# *Antiemetic Superiority of Lorazepam Over Oxazepam and Methylprednisolone as Premedicants for Patients Receiving Cisplatin-Containing Chemotherapy*

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**Lorazepam, oxazepam, and methylprednisolone were compared for antiemetic efficacy in patients receiving cisplatin chemotherapy. Three consecutive courses of cisplatin-containing chemotherapy were administered at equal doses so that each patient acted as his own control. Of 100 patients randomized, 85 received at least two of the three agents and were evaluable for analysis. Lorazepam significantly reduced the number of patients with more than ten vomits compared to either oxazepam ($P < 0.05$) or methylprednisolone ($P < 0.001$). Lorazepam also significantly reduced the number of patients with the most severe degrees of vomiting compared to either oxazepam or methylprednisolone (both $P < 0.005$). The duration of vomiting was reduced significantly after the first 48 hours postchemotherapy for those patients receiving lorazepam over those receiving methylprednisolone ($P < 0.05$). Lorazepam significantly reduced the number of patients with severe nausea compared to both oxazepam and methylprednisolone (both $P < 0.05$), but there were no significant differences in duration of nausea among the groups. The results of linear analogue self-assessment scores indicated a strong patient preference for lorazepam over both oxazepam and methylprednisolone. Drowsiness was significantly more common with both lorazepam and oxazepam compared to methylprednisolone (both $P < 0.001$). Patients who received lorazepam or oxazepam also experienced significantly more severe drowsiness than those patients receiving methylprednisolone (both $P < 0.01$). Lack of recall was significantly more common with lorazepam than with oxazepam and methylprednisolone (both $P < 0.001$) and was more profound when lorazepam was compared with oxazepam ($P < 0.05$) and with methylprednisolone ($P < 0.001$). Methylprednisolone was administered with minimal side effects. The results of this randomized cross-over study indicate that, in the dosage/schedule used, lorazepam is a significantly superior premedicant than is either oxazepam or methylprednisolone in alleviating the distress of cytotoxic-induced emesis in patients receiving cisplatin-containing chemotherapy.**

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CYTOTOXIC-INDUCED EMESIS (CIE) continues to be the most distressing side effect of current chemotherapy.[1] Dissatisfaction with currently used antiemetics has led many clinicians to rethink antiemetic usage and to investigate the potential value of several less traditional agents.

Lorazepam is a 3-hydroxy-1, 4-benzodiazepine of relatively long half-life (15 hours) which acts mainly on the cerebral cortex, limbic system, and brain stem reticular formation to induce anxiolysis/sedation, anterograde amnesia, and a dampened response of the vomiting center to a variety of afferent stimuli.[2] Previous studies have shown that lorazepam, either on its own or with standard antiemetics, can significantly improve patient tolerance of highly emetogenic cytotoxics.[3,4]

Clinicians have recently reported impressive antiemetic results in many small pilot and nonrandomized single-arm antiemetic studies when corticosteroids have been used to combat CIE.[5,6] A number of recent randomized controlled trials have further attested to the antiemetic benefit of corticosteroids.[7,8] Although the mechanism of corticosteroid action is unknown, inhibition of prostaglandin release within the central nervous system may be a key factor.[6] Investigations are currently in progress to further explore the value of corticosteroids and to establish an optimal dosage/schedule for their use.

This randomized crossover study compares the anti-

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TABLE 1. Breakdown of Patients by Site of Primary Disease

| | | |
|---|---|---|
| Ovary | 47 | (55.3%) |
| Head and neck | 16 | (18.9%) |
| Cervix | 12 | (14.1%) |
| Testis | 7 | (8.2%) |
| Unknown primary | 2 | (2.3%) |
| Bladder | 1 | (1.2%) |
| Total | 85 | (100.0%) |

emetic efficacies of lorazepam and methylprednisolone. The addition to the study of a second benzodiazepine was made to assess whether oxazepam (a cheaper and more readily available benzodiazepine) possesses similar antiemetic potential to that reported for lorazepam.

