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A single-dose-finding study of the antiemetic effect and associated plasma levels of MDL 72222 in patients receiving cisplatin

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Summary. A total of 25 patients (5 groups of 5) were given single i.v. doses of 5, 10, 20, 40 and 60 mg MDL 72222 (a 5-HT_3 receptor antagonist) at 15 minutes before the commencement of a 24-h cisplatin infusion (total dose, 120–200 mg) to determine the efficacy and safety of the former in the prevention of nausea and vomiting associated with such chemotherapy. All patients completed the study. The time to onset of vomiting was significantly correlated with dose. All patients vomited following doses of 5 and 10 mg (range, 1–6 episodes), with onset being noted at 5–8 h. At the 20-mg level, only one episode of vomiting was observed in $^3/_5$ patients, with onset being observed at 18–22 h. Following doses of 40 and 60 mg, $^3/_{10}$ patients did not vomit; in the remaining patients the number of episodes ranged from 1 to 6, but a significant increase occurred in the time to onset of symptoms. At the higher doses, nausea tended to be milder in nature both at onset and at the time of maximal severity. A similar dose-effect trend was seen in the time to onset of the maximal severity of nausea. The time to and requirement for escape medication was similarly extended at doses of $\geq$20 mg MDL 72222. Pain at the injection site in one patient was the only unwanted effect associated with MDL 72222. The results suggest that the i.v. injection of 20 mg MDL 72222 should be further explored in the control of nausea and vomiting associated with cisplatin administration.

Introduction

Cisplatin is an effective chemotherapeutic agent but is also one of the most emetogenic [14, 17] and antiemetic adjuvant therapy is mandatory for its use. Currently available antiemetic regimens consisting of the coadministration of dopamine antagonists and corticosteroids with or without a benzodiazepine have greatly improved the management of patients, but protection has been less than satisfactory in 40% of patients [16], rendering them liable to default from further chemotherapeutic sessions and, hence, from potentially curative treatment. A single safe and effective antiemetic would not only improve patient care but would also reduce the risk of interactions between the various drugs constituting the antiemetic and chemotherapeutic regimens.

The rationale for the use of 5-hydroxytryptamine (5-HT_3) receptor antagonists was suggested by the identification of 5-HT_3 receptors in the gastrointestinal tract [8] and by observations that MDL 72222, a highly selective 5-HT_3 receptor antagonist [5], prevents vomiting associated with the administration of cisplatin in the ferret [12]. This was subsequently strengthened by the identification of binding sites in the area postrema [9] and by the finding that cisplatin produced an increase in 5-HT in the small intestine of the ferret [7]. Recent clinical findings have demonstrated the safety and efficacy of several 5-HT_3 receptor antagonists in the treatment and prevention of nausea and vomiting associated with cancer chemotherapy [3, 4, 9, 10]. The i.v. administration of 20 mg MDL 72222 has previously been shown to inhibit the dermal flare response to 5-HT [13] with good tolerability.

The present dose-finding study was established to evaluate the safety, efficacy, duration of action and associated plasma concentrations following single doses of 5, 10, 20, 40 and 60 mg MDL 72222 given i.v. over 4 min at 15 min before the commencement of a 24-h infusion of cisplatin for the treatment of various malignant tumours.

Patients and methods

A total of 25 hospitalised patients (5 groups of 5) entered and completed the study (Table 1), which was open and dose-rising in design. All patients were receiving their first course of cisplatin. The total cisplatin dose was 120–200 mg, depending on tumour type, given as a constant 24-h infusion. The total dose and doses adjusted for body-surface area are shown in Table 2.

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Table 1. Patients' characteristics

Number of patients		25 (21 F, 4 M)
Mean age (± SD) in years:	M	47 ± 15.6
	F	45 ± 9.9
Mean weight (± SD) in kg:	M	69 ± 9.8
	F	61 ± 8.1
Primary site of tumour:		
Ovary		13
Uterus/cervix		7
Testes		2
Vagina		1
Bladder		1
Ureter		1

Patients were excluded if they presented with cerebral metastases that might have interfered with communication or with other severe concomitant diseases. Before entry, subjects underwent a full medical examination and biochemistry, haematology and urinalysis were assessed. All patients gave written informed consent to participate and the study was approved by the Ethics Committee of the Christie Hospital.

