Zomepirac as an analgesic premedication: A comparison of three dosage regimens

Geoffrey L. Dunn MB BS,
David H. Morison MB CH B,
Angelica M. Fargas-Babjak MD

Three regimens of oral zomepirac premedication – 100 mg and 200 mg administered one hour preoperatively, and 100 mg administered 30 minutes preoperatively – were compared in terms of the control of postoperative pain. Primary outcomes were postoperative analgesic requirements, pain intensities and side effects. Sixty patients undergoing laparoscopic sterilization by Fallop ring were studied, using a double blind randomized design. All patients received a standardized general anaesthetic in which narcotic supplementation was avoided. Zomepirac 100 mg, when administered 30 minutes preoperatively, was the preferred regimen in terms of postoperative remedication rates, pain intensity, and side effects. However, the overall rate of remedication was high and was probably a result of the severe pain experienced by these patients in the early postoperative period. Plasma levels of zomepirac at termination of anaesthesia were consistent with the differences in remedication profiles and showed significant correlations with initial postoperative pain intensity, as assessed by an ordinal descriptive scale ($r = 0.431$, $p = 0.025$) and time to remedication ($r = 0.541$, $p = 0.004$), thus adding validity to the model.

Key words

ANALGESIC: zomepirac, ANAESTHESIA: outpatient, premedication.

For many years, narcotics have been used as premedicants to produce preoperative sedation, allay anxiety, and to provide per- and postoperative analgesia. Although methods have been developed to assess the preoperative sedative and anxiolytic properties of different premedications,¹ few studies have been conducted to compare their efficacy in control of postoperative pain.²⁻⁴ Previously adopted strategies appear to lack sensitivity in the latter area. This study utilises a design which compares analgesic premedicants in terms of postoperative remedication requirements and pain intensity. Although orally administered anxiolytic drugs such as diazepam are frequently used for premedication, oral analgesics have not gained widespread use, probably because of their limited analgesic efficacy. Zomepirac, an orally administered non-narcotic, may compare favourably with intramuscular morphine in the treatment of postoperative pain.^{5,6} The objective of the study was to compare three regimens of zomepirac, each differing in terms of dose or time of administration, on the basis of postoperative remedication profile, pain scores, and side effects.

Methods

The study protocol received institutional approval, and all patients gave their informed, written consent. Patients included in the study were those scheduled for elective laparoscopic sterilization by Fallop ring, and were hospitalized only for the day of surgery. Sixty patients were studied, all of whom were A.S.A. physical status I, aged between 18 and 40 years, and weighed 45 to 90 kg. Three dosage regimens of zomepirac were used; 100 mg given approximately 30 minutes preoperatively (Group A) and 100 mg and 200 mg administered approxi-

From the Department of Anaesthesia, McMaster University, Hamilton, Ontario.

Address correspondence to: Dr. G.L. Dunn, Department of Anaesthesia, McMaster University, Box 2000, Station A, Hamilton, Ontario L8N 3Z5, Canada.

TABLE I Time of administration and type of medication capsule* are shown for each premedication regimen

Group	60 minutes	30 minutes
A	2 Placebo	1 Zomepirac
B	1 Placebo + 1 Zomepirac	1 Placebo
C	2 Zomepirac	1 Placebo

*Capsules contained either lactose placebo or zomepirac 100 mg.

mately 60 minutes prior to anaesthesia (Groups B and C respectively). Patients were randomized to premedication regimen within blocks of six. A double blind design was achieved by the use of appropriate combinations of zomepirac and placebo (lactose) capsules of identical appearance, prepackaged into numbered envelopes (Table I). A standard anaesthetic was administered which comprised induction with thiopentone and succinylcholine, orotracheal intubation, and maintenance by nitrous oxide and enflurane in oxygen with controlled ventilation. Muscle relaxation was facilitated by a succinylcholine infusion.