## Patients and Methods

All adult cancer inpatients aged 16 to 70 years, who had not received prior chemotherapy, and for whom cisplatin had been prescribed, were eligible for randomization. Patients prescribed continuous daily cisplatin infusions or drugs likely to have an antiemetic effect were excluded. Any patients allergic to benzodiazepines or corticosteroids, or with respiratory depression in whom sedation may be undesirable, were excluded. Written informed consent was obtained by the pharmacist from each patient in accordance with Helsinki guidelines.

### *Study Design*

This study was designed to determine the antiemetic efficacy and side effects of lorazepam (L), oxazepam (O) and methylprednisolone (M) against cisplatin-induced emesis. Patients were randomly assigned by a single-blind technique to receive one of three potential antiemetics before each of three consecutive courses of cisplatin-containing chemotherapy. Individual cytotoxic agents within the cisplatin-containing regimens were administered at constant dosage for the three consecutive courses. Allocation of patients to the potential antiemetics was made according to one of six possible sequences, *i.e.*, LMO, LOM, OLM, OML, MOL, or MLO. Patients were allowed parenteral metoclopramide or prochlorperazine if emesis became uncontrollable or intolerable. Having received at least two of the three study agents, patients were then asked to express a preference for future treatments. A blinded nurse observer was designated before chemotherapy and was responsible for the quantitation of the actual number vomiting episodes.

TABLE 2. Antiemetic Efficacy (Vomiting)

| | | Antiemetic | | |
|---|---|---|---|---|
| Symptom | Severity | L | O | M |
| No. of vomits | Nil | 14 | 8 | 10 |
| | 1 | 5 | 3 | 3 |
| | 2–5 | 33 | 30 | 18 |
| | 6–10 | 14 | 22 | 24 |
| | >10 | 5 | 15 | 26 |
| Severity of vomiting | Nil | 14 | 8 | 10 |
| | Mild | 18 | 9 | 7 |
| | Moderate | 30 | 34 | 36 |
| | Severe | 9 | 27 | 28 |
| Duration of vomiting (hrs) | Nil | 14 | 8 | 10 |
| | <12 | 31 | 31 | 30 |
| | 12–24 | 13 | 22 | 19 |
| | 24–48 | 6 | 4 | 3 |
| | >48 | 7 | 13 | 19 |

L: lorazepam (n = 17); O: oxazepam (n = 78); M: methylprednisolone (n = 81).

### *Antiemetic Dosage*

Patients received a single oral dose of lorazepam 2.5 mg/m$^2$ (taken to the nearest 0.5 mg), or oxazepam 60 mg orally, or methylprednisolone 500 mg intravenously over 30 minutes, 1 hour before cisplatin administration.

### *Cisplatin Administration*

All patients were hospitalized and received cisplatin at a dose ranging between 50 to 100 mg/m$^2$. Cisplatin treatment followed 4 to 6 hours after intravenous hydration with 2 to 3 liters of alternating 5% dextrose and 0.9% sodium chloride. A dosage of 12.5 g of mannitol was administered intravenously over the 30 minutes immediately before cisplatin administration. Cisplatin was diluted in 500 ml of normal saline and infused over 2 hours, and intravenous hydration was continued at a rate of 150 to 200 ml per hour for 12 to 18 hours after completion of cisplatin administration.

### *Assessment of Study Parameters*

On the morning after cytotoxic administration, patients were asked to complete a questionnaire which was repeated just before a subsequent cycle of chemotherapy, or 3 weeks after the third (final) cycle. The questionnaire was designed to analyze objectively the number of vomiting episodes and the duration of nausea and vomiting after each course of chemotherapy. A 0-point to 10-point linear analogue self-assessment (LASA) scale was used to analyze quantitatively the severity of nausea and vomiting, treatment-related side effects, and comparative and overall antiemetic preferences.

