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Amelioration of cytotoxic-induced emesis with high-dose metoclopramide, dexamethasone and lorazepam

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Summary. A double-blind randomised controlled trial comparing the antiemetic effects of sublingual lorazepam combined with high-dose, short course metoclopramide (3 mg/kg) infused twice 3 h apart with or without i.v. dexamethasone is reported. Sixty patients receiving a total of 209 cycles of potentially severely emetic cytotoxic chemotherapy were randomised to receive one or other antiemetic regimen. In those receiving platinum-based chemotherapy the addition of dexamethasone was associated with an improvement in freedom from nausea ($P<0.01$) and freedom from vomiting ($P<0.05$). In the non-platinum-based chemotherapy group the addition of dexamethasone led to a reduction in the duration and severity of nausea, and duration of vomiting ($P<0.05$ in each case). Both antiemetic regimens were well tolerated with a low incidence of adverse effects and could be administered easily in an outpatient setting.

Introduction

Cytotoxic-induced emesis remains an important problem in clinical oncology, causing metabolic disturbances and patient discomfort. It detracts from the patient's quality of life and may induce noncompliance in those receiving palliative or curative treatments [10].

Many agents and combinations of such agents are useful in controlling cytotoxic-induced emesis [4, 8, 9]. One such combination has been reported by Kris et al. [9]. Their study examined the efficacy of short-course (two infusions) high-dose metoclopramide (3 mg/kg) in combination with dexamethasone and diphenhydramine in patients receiving platinum-containing combination chemotherapy. Our study looks at patients receiving non-platinum-containing cytotoxic combinations (with high potential for emesis) as well as platinum-containing regimens.

The aim of the study was to establish the efficacy of high-dose short-course metoclopramide, lorazepam and dexamethasone in the management of cytotoxic-induced emesis and thereby to develop an antiemetic regimen suitable for use in outpatients.

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Materials and methods

Between August 1985 and April 1986 patients were entered into this prospective, randomised, double-blind trial. Patients 65 years or under receiving one or more of the following cytotoxic agents: platinum, adriamycin, mustine, DTIC, or the combination of cyclophosphamide, methotrexate and 5-fluorouracil (Table 1) were included in this trial. Some older patients were included if cytotoxic-induced emesis proved difficult to control by other means. Patients receiving platinum-containing chemotherapy had no previous exposure to cytotoxic agents. The majority of those receiving non-platinum combinations had previous experience of chemotherapy. Informed consent was obtained and patients were invited to express a preference at any time for the antiemetic regimen associated with any particular cycle of chemotherapy; they were told they would then receive only the preferred antiemetic regimen, no longer participating in the trial.

There were two arms in the trial. Regimen A contained: Lorazepam 2 mg sublingually 15 min before chemotherapy; metoclopramide (3 mg/kg) in 100 ml normal saline infused i. v. over 15 min immediately before chemotherapy and repeated 3 h later.

Regimen B contained: Lorazepam and metoclopramide as for regimen A, plus dexamethasone 16 mg i. v. immediately before chemotherapy.

Patients were randomised to one or other arm each time they received chemotherapy. Following each cycle of treatment and prior to receiving further cytotoxic chemotherapy each patient was interviewed by our data collator, who was unaware of the patient's randomisation, and a standard questionnaire was completed. Questions referred to the incidence of nausea and of vomiting, the time of onset of both following chemotherapy, the duration of each and the severity of nausea (as assessed by the patient on a linear analogue scale). The number of episodes of vomiting was also recorded. The incidence and nature of potential toxicity from the antiemetics was sought with particular attention to extrapyramidal manifestations, diarrhoea and dysphoria. Sedation was not regarded as an adverse effect, as this effect was one of our objectives in adding lorazepam to both arms of the trial.

Because platinum administration is associated with an extensive pre- and post-hydration protocol, the platinum group always received their treatment on an inpatient basis. However, the non-platinum group routinely received

Table 1. Cytotoxic regimens

	No. of patients
PVB (platinum 50 mg/m^2) (modified for advanced cervical cancer)	3
PVB/POMB (platinum 100 mg/m^2)	3
PAC (platinum 50 mg/m^2)	8
CAP	15
CHOP	9
COA	8
CMF	7
CAMV	1
MOPP ± ABV/MVPP	4
Adriamycin + BCNU	1
BELD	1

PVB, platinum, vinblastine, bleomycin; POMB, platinum, vincristine, methotrexate, bleomycin; PAC, platinum, adriamycin, cyclophosphamide; CAP, cyclophosphamide, adriamycin, prednisone; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; COA, cyclophosphamide, vincristine, adriamycin; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; MO(V)PP, mustine, vincristine (vinblastine), procarbazine, prednisone; ABV, adriamycin, bleomycin, vinblastine; BELD, bleomycin, vindesine, lomustine, DTIC

treatment on an outpatient basis unless admission was required for other reasons.