Successive groups of five patients each received a single i. v. dose of 5, 10, 20, 40 and 60 mg MDL 72222 at approx. 15 min before the beginning of cisplatin infusion. MDL 72222 (Anemet) was prepared in 10-ml sterile ampoules, each containing 10 mg active compound. The appropriate volume was injected over 4 min. Tolerability and safety were fully assessed before the dose was increased to the next higher level. Assessment was based on a 100-mm visual analogue scale (VAS) for nausea (from 0, no nausea, to 100, maximally severe nausea) that was presented at 1, 2, 3, 4, 5, 6, 8, 12, 18 and 24 h after the commencement of cisplatin infusion.

Episodes of vomiting were counted. The time to onset of nausea and vomiting was accurately recorded, as was the need for and the time to escape antiemetic therapy, which was permitted 6 h after the beginning of cisplatin infusion. Heart rate and blood pressure were recorded over the 24-h observation period. Plasma concentrations of MDL 72222 were determined before and at 0.5, 1.25, 2.25, 4.25, 8.25 and 24.25 h after the injection of the antagonist.

Analysis of MDL 72222 was carried out by combined gas chromatography-mass spectrometry (Merrell Dow Research Institute, data on file). An internal standard, MDL 72422, was used throughout the work-up of the samples and was added to the plasma sample prior to extraction. The extraction was effected with *n*-hexane. After evaporation of the mixture, the sample was dissolved in dichloromethane and reacted with trifluoroacetic anhydride to render potentially interfering natural constituents more volatile. Mass spectrometric analyses were run on a Finnigan TSQ 46 gas chromatograph-mass spectrometer system coupled on line to an INCOS data system. A methylsilicone-fused capillary column (Hewlett Packard) was used to separate the constituents. The compounds were measured in the positive chemical ionization mode using ammonia as the reagent gas. Calibration curves were obtained from a range of 1–400 ng/ml and showed excellent linearity, with the typical correlation coefficient being $r = 0.999$ or better. The limit of detection was 1 ng/ml with an approximate signal-to-noise ratio of 3. A detailed account of the analytical method used for MDL 72222 will be published elsewhere.

Haematology, biochemistry and urinalysis were repeated at 24 h after the commencement of cisplatin infusion and unwanted effects were recorded. ANOVA was used to examine dose-dependent differences in the number of vomiting episodes, the time to the first vomiting episode, the time to the onset of nausea and laboratory safety parameters. If the overall F statistic indicated statistical significance, multiple comparisons were carried out. A probability of $P < 0.05$ was considered to indicate statistical significance.

Table 2. Effect of single i. v. doses of MDL 72222 on nausea and vomiting induced by a 24-h infusion of cisplatin

Dose MDL 72222 (mg)	Patient	Sex	Dose of cisplatin		Vomiting episodes (*n*)	Time to 1st vomiting episode	Time to onset of nausea (h)	Maximal VAS score (mm)	Time of maximal VAS score (h)
			Total (mg)	(mg/m²)					
5	1	F	120	79	6	5 h 50 min	5	76	6
	2	F	120	71	5	6 h	5	13	6
	3	F	120	82	1	5 h	4	44	5
	4	F	120	70	5	5 h 20 min	6	22	12
	5	F	160	100	2	5 h	5	83	5
10	6	F	170	100	1	8 h	4	75	6
	7	M	170	100	2	6 h	5	57	6
	8	F	120	74	5	5 h 20 min	6	76	6
	9	F	180	100	2	5 h	4	69	12
	10	F	160	100	3	5 h 15 min	5	12	8
20	11	M	170	100	1	18 h 15 min	5	62	18
	12	F	180	100	0	–	8	12	8
	13	M	200	100	1	20 h 40 min	5	21	5
	14	M	180	100	1	22 h 15 min	18	15	24
	15	F	150	100	0	–	–	–	–
40	16	F	150	100	3	19 h 20 min	12	16	24
	17	F	150	100	5	8 h 15 min	12	22	12
	18	F	160	100	0	–	4	51	6
	19	F	150	100	2	18 h	24	15	24
	20	F	170	100	5	3 h 45 min	3	99	3
60	21	F	160	103	0	–	–	–	–
	22	F	160	100	4	10 h 45 min	4	60	24
	23	F	120	100	0	–	–	–	–
	24	F	150	97	6	5 h	4	67	24
	25	F	160	107	1	23 h 25 min	8	10	8

–, No vomiting, nausea or escape antiemetics (nausea, 0–100 mm)

Results

All 25 patients completed the study. Demographic details are shown in Table 1. The Karnofsky scale was 100% in 24 cases and 70% in 1. Additional chemotherapy consisted of doxorubicin (11 subjects), methotrexate (10 patients), vinblastine (4 cases) and etoposide (2 subjects). Some patients received more than one additional agent; only one patient received cisplatin alone. The sex distribution of the patients in each group is shown in Table 2.