The times of administration of preoperative medication, and procedural data, were noted. "Recovery time" was assessed as the time from termination of anaesthesia until the patient could first recall her date of birth, and "street fitness" time was assessed using a modification of the Fay⁷ scoring system. All observations were made by an experienced research nurse. Pain intensity was assessed using a 10 cm visual analogue scale (VAS) and a five-point ordinal descriptive scale. Patients were familiarized with these scales in the preoperative period, and pain intensity was assessed postoperatively at 2, 2.5, 3, 4, 5 and 6 hours from the time of administration of the first premedication capsules. In the postoperative period, additional analgesia was allowed on request, after assessment of the patient by the research nurse. In order to facilitate the subsequent comparison of pain measurements, a standardized analgesic regimen was used comprising intramuscular meperidine 50 mg during the first postoperative hour and 100 mg zomepirac by mouth thereafter.

Following each pain assessment, patients were asked if they had experienced any side effects, and those volunteered were recorded. At the completion of the study period, both patient and observer

recorded their global impression of the analgesic efficacy of the premedication regimen received.

Two 10 ml heparinized blood samples were taken at the time of induction and termination of anaesthesia, from a subgroup of 29 patients. Plasma was subsequently separated and then stored at -10°C until analyzed for zomepirac using a sensitive high-pressure liquid chromatographic method.⁸

Statistical methods

Patient and procedural variables and plasma levels of zomepirac were compared between groups by one-way analysis of variance: when significant differences were found, individual group means were compared using Scheffé's multiple comparison procedure. Remedication times were analysed using the proportional hazards model of Cox⁹ and pain intensities by repeated measures ANOVA.¹⁰ Side effects were compared using a Chi-square analysis. $P < 0.05$ was regarded as indicating statistical significance.

Results

Patients in each premedication group were similar with respect to age ($30.6 \text{ year} \pm 5.24$) and weight ($61.3 \text{ kg} \pm 9.44$) (overall mean $\pm$ S.D.), and there were no statistically significant differences between procedural variables (Table II).

Figure 1 shows the administration of additional analgesic plotted against time from recovery of anaesthesia for the three premedication regimens. There was a significant overall treatment effect ($p < 0.001$) and pair-wise comparisons indicated that Groups A and C were similar, but both differed from Group B (A vs B, $p = 0.038$; B vs C, $p = 0.046$). Adjustment for age, weight and anaesthetic time in the statistical analysis revealed that these variables did not affect time to remedication.

TABLE II Procedural variables are shown as mean (S.D.)

Group	Premedication to induction (min)	Anaesthesia time (min)	Recovery time (min)	Street fitness time (hr)
A	72.0 (14.3)*	32.1 (9.61)	9.2 (5.16)	5.5 (0.66)
B	69.6 (19.7)	33.4 (8.50)	8.6 (5.90)	5.8 (0.59)
C	72.6 (16.4)	38.0 (10.97)	9.7 (8.84)	5.8 (0.78)

*Time from administration of zomepirac capsule was 42.2 (14.0).

FIGURE 1 The cumulative number of patients who have received additional analgesia is plotted against time from recovery from anaesthesia for each treatment regimen. Group A received 100 mg of zomepirac 30 minutes preoperatively; Group B 100 mg and Group C 200 mg each 60 minutes preoperatively.

Mean visual analogue scores (Figure 2) for the three groups were maximal at the first postoperative observation (two hours from the time of the first premedication capsules) and declined progressively thereafter. The change of pain scores over time was highly significant ($p = 0.001$). Mean VAS in Group B was consistently higher than in Group A or C, but this difference did not reach statistical significance. Mean ordinal pain scores showed similar temporal changes and between group differences. Patient and observer global impressions were similar for all three groups.

Table III indicates that 12 patients (60 per cent) in Group A volunteered at least one side effect compared to 18 patients (90 per cent) in Group B and 17 (85 per cent) in Group C. Nausea and vomiting occurred in 12 patients in Group A, in 17 patients in Group B and in 16 patients in Group C, but these differences were not statistically significant.

Mean plasma levels of zomepirac (Table IV) at induction of anaesthesia were significantly higher in Group C ($2.82 \mu\text{g}\cdot\text{ml}^{-1}$) than in Group B ($0.73 \mu\text{g}\cdot\text{ml}^{-1}$) ($p < 0.001$). The mean value for Group A was $1.81 \mu\text{g}\cdot\text{ml}^{-1}$ and did not differ significantly from either of the other two groups. At termination of anaesthesia, mean plasma levels of zomepirac were similar for Groups A and C (1.9 and $1.61 \mu\text{g}\cdot\text{ml}^{-1}$ respectively) and were both significantly higher than the mean for Group B ($0.50 \mu\text{g}\cdot\text{ml}^{-1}$) ($p < 0.05$). There were significant correlations between plasma level of zomepirac at termination of anaesthesia and first postoperative ordinal pain

FIGURE 2 Mean visual analogue scores (VAS) are plotted against time from premedication for each treatment regimen.

intensity ($r = -0.431$, $p = 0.025$) and time to remedication ($r = 0.541$, $p = 0.004$).