### *Statistical Methods*

Comparisons of antiemetic efficacy and antiemetic side effects during sequential chemotherapy cycles were made and tested using the Wilcoxon test for paired observations.[9] A chi-squared test was used to test the significance of patients' antiemetic preferences.[10]

TABLE 3. Antiemetic Efficacy (Nausea)

| Symptom | Severity | Antiemetic L | O | M |
|---|---|---|---|---|
| Severity of nausea | Nil | 23 | 18 | 17 |
| | Mild | 14 | 6 | 7 |
| | Moderate | 25 | 32 | 33 |
| | Severe | 9 | 22 | 24 |
| Duration of nausea (hr) | Nil | 23 | 18 | 17 |
| | <12 | 4 | 2 | 3 |
| | 12–24 | 4 | 5 | 2 |
| | 24–48 | 8 | 11 | 10 |
| | >48 | 32 | 42 | 49 |

L: lorazepam; O: oxazepam; M: methylprednisone.

TABLE 4. Paired Comparisons of Antiemetic Preference

| | |
|---|---|
| Lorazepam > oxazepam | 62.5 |
| Oxazepam > lorazepam | 15.7 |
| Lorazepam = oxazepam | 21.8 |
| 100% (64 patients) | |
| Lorazepam > methylprednisolone | 64.2 |
| Methylprednisolone > lorazepam | 22.4 |
| Lorazepam = methylprednisolone | 13.4 |
| 100% (67 patients) | |
| Oxazepam > methylprednisolone | 48.7 |
| Methylprednisolone > oxazepam | 29.7 |
| Oxazepam = methylprednisolone | 21.6 |
| 100% (74 patients) | |

## Results

Of 100 patients randomized, 85 (64 women, 21 men) were evaluable for assessment of antiemetic efficacy. Sixty patients received all three trial drugs and 25 patients received only two agents. The majority of evaluable patients were women receiving cisplatin treatment for advanced ovarian cancer (Table 1). Fifteen were not evaluable for a number of reasons; these included inappropriate chemotherapy (two patients) change in chemotherapy regimen or dose (six patients), concomitant sedative intake (four patients), and death due to progressive malignancy (three patients).

Quantitative data derived from this study and data dealing with the comparative efficacies of the three agents for a range of assessment criteria are shown in Tables 2 through 5, respectively.

### *Number of Vomiting Episodes*

There was no overall statistically significant difference in the number of vomiting episodes among the three potential antiemetics in question. However, the number of patients who experienced severe vomiting (> 10 episodes) was significantly less in the group receiving lorazepam compared to patients receiving either oxazepam ($P < 0.05$) or methylprednisolone ($P < 0.001$).

There was no significant difference in efficacy among the three agents in their ability to completely abolish cisplatin-induced vomiting (scored as "0" vomits).

### *Severity of Vomiting*

Lorazepam was significantly more efficacious in reducing the number of patients who experienced the most "severe" degrees of vomiting (as assessed on LASA score) than was either oxazepam ($P < 0.005$) or methylprednisolone ($P < 0.005$). Otherwise, there were no significant differences between antiemetic premedicants and degree of emetic severity.

### *Duration of Vomiting*

There was no statistically significant difference among the three agents in reducing the duration of vomiting within the first 48 hours after chemotherapy. However, lorazepam was significantly superior to methylprednisolone in reducing the duration of vomiting after 48 hours ($P < 0.05$).

### *Severity of Nausea*

Lorazepam significantly reduced the number of patients with the most severe degrees of nausea when compared to either oxazepam and methylprednisolone (both $P < 0.05$).

There were no other significant differences among the three agents.

### *Duration of Nausea*

There were no significant differences among the three agents under study.

### *Effect of Antiemetic Sequence*

There was no correlation between sequence of antiemetic administration and the relative antiemetic efficacy of the three agents under study.

TABLE 5. Antiemetic Side-Effects

| Symptom | Severity | Antiemetic L | O | M |
|---|---|---|---|---|
| Drowsiness | Nil | 1 | 7 | 57 |
| | Mild | 7 | 12 | 14 |
| | Moderate | 21 | 19 | 8 |
| | Severe | 42 | 40 | 2 |
| Lack of recall | Nil | 25 | 38 | 79 |
| | Moderate | 37 | 38 | 2 |
| | Profound | 9 | 2 | 0 |

L: lorazepam; O: oxazepam; M: methylprednisone.