Efficacy

At 6 h, only 1 patient was totally protected (0 vomiting episodes) in the groups receiving 5 and 10 mg as compared with 5, 4 and 4 subjects following doses of 20, 40 and 60 mg, respectively. Partial protection (1–2 episodes) was observed in 5 and 4 patients at 5 and 10 mg, respectively and in the remaining patients at doses of 40 and 60 mg. Following doses of 5 and 10 mg, protection decreased after 6 h and all patients vomited, with ranges of 1–6 and 1–5 vomiting episodes, respectively.

After a 20-mg dose, complete protection was maintained in all patients for up to 18 h and in 2 cases for up to 24 h, the 3 remaining subjects in this group having vomited on one occasion during the period between 18 and 24 h. In the 40-mg group, 3, 2 and 1 patient(s) were completely protected at 12, 18 and 24 h, respectively. In all, 2 patients vomited on 1–2 occasions at 12 and 18 h and 1 did so at 24 h, whereas 3 subjects had vomited on 3–5 occasions by 24 h. Following a 60-mg dose, 3, 3 and 2 patients retained complete protection from vomiting at 12, 18 and 24 h, respectively. Protection decreased over the 24-h period, with 3 patients having vomited on 1, 4 and 6 occasions at 24 h.

The time to onset of vomiting was significantly (P <0.005) increased with increasing dose. Further analysis showed that the time to the first vomiting episode was significantly greater when the groups receiving the two lower doses of 5 and 10 mg MDL 72222 were compared with the group given 20 mg (P <0.001 for each group and with the groups receiving 40 (P <0.001 vs 5 mg; P <0.03 vs 10 mg) and 60 mg (P <0.003 vs 5 mg; P <0.004 vs 10 mg) and when a time of 24 h was arbitrarily assigned to patients in these groups who did not vomit. All patients experienced nausea following doses of 5, 10 and 40 mg MDL 72222. After receiving 20 and 60 mg MDL 72222, respectively, 1 and 2 subjects were free of nausea throughout the 24-h cisplatin infusion.

At the higher doses, nausea tended to be milder in nature at both its onset and its maximal severity. A similar trend towards a dose-effect relationship was seen in the time to onset of nausea and the time to its maximal severity. At doses of 5 and 10 mg, nausea had been reported by all patients by 6 h and had achieved maximal severity by 12 h.

All patients received escape medication following 5 and 10 mg MDL 72222. The time to first escape medication ranged from 6 to 11.75 h. Following a 20-mg dose, escape medication was not required in three patients; two subjects in this group received escape medication at 15.5 and 7.25 h. After receiving 40 mg one patient did not require escape medication; in the remaining subjects it was given from 4.25 (patient 20) to 23.75 h. Following 60 mg MDL 72222, three patients did not require escape medication whereas in the remaining two subjects it was given at 18.25 and 33.3 h, respectively.

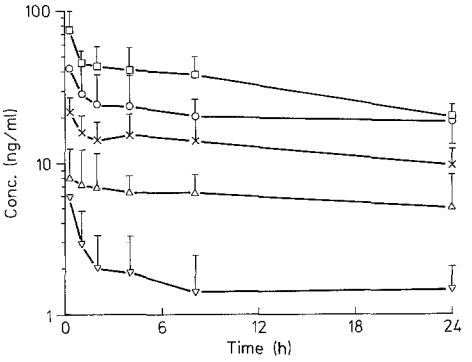

Fig. 1. Time course of mean plasma concentrations (± SD) of MDL 72222 after single i.v. doses of 60 (□), 40 (✳), 20 (×), 10 (△) and 5 mg (▷◁) (n = 5 except at 8.25 and 24.25 h, when n = 3–5)

Safety and tolerability

Pain at the injection site that lasted for several seconds in one patient was the only drug-related unwanted effect. Heart rate and blood pressure showed no significant or clinically meaningful changes over the 24-h period. One patient described bilateral hearing loss, but this was reported during subsequent exposure to cisplatin without the administration of MDL 72222.

Decreases were seen in haemoglobin (from 12.3 ± 1.6 to 11.4 ± 1.7 g/dl, P <0.0001), haematocrit (from 40% ± 4.5% to 34% ± 4.9%, P <0.0001), red blood cells (from 4.33 ± 0.98 to 3.87 ± 0.67 × 10µl, P <0.04), platelets (from 432,000 ± 156,000 to 361,000 ± 141,000/mm^3, P <0.0006) and monocyte differential (from 4% ± 2.4% to 2.7% ± 2.2%, P <0.023). A significant increase in the neutrophil differential was found (from 74% ± 10% to 77% ± 10%, P <0.043). These changes corresponded to those expected following the cytotoxic therapy given.

