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Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism

Wesley D. Miner & Gareth J. Sanger[1]

Beecham Pharmaceuticals Research Division, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD

MDL 72222, the selective 5-hydroxytryptamine (5-HT) M-receptor antagonist, prevented or reduced cisplatin-induced emesis in ferrets. It is suggested that cisplatin-induced, and possibly other cytotoxic drug-induced vomiting may involve a 5-HT M-receptor mechanism.

Introduction Conventional doses (10–30 mg) of metoclopramide (Maxolon; Beecham Pharmaceuticals) antagonize dopamine receptors at the chemoreceptor trigger zone (CTZ) within the area postrema of the medulla (Perrot *et al.*, 1982), and this may account for the anti-emetic activity of metoclopramide in many different clinical situations (Harrington *et al.*, 1983). However, only high intravenous doses of metoclopramide (2 mg kg^{-1} every 2 h, up to 10 mg kg^{-1} over 24 h) reduce emesis in patients receiving cisplatin for various types of cancer; conventional doses are poorly effective (Gralla *et al.*, 1981). Since dopamine is not the only neurotransmitter which may be important in the control of emesis (Pickel & Armstrong, 1984), we considered the possibility that the anti-emetic action of metoclopramide at high doses is unrelated to dopamine antagonism and therefore different from the actions of metoclopramide given in lower doses.

Relatively high doses of metoclopramide antagonize 5-hydroxytryptamine (5-HT) M-receptors in the peripheral nervous system (Fozard, 1984a), so we investigated whether MDL 72222, a selective 5-HT M-receptor antagonist (Fozard, 1984b), could block cisplatin-induced vomiting in ferrets. This species has previously been used to demonstrate the anti-emetic activity of metoclopramide against cisplatin (Florczyk *et al.*, 1982).

Methods Male ferrets, 1–1.9 kg, with surgically implanted indwelling venous catheters were used. Intravenous cisplatin, 10 mg kg^{-1}, evoked a reproducible vomiting response and this dose was used for all experiments. MDL 72222 or vehicle was administered intravenously 30 min before and 45 min after dosing with cisplatin (see Florczyk *et al.*, 1982). Each individual vomiting episode was recorded, as was the time interval from injection of cisplatin to the first vomiting episode (latency period). The ferrets were observed for 240 min after dosing with cisplatin and for those ferrets which did not vomit, the latency period was taken as 240 min.

Cisplatin was prepared by diluting Neoplatin (Mead Johnson) with water BP. MDL 72222 (1αH, 3α, 5αH-tropan-3-yl-3, 5 dichlorobenzoate methane sulphonate; Merrell-Dow) was dissolved in 0.9% saline. Doses are given as base weights.

Results In animals which did not receive MDL 72222, cisplatin produced a characteristic pattern of vomiting which began 84.1 ± 11.5 min after injection of cisplatin. Vomiting episodes normally occurred in 4–6 groups with 3–4 individual emetic episodes per group. Vomiting-free periods separated the groups of vomiting episodes (Table 1).

MDL 72222, 2 × 0.5 mg kg^{-1} prevented vomiting in 3 of 4 animals (Table 1); the fourth animal vomited very near the end of the observation period (3 episodes 215 min after dosing with cisplatin). The three completely protected animals exhibited normal behaviour throughout the observation period, suggesting an absence of nausea or sedation. This was in contrast to control animals which often displayed behaviour indicative of discomfort or nausea during the intervals between groups of vomiting episodes. A lower dose of MDL 72222 (2 × 0.05 mg kg^{-1}) reduced the severity but did not prevent the vomiting response (Table 1).

Discussion The selective 5-HT M-receptor antagonist, MDL 72222 prevented cisplatin-induced emesis in ferrets. Since metoclopramide is also a 5-HT M-receptor antagonist, at least part of the anti-emetic action of high-doses of metoclopramide in man may be explained by antagonism of 5-HT M-receptors and not by dopamine receptor antagonism. This finding may

[1]Author for correspondence.

Table 1 Effect of MDL 72222 on cisplatin-induced vomiting in the ferret

Treatment (mg kg^{-1})	*Number of ferrets* Vomiting/Tested	*Latency period to first vomit* (min)	*Number of vomiting episodes*
Control —	14/15	84.1 ± 11.5	15.7 ± 1.8
MDL 72222 2 × 0.05	4/ 4	94.3 ± 6.8*	5.8 ± 1.1**
MDL 72222 2 × 0.5	1/ 4	233.8 ± 6.3**	0.8 ± 0.8**

Ferrets were injected intravenously (i.v.) with MDL 72222 or vehicle 30 min before and 45 min after dosing with cisplatin (10 mg kg^{-1} i.v.). The vomiting responses of vehicle dosed ($n = 11$) and non-vehicle dosed ($n = 4$) controls were not different ($P > 0.1$ for latency period and number of vomiting episodes) and the results were combined for statistical analysis: Mann-Whitney U-test; compared with controls $^*P < 0.1$; $^{**}P < 0.02$. If a ferret did not vomit, latency period was taken as equal to the observation period (240 min). Results are given as means ± s.e.mean.

also explain the poor efficacy shown by more selective dopamine antagonists, such as domperidone, in the management of cisplatin-induced emesis (Tonato *et al.*, 1985).

It is not clear how 5-HT M-receptors are affected by cisplatin. However, Harris (1982) suggested that cytotoxic drugs may exert their emetic effects by inhibiting enzymes which break down neurotransmitters such as enkephalins, which are involved in the emetic response. We would now suggest that 5-HT should also be considered as a possible neurotransmitter involved in cisplatin-induced emesis, particularly since large numbers of 5-HT-containing neurones can be found within the area postrema (Pickel & Armstrong, 1984). In cats, ablation of the area postrema prevents cisplatin-induced emesis (McCarthy & Borrison, 1984), but this is not evidence for a direct action of cisplatin in the CTZ. Peripheral nerve input to the vomiting centre is mostly via the area postrema (Leslie & Gwyn, 1984) and ablation of this area may therefore prevent emesis caused by certain actions within the CTZ or on the peripheral nerves.

An alternative mechanism could therefore involve the peripheral nervous system and this is as yet the only system in which 5-HT M-receptors have been shown to exist (Fozard, 1984a). Thus, emesis could be evoked by activation of 5-HT M-receptors located on afferent nerve pathways leading from the viscera to the area postrema. Evidence for this suggestion includes the potent ability of MDL 72222 to block 5-HT-induced activation of the afferent nerves leading from the heart and subserving the Bezold-Jarisch reflex (Fozard, 1984b).

We are conducting further studies with other cytotoxic drugs, and preliminary results indicate that selective 5-HT M-receptor antagonists are also highly effective in preventing emesis evoked by doxorubicin and cyclophosphamide. Different cytotoxic drugs may therefore induce emesis by acting through a common mechanism involving 5-HT M-receptors.

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