*Antiemetic Preference*

Table 4 lists paired comparisons of antiemetic preference for all patients included in the study. A very strong preference was expressed for lorazepam over both oxazepam ($P < 0.001$) and methylprednisolone ($P < 0.001$). The preference for oxazepam over methylprednisolone was less strong, but still reached statistical significance ($P < 0.01$).

In the 60 patients who received all three agents, lorazepam was chosen as first preference by significantly more patients than either oxazepam (46.7% *versus* 13.3%; $P < 0.01$) or methylprednisolone (46.7% *versus* 16.7%; $P < 0.01$). There was no significant difference in the choice of clear first preference between oxazepam and methylprednisolone.

When clear last preferences were analyzed, it was apparent that methylprednisolone was chosen by significantly more patients than was lorazepam (43.3% *versus* 5%; $P < 0.01$), and oxazepam by significantly more patients than was lorazepam (25% *versus* 5%; $P < 0.01$). Methylprednisolone was also chosen as last preference by more patients than was oxazepam (43.3% *versus* 25.0%; $0.1 < P < 0.05$).

*Side Effects*

*Drowsiness:* As expected, both lorazepam and oxazepam produced statistically significant more drowsiness than did methylprednisolone ($P < 0.001$). There was no significant difference in severe drowsiness between either lorazepam or oxazepam, as compared to the very significant difference in severe drowsiness seen with lorazepam and oxazepam in comparison to that seen with methylprednisolone ($P < 0.01$).

Drowsiness was assessed by patients to be severe in 59% (42/71) of patients receiving lorazepam, 51% (40/78) of patients receiving oxazepam, and in 2% (2/81) of patients receiving methylprednisolone.

*Lack of recall:* There was no significant difference in the presence of lack of recall between lorazepam and oxazepam. However, both lorazepam and oxazepam produced statistically more significant lack of recall than did methylprednisolone ($P < 0.001$). When patients who experienced profound lack of recall were compared, there was a significant difference between lorazepam and methylprednisolone ($P < 0.001$) and between lorazepam and oxazepam ($P < 0.05$). There was no significant difference between patients with profound lack of recall when oxazepam and methylprednisolone were compared.

At the dosage used, lack of recall was recorded as profound in 12% (nine of 71) and in 2% (two of 78) of patients who received lorazepam and oxazepam, respectively. Two patients receiving methylprednisolone experienced amnesia. Eight patients (11%) commented unfavorably on the sedation/amnesia induced by lorazepam. These patients preferred to be awake and "in control" rather than suffer possible loss of bladder and/or bowel function while obtunded, even though objective emetic parameters were better with lorazepam. However, despite the frequency of heavy sedation induced by both benzodiazepines, patients were generally rousable and no patient aspirated vomitus.

*Other:* Two patients experienced severe facial flushing and burning from methylprednisolone, and oxazepam and methylprednisolone were associated with diarrhea in two patients each.

## Discussion

The results of our study indicate that lorazepam is of particular benefit in reducing the most severe degrees of vomiting in patients receiving cisplatin chemotherapy. Although no overall difference among the three agents was shown over a range of assessment criteria, lorazepam was significantly effective in the subset of patients with more than ten vomits and in patients with the most severe subjective emetic symptoms.

The antiemetic efficacy of lorazepam over oxazepam and methylprednisolone was also most apparent in patients who received cisplatin at high dosage (data not shown). Of seven patients who received all three antiemetic agents before receiving cisplatin doses of 100 mg/m$^2$ (five testicular cancer, two ovarian cancer), lorazepam was nominated as clear first preference in six cases (in the seventh case, lorazepam and oxazepam were assessed as having equal efficacy over methylprednisolone). Although the numbers are relatively small, it was apparent that those patients who received higher doses of cisplatin experienced much more cytotoxic-related distress when they were given either oxazepam or methylprednisolone rather than lorazepam.

