced emesis in cats. The average time to onset of emesis was decreased significantly (4·0 min versus 100·6 min) when cisplatin was administered i.c.v. Zacopride administered either i.c.v. (0·02 mg) or i.v. (0·1 mg kg^{-1}) completely blocked the emesis due to cisplatin given by either route. Their data show that cisplatin possesses a central emetic component and that this is blocked by zacopride.

McCarthy & Borison (1984) demonstrated in cats that the emesis due to i.v. cisplatin could be prevented by lesion of the area postrema. Alphin et al (1986a) recently proposed that the activity of metoclopramide and dazopride against cisplatin-induced emesis was due to their gastrokinetic properties. These results in addition to those obtained by Akwari (1983) suggest that cisplatin possesses a peripheral mechanism in inducing emesis. Zacopride is a potent gastrokinetic and antiemetic agent devoid of dopamine blocking properties (Smith et al 1986; Alphin et al 1986b). The present study will show that, in cats, cisplatin produces emesis when administered i.c.v. and that zacopride administered i.c.v. or i.v. blocks the emetic response.

Materials and methods

Adult mongrel cats, of either sex, between 2·5 and 3·0 kg, were used.

In Study 1, cats were injected i.v. with cisplatin (7·5 mg kg^{-1}) and observed for 5 h for the time to onset and number of emetic episodes (expulsion of vomitus). In Study 2, cats were anaesthetized with halothane. A 25-gauge stainless-steel cannula was placed into the 4th cerebral ventricle using a David Kopf stereotaxic apparatus. The animals were allowed to recover for 24 h. After recovery each animal was dosed with cisplatin (0·3 mg in 0·1 mL) or saline (0·1 mL) into the 4th ventricle. Each animal was then observed for 5 h for time to onset and number of emetic episodes. In Study 3, cats were dosed either i.v. (7·5 mg kg^{-1}) or i.c.v. (0·3 mg) with cisplatin. In those animals dosed i.v. with cisplatin, zacopride (0·02 mg in 0·1 mL) was administered i.c.v. immediately after the first emetic episode. In those animals dosed i.c.v. with cisplatin, zacopride (0·1 mg kg^{-1}) was administered i.v. 15 min before the cisplatin dose.

For the studies with cannulas placed in the 4th ventricle, the location of the cannula was confirmed by passing a 1 MV current through the cannula for 30 s after the animals were killed by lethal injection. The brains were removed and placed in a potassium ferricyanide solution. The cannula track was stained blue by this procedure and was readily visualized upon dissection of the brain.

Cisplatin was obtained from Sigma Chemical Company and prepared for injection by adding 70°C deionized water to volume. The resulting solutions (3 mg mL^{-1} for i.c.v. and 7·5 mg mL^{-1} for i.v.) were maintained at 40°C until administration. Solutions were freshly prepared, immediately before use. Zacopride, A. H. Robins, Company, Inc., was prepared for injection by adding deionized water to volume. The resulting solutions (0·2 mg mL^{-1} for i.c.v. and i.v.) were prepared immediately before use.

Results

Table 1 gives the results seen when cisplatin was administered alone either i.v. or i.c.v. Cisplatin given i.v. produced emesis with a relatively long time to onset when compared with cisplatin given i.c.v. Saline given either i.v. or i.c.v. did not produce emesis.

When zacopride was administered i.c.v. immediately following the onset of emesis from i.v. cisplatin, no further emesis occurred. When zacopride was administered i.v. 15 min before i.c.v. cisplatin, no emesis occurred (Table 2).

Discussion

The mechanism of action for emesis produced by cisplatin is unclear. After intravenous or intraperitoneal injection, high levels of cisplatin are found in the gastrointestinal tract, and cisplatin is known to produce marked gastrointestinal effects in addition to nausea and vomiting (Pretorius et al 1981). Akwari (1983) as well as Alphin et al (1986a) suggest that emesis due to cisplatin is caused by a peripheral action, specifically an action on the gastrointestinal tract. McCarthy & Borison (1984) found that cats with lesions of the area postrema, the site of the chemoreceptor trigger zone, failed to develop emesis after i.v. cisplatin (7·5 mg kg^{-1}). This finding suggests a central site for the emetogenic activity of cisplatin. The finding in this study that emesis occurs only after a considerable time delay following i.v. injection and immediately after i.c.v. injection would seem consistent with the concept of a direct gastrointestinal effect. Cisplatin does not readily cross the blood brain barrier, but does readily accumulate in the intestinal tract (Rosenberg 1985). The delay in onset of emetic effects after i.v. administration could reflect the time required to reach a central site of action. That site may be located in the area postrema. Our findings as well as those of McCarthy & Borison (1984) would seem to support the

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Table 1. Emetic effect of cisplatin in cats when administered intravenously or intracerebroventricularly.

Treatment	Route	Dose	No. with emesis/ no. of cats	Number of emetic episodes (mean ± s.d.)	Time (min) to onset (mean ± s.d.)
Cisplatin	i.v.	7·5 mg kg^{-1}	5/5	7·7 ± 5·4	100·6 ± 32·1
Saline	i.v.	1 mL kg^{-1}	0/6	0	0
Cisplatin	i.c.v.	0·3 mg[a]	5/5	3·0 ± 0·7	4·0 ± 5·2[b]
Saline	i.c.v.	0·1 mL	0/4	0	0

[a] Dose given in a total volume of 0·1 mL.
[b] $P < 0·05$ when compared with cisplatin IV group; Student's t-test.

Table 2. Inhibitory effect of intravenously or intracerebroventicularly administered zacopride on cisplatin-induced emesis in cats.

Treatment	Route	n	Dose	Number of emetic episodes (mean ± s.d.)
Cisplatin	i.v.	5	7·5 mg kg^{-1}	7·7 ± 5·4
Cisplatin + zacopride[a]	i.v. / i.c.v.	4	7·5 mg kg^{-1} / 0·02 mg[c]	0[d]
Cisplatin	i.c.v.	5	0·3 mg	3·0 ± 0·7
Zacopride[b] + cisplatin	i.v. / i.c.v.	4	0·1 mg kg^{-1} / 0·3 mg[c]	0[d]

[a] Zacopride given after the first emetic episode.
[b] Zacopride given 15 min before cisplatin dose.
[c] In total volume of 0·1 mL.
[d] $P < 0·05$ when compared with respective cisplatin group; Student's t-test.

concept of a central site of action. Furthermore, the ability of zacopride given i.c.v. to inhibit cisplatin-induced emesis supports the concept of a central locus of action. Recently, reports have appeared indicating drug action at 5-HT$_3$ receptors as the mechanism of action for inhibition of cisplatin-induced emesis (Miner & Sanger 1986; Costall et al 1986) and zacopride is a potent 5-HT$_3$ receptor antagonist (Smith et al unpublished data). Large numbers of 5-HT-containing neurons have been found in the area postrema (Pickel & Armstrong 1984) but, it remains to be elucidated as to whether 5-HT$_3$ receptors are present in brain areas known to be involved in emesis.

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