Of the biochemical parameters, glucose (serum) fell from 5.70 ± 1.57 to 5.31 ± 1.08 g/l (P <0.013), whereas other variables were not significantly changed. Elevations of alkaline phosphatase and gamma GT seen in one patient had previously been noted in the same patient and were judged not to be related to MDL 72222. Urinalysis showed minor variations that were not clinically significant.

Plasma concentrations

The mean plasma concentrations of MDL 72222 after doses of 5, 10, 20, 40 and 60 mg are shown in Fig. 1. At the 4.25-h sampling point, the observed mean plasma concentrations were 1.9, 6.3, 15.3, 23.6 and 40.6 ng/ml for the 5 respective doses. At the last sampling point, i.e. at 24.25 h after the administration of MDL 72222, mean plasma con-

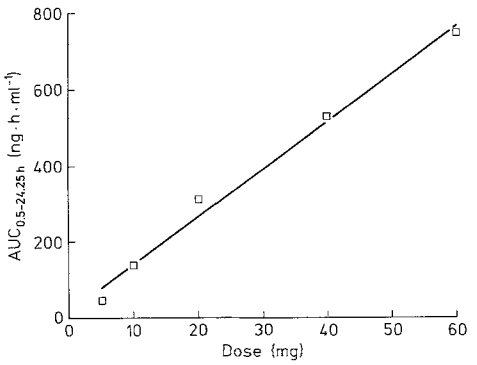

Fig. 2. Linear relationship of the mean plasma concentration-time AUC values with the delivered dose of MDL 72222

centrations were 1.4, 4.9, 9.6, 18.5 and 19.9 ng/ml, respectively. If the mean plasma concentrations observed after the 20-mg i.v. dose are set arbitrarily as "1" and linear regression analysis is performed on the observed concentrations as a function of the dose, the linear relationships obtained show correlation coefficients of 0.992 and 0.961 for the 4.25- and 24.25-h observation points, respectively.

A similar linear relationship was observed for the AUC values determined for the observation period 0.5–24.25 h. Figure 2 shows that the mean AUC values increased in a dose-linear relationship with the delivered dose ($r = 0.994$, $P < 0.001$). These results suggest that drug concentration increases in a linear fashion with increasing MDL 72222 dose over the dose range studied.

Discussion

In view of the increasing tendency towards the administration of combination antiemetic therapy for emesis associated with cancer chemotherapy and, hence, the increased potential for drug interaction, a single, effective and well-tolerated agent would provide an important improvement in the treatment of such patients.

Cisplatin produces severe emesis that can start around 1 h after the beginning of administration [14, 17], and the severity of the vomiting increases with the dose [17]. The number of vomiting episodes also varies for a given dose ranging from 5 to 25 episodes in the 24-h period following the administration of 120 mg/m^2 cisplatin over 20 min, during which the antiemetic therapy consisted of placebo [6].

In the present study, cisplatin was given at total doses of 120–200 mg by constant infusion over 24 h. By this technique the plasma level increases and, at a time equivalent to 5 times the terminal elimination half-life, the plasma concentration would be expected to lie within 5% of the steady-state concentration [15]. The terminal elimination half-life of cisplatin is 0.64 h [1]. Thus, the approximate steady-state concentration would occur at around 3.2 h and would be maintained until completion of the infusion, at which point the plasma concentration would decay at the half-life stated above.

Although this technique avoids the very high initial plasma concentrations of cisplatin that occur when similar doses are delivered over much shorter periods, all patients were expected to vomit in the absence of antiemetic cover. The emetogenic effect of the administration of cisplatin by continuous infusion was confirmed by the finding that all patients who received 5 and 10 mg MDL 72222 at 15 min before the beginning of the cisplatin infusion indeed vomited during the 24-h period, with a range of 1–6 episodes being noted. Furthermore, in $^9/_{10}$ patients who received these doses of MDL 72222, the onset of vomiting occurred within 2–3 h after the time anticipated for the achievement of cisplatin steady-state plasma concentrations (i.e., 5–6 h after the commencement of cisplatin infusion).

The effects of the higher doses of MDL 72222 can be assessed on the basis of the above observation. Thus, the time to onset of vomiting was significantly increased as the dose increased to $\geq$20 mg. Further analysis revealed that the time to onset of vomiting was significantly longer following a dose of 20 mg MDL 72222 than after doses of 5 and 10 mg and that following the administration of 40 and 60 mg, the increase was statistically significant when 24 h was arbitrarily assigned as the time to the first vomiting episode for patients who did not vomit. No statistically significant differences were observed between the 20-, 40- and 60-mg doses.