Statistical analysis. Results for all parameters measured were compared between the two antiemetic regimens, with the platinum and non-platinum groups being analysed independently. The incidence of nausea and vomiting was assessed using the Chi-square test, and the severity of nausea and the number of episodes of vomiting were analysed. The time to onset of nausea and vomiting and the respective durations were compared using survival analysis, with the Mantel-Cox test statistic on the BMDP programme P1L [6]. With respect to the time to onset of nausea and vomiting, all patients were entered, but if nausea or vomiting did not occur within 3 weeks they were censored, as this was deemed an appropriate end-point for these side effects of chemotherapy. The analysis of the durations of nausea and of vomiting included only those patients who felt nauseated or actually vomited.

Results

The results were analysed in two separate groups – those for patients receiving platinum-containing regimens and those for patients receiving non-platinum-containing regimens.

Fourteen patients received a total of 53 cycles of platinum-containing chemotherapy (Table 2). Three patients received platinum in a dose of 100 mg/m^2 (a total of nine cycles, four associated with regimen A, and five with regimen B) and the remainder at 50 mg/m^2. Antiemetic regimen B (containing dexamethasone) resulted in 50% of platinum-based chemotherapy cycles being completely free of nausea (compared with 16% in regimen A, $P<0.01$). Among the regimen B-treated patients there were 36% who did not vomit, as against 12% receiving regimen A ($P<0.05$). The onset of nausea and vomiting was later in patients receiving antiemetic regimen B ($P<0.01$ and $P<0.05$ respectively). The median duration of nausea was 72 h in regimen A patients and 24 h in regimen B patients, but this reduction did not achieve statistical significance. There were trends demonstrating that regimen B reduced the severity of nausea, the number of episodes of vomiting and the duration of vomiting in the platinum-treated group of patients who did not attain complete abolition of their nausea and vomiting. However, these fell short of achieving statistical significance.

Fortysix patients received a total of 156 cycles of non-platinum-containing combination chemotherapy (Table 3).

Table 2. Results: platinum group

Total number of cycles	Regimen A	Regimen B with dexamethasone	Statistical significance
	25	28	
Number free of nausea	4 (16%)	14 (50%)	$P<0.01$
Median time to onset of nausea (h)	4.00	24.00	$P<0.01$
Median duration of nausea (h)	72.00	24.00	NSS[b]
Severity of nausea (mean)[a]	2.14	2.38	NSS
Number free of vomiting	3 (12%)	10 (36%)	$P<0.05$
Median time to onset of vomiting (h)	3.0	8.00	$P<0.05$
Median number of vomiting episodes	7.59	6.12	NSS
Median duration of vomiting (h)	6.00	4.00	NSS

[a] Linear analogue scale 1–4: 1, mild nausea; 4, severe nausea
[b] Not statistically significant

Table 3. Results: non-platinum group

Number of cycles	Regimen A	Regimen B with dexamethasone	Statistical significance
	80	76	
Number free of nausea	24 (30%)	33 (44%)	NSS
Median time to onset of nausea (h)	12.00	24.00	$P<0.05$
Median duration of nausea (h)	48.00	24.00	$P<0.05$
Severity of nausea (mean)	2.36	1.88	$P<0.05$
Number free of vomiting	39 (49%)	37 (49%)	NSS
Median time to onset of vomiting (h)	24.00	24.00	NSS
Number of episodes of vomiting	7.73	5.10	NSS
Median duration of vomiting (h)	12.00	4.00	$P<0.05$

Table 4. Incidence of diarrhoea

	Regimen A	Regimen B	Total incidence
Platinum group	6/25 (24%)	6/28 (21%)	12/ 53 (23%)
Non-platinum group	9/80 (11%)	4/76 (5%)	13/156 (8%)

The median time to onset of nausea was delayed, and the duration and severity of nausea were reduced in patients receiving regimen B (containing dexamethasone), with a *P*-value of less than 0.05. There was a trend towards freedom from nausea in regimen B, but this did not reach statistical significance. Neither the incidence nor the median time to onset of vomiting was different between the two groups, but the median duration of vomiting was shorter in those receiving antiemetic regimen B than in those receiving antiemetic regimen A ($P < 0.05$). There was a trend toward a lower number of vomiting episodes, but this did not achieve statistical significance.