At higher cisplatin doses patients vomited more frequently compared with patients receiving doses less than 100 mg/m$^2$, irrespective of which premedicant was given. However, patients receiving lorazepam tended to significantly underestimate the actual number of vomiting episodes. Lorazepam-induced amnesia was less complete in patients receiving higher cisplatin doses in this study, although vomiting occurred with very little concomitant distress and lorazepam was significantly more popular with patients than were either oxazepam or methylprednisolone (Table 4).

Lorazepam has been used successfully as a premedicant for minor surgical procedures over a number of years, and its value as an anxiolytic/amnesic agent (without severe concomitant sedation) has been stressed by a number of authors.[11,12] One of us (J.H.K.) has previously shown that oral lorazepam is an effective and safe amnesic agent which significantly improves patient acceptance of cytotoxic chemotherapy.[13] By rendering the patient amnesic for events related to the treatment period, fear of cytotoxic-induced emesis can be greatly reduced. A number of patients who would otherwise have refused to continue potentially curative chemotherapy because of distressing cytotoxic-induced emesis have had dramatically improved

tolerance of chemotherapy when lorazepam was substituted for previously ineffective conventional antiemetics. Our data lends further support to the observation that lorazepam is most dramatically beneficial in patients receiving cisplatin at dosages > 100 mg/m.[2]

The current data support a number of previous studies in suggesting that lorazepam has gained a rightful place in the treatment of cytotoxic-induced emesis.[4,14,15] Bishop *et al.* have confirmed our original findings that beneficial effects of lorazepam are dramatic and clinically significant in subsets of patients receiving either cisplatin or Adriamycin (doxorubicin) and cyclophosphamide.[14] A more recent study by Bishop *et al.* has demonstrated that the combination of high-dose metoclopramide and lorazepam is also particularly beneficial in reducing cisplatin-induced emesis.[16]

A majority of patients found the use of lorazepam and oxazepam desirable, and we view amnesia as a highly desirable effect as long as patients are prepared to accept the concomitant sedation. It is clear that some 10% to 15% of patients found the sedation and amnesia undesirable, even distressing at times. In our study, oxazepam-induced amnesia occurred much less frequently than with lorazepam, lasted for a shorter time, and was often incomplete. Although not borne out in the statistical analysis, it was our impression that patients receiving oxazepam were more commonly obtunded and more difficult to rouse than were patients who received lorazepam. Five patients preferred methylprednisolone over either lorazepam or oxazepam because of unwelcome sedation, even though objective parameters suggested that methylprednisolone was less able to control their cytotoxic-induced emesis. A number of female patients became incontinent of urine as a result of profound sedation in the face of hydration associated with cisplatin administration.

We should emphasize, however, that no patient experienced any life-threatening complications, such as aspiration of vomitus or respiratory depression as a result of drug-induced sedation.

One of the surprising aspects of our study was the poor antiemetic protection afforded by methylprednisolone. Numerous uncontrolled single-arm pilot studies have suggested a significant role for corticosteroids against highly emetogenic cytotoxics, such as cisplatin.[5,6] Despite these early promising reports, however, we found methylprednisolone to be a very disappointing antiemetic in terms of both objective and subjective assessment criteria. Despite initial enthusiasm for corticosteroids as antiemetics, recent reports cast some doubt on the real antiemetic efficacy of dexamethasone.[17,18] In addition to its poor performance as an antiemetic, methylprednisolone was significantly more expensive than either of the two benzodiazepines with which it was compared (methylprednisolone $22.50 per dose; lorazepam $0.40 per dose; oxazepam $0.10 per dose).

Our results highlight the importance of performing a randomized study using objective and subjective parameters in assessing the cost-effectiveness of potentially effective new agents. As a result of this analysis, lorazepam premedication has become an integral part of our antiemetic regimens, particularly in patients receiving high doses of cisplatin.

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