The increase in the time to the first vomiting episode was associated with a trend towards an increase in the time to administration of the first escape antiemetic medication at the higher doses, and fewer patients required such treatment following doses of 20, 40 and 60 mg as compared with 5 and 10 mg. Although the time to onset of vomiting was extended at the higher doses of MDL 72222, in $^3/_5$ patients in the 20-mg dose group, nausea did occur beginning at 5–8 h, at 3 and 4 h in 2 patients who received 40 mg and at 4–8 h in 3 patients given 60 mg. In the three higher dose groups, nausea at its onset was mild in all subjects except one (patient 20 – severe) and at its maximal severity it remained mild (6 cases) to moderate (4 patients). Nausea remained severe in one subject (patient 20) who showed no therapeutic response to MDL 72222.

The plasma concentrations of MDL 72222 seen in the present study in patients with malignant disease were similar to those previously found in normal volunteers (Merrell Dow Research Institute, data on file). Although only one dose was the same in these two studies (20 mg i.v.), the dose linearity of MDL 72222 observed in both investigations implies that if one common dose can be compared, parameters such as plasma concentrations and AUCs after the other doses can be extrapolated. The mean plasma concentration in normal volunteers was 11 ± 3.2 ng/ml at 4 h in the previous study vs 15.3 ± 5.8 ng/ml at 4.25 h after administration in the present study. At 24 h, the mean plasma concentration was 9 ± 0.9 ng/ml in volunteers vs 9.6 ± 2.7 ng/ml at 24.25 h in our patients. These differences are not statistically significant. Thus, the disease state and the associated medication do not appear to influence the plasma levels of MDL 72222. The dose linearity observed in the dose range of 5–60 mg in the present study confirms previous results obtained in two studies in normal volunteers (Merrell Dow

Research Institute, data on file). The mean $t_{1/2}$ value for MDL 72222 in normal volunteers was 93 h (range, 56–143 h). Due to the long plasma half-life of MDL 72222 and the relatively short sampling period in the present patients, no attempt at further pharmacokinetic evaluation was made. However, it is obvious that the concentrations noted in the present study decay slowly, apparently at a rate similar to that previously seen in volunteers. The plasma concentrations of MDL 72222 found after an i.v. dose of 20 mg have been described as representing very low concentrations when <1% of such a dose was accounted for by the plasma concentrations observed 5 min after injection in normal volunteers (Merrell Dow Research Institute data on file). This demonstrates the rapidity of drug distribution or binding to tissues; furthermore, this could result in the formation of a deep compartment from which the drug may be slowly released, resulting in the long half-life (Merrell Dow Research Institute, data on file). In the same study very little parent drug was excreted in the urine over 48 h (range, $1.9\% \pm 1.3\%$), indicating extensive metabolism in addition to rapid distribution and/or binding.

Thus, despite the relatively constant plasma concentrations of MDL 72222 found in the present study, both vomiting and nausea did occur. This suggests that the actual plasma concentration is not related to the observed therapeutic effect and lends strength to clinical observations [11] that further doses of 20 mg MDL 72222 were required to provide and maintain an antiemetic effect when cisplatin was given at high doses over a short period of 20 min. It could be postulated that as the drug redistributes, the tissue levels gradually fall below those required to maintain appropriate receptor occupancy and, thus, a therapeutic effect, whereas the plasma level remains the same; therefore, only by the administration of a further dose would the tissue level be boosted to that required to maintain a therapeutic effect. MDL 72222 was well tolerated, the only unwanted drug-related effect being pain at the injection site that lasted a "few seconds". Changes in haematological variables corresponded to those expected from the cytotoxic therapy given [2].

In conclusion, a single i.v. dose of MDL 72222 was well tolerated and produced a significant increase in the time to onset of vomiting at doses of 20, 40 and 60 mg as compared with 5 and 10 mg in patients receiving cisplatin by constant 24-h infusion. The time to onset of nausea was not significantly prolonged, despite the observation that plasma concentrations remained stable during this period, but nausea tended to be of a milder nature at the higher doses. The plasma levels of MDL 72222 were not affected by the disease state or the chemotherapeutic regimens given to the patients. A dose of ≥ 20 mg MDL 72222 resulted in a significant reduction in emesis during the administration of cisplatin as well as in similar reductions in vomiting episodes, as has been reported for other 5-HT_3 receptor antagonists [3, 4, 10], suggesting that further studies are warranted to identify further the efficacy and safety of MDL 72222 in this indication.

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