Among the 60 patients there were 6 who asked for the protocol to be broken, and each identified a cycle of chemotherapy associated with the addition of dexamethasone as being more efficacious.

During the trial one patient experienced a dystonic reaction manifest as trismus, which was prevented on subsequent occasions by the use of benztropine. One other patient complained of restlessness controlled with lorazepam.

Of the 156 cycles of chemotherapy, 13 were associated with diarrhoea in the non-platinum group giving an incidence of 8% overall. Diarrhoea was less often seen in patients receiving dexamethasone, but the difference did not achieve statistical significance (Table 4). In the patients receiving platinum the incidence of diarrhoea was much higher, at 23%, and the addition of dexamethasone did not appear to have an impact upon its incidence. It was found that the diarrhoea could be attenuated or completely blocked by the use of codeine. Only one person withdrew from the trial because of diarrhoea.

In most patients, the administration of i. v. dexamethasone was followed within a few seconds by an unpleasant tingling sensation localised to the scrotum in men and to the perineum in women. It followed both bolus and slow push injections. The precise incidence is not known, as it was not prospectively sought. We have subsequently found that the addition of dexamethasone to the first metoclopramide infusion bag given over 15 min avoids this complication.

No patient experienced a dysphoric reaction and no other toxicity attributable to the antiemetic drugs was noted.

Discussion

We have shown that short-course high-dose metoclopramide in combination with lorazepam and dexamethasone is effective in ameliorating the severity and duration of emesis due to cytotoxics other than platinum, while confirming the findings of others with reference to its efficacy in platinum emesis [1, 9].

The findings in the two cytotoxic treatment groups were not identical, the platinum group receiving greater benefit. We speculate that the mechanism by which different cytotoxics produce emesis may not be the same, accounting for the difference in benefit accrued from any one antiemetic regimen.

Currently our platinum regimens are administered on an inpatient basis because of our intensive pre- and post-platinum hydration programme. However, all other regimens are given routinely on an outpatient basis. We found that the antiemetic regimen described here could be given conveniently over 3 h in our day ward. Avoiding admission purely for antiemetic management clearly has benefits for both the patient and the ward staff. The quality of life is improved for the patient through not having to spend so much time in hospital, while the obvious benefit for the inpatient service is to decrease pressure on bed allocation.

We found the incidence of toxicity attributable to metoclopramide to be low. During 1 of the 209 cycles of treatment administered, the patient experienced an acute dystonic reaction during the trial period. This was prevented in subsequent treatment by the use of benztropine. We conclude from this that the routine use of anticholinergic drugs, as suggested by Kris et al. [9], is unnecessary when high-dose metoclopramide is used.

Diarrhoea has previously been reported as a complication of high-dose metoclopramide [1, 7]. Our results suggest that this is more closely associated with platinum than with metoclopramide. The incidence of diarrhoea was much higher in patients receiving platinum compared with those receiving non-platinum-containing regimens with a *P*-value of less than 0.01 (Table 4). However, there is little doubt that metoclopramide also contributes to the incidence and severity of diarrhoea. The addition of dexamethasone halved the incidence of diarrhoea in the non-platinum group but did not appreciably affect it in the platinum group. However, prophylactic oral codeine (60 mg 4-hourly over the first 24 h) attenuated or completely prevented diarrhoea in all patients, with the exception of the one patient who withdrew from the trial after one cycle of treatment because of diarrhoea.

The sole side effect we noted to be associated with dexamethasone was one of paraesthesiae localised to the perineum. We were not previously aware of this side effect of dexamethasone, but note a recent reference to it [2] in the literature and were able to find a reference to a similar phenomenon following i.v. hydrocortisone sodium phosphate [3]. We cannot accurately report the incidence of this phenomenon in our trial, as it was not studied prospectively. This side effect is transient and was not attenuated by giving dexamethasone as a slow i. v. push. However, it can be eliminated by giving the dexamethasone with the metoclopramide infusion over 15 min.

We note a recent report [5] of a single case of early bilateral posterior subcapsular cataracts following only four courses of intermittent dexamethasone, which the authors suggest might be causally related. None of our 60 patients experienced any visual disturbance.

The sedative and amnesic properties of lorazepam proved invaluable in this trial. No patient regarded sedation as an adverse effect, and there were no reports of oversedation.

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