Discussion

Three regimens of zomepirac were compared which differed in dose or time of administration. In terms of postoperative remedication rates, zomepirac 100 mg administered approximately 30 minutes preoperatively was equivalent to zomepirac 200 mg administered 60 minutes preoperatively. Both of these regimens were superior, in this respect, to 100 mg of the drug given 60 minutes prior to

TABLE III The incidence of side effects is shown for each premedication group together with the total number of patients experiencing at least one side effect in each group

	A	B	C
Dizziness	0	4	2
Drowsiness	0	0	1
Faintness	0	0	2
Gastric discomfort	0	0	1
Headache	1	1	0
Nausea	3	8	3
Vomiting	9	9	13
Total patients	12 (60%)	18 (90%)	17 (85%)

TABLE IV Plasma levels ($\mu\text{g}\cdot\text{ml}^{-1}$) of zomepirac at induction and termination of anaesthesia are shown by premedication group as mean (S.D.)

Premedication Group	n	Induction of anaesthesia	Termination of anaesthesia
A	9	1.81 (1.206)	1.93† (1.430)
B	10	0.73 (0.693)	0.50 (0.450)
C	10	2.82‡ (1.531)	1.61* (0.949)

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, when compared to Group B.

surgery. Pain scores and observer and patient global impressions showed similar differences between groups but did not reach statistical significance. The incidence of side effects was lowest when 100 mg of zomepirac was administered approximately 30 minutes preoperatively and may be due, at least in part, to the reduced need for additional postoperative analgesia. The incidence of remedication was high even in this group, and reflects the severe pain levels experienced by patients following sterilization by Fallop ring.

The mean plasma levels of zomepirac measured at termination of anaesthesia are consistent with the remedication profiles and early postoperative pain levels found in this study. In both groups in which zomepirac was administered 60 minutes preoperatively, mean plasma levels were lower at termination of anaesthesia than at induction. However, when 100 mg of zomepirac was administered approximately 30 minutes preoperatively, mean plasma levels at induction and termination of anaesthesia were similar, and equated to that found at termination of anaesthesia following the administration of 200 mg 60 minutes preoperatively. However, the mean plasma levels in all groups were somewhat lower than would have been anticipated from pharmacokinetic data.¹¹ While this finding suggests that absorption of zomepirac was incomplete, peak plasma levels do not appear to have been unduly delayed. This issue can only be clarified by a further study in which more frequent and extended blood sampling is performed.

The study design employed was developed as an improvement over methodology previously described for the comparison of analgesic premedications in terms of the control of postoperative pain.^{2-4,12} Specific features incorporated to increase model sensitivity include the nonparametric analy-

sis of remedication rates and the use of a patient population in whom postoperative pain is usually moderate or severe. The use of a standardized postoperative analgesic regimen also allowed the subsequent comparison of postoperative pain intensities.

A placebo group was not included in the present study since this would have been contrary to prevailing clinical practice in this institution. The ethical implications of the use of placebo groups in pain studies have been acknowledged by Dundee.¹³ Lasagna¹⁴ stated that such a group is only necessary when there is no difference between the treatments being compared. In this situation, it is impossible to determine in retrospect whether the treatments are truly comparable or whether the research design lacks sensitivity. He also regarded the demonstration of a dose response effect as establishing model sensitivity, but notes that the problem of interpretation of the effects seen with the lowest dose of the new drug may remain.

This design appears to possess adequate sensitivity in terms of remedication rates. Furthermore, the validity of the time to remedication as an outcome measure is supported by the highly significant correlation with plasma zomepirac level ($r = 0.541$, $p = 0.004$). However, the absence of statistically significant differences between premedications in terms of postoperative pain intensity and global impressions by patient and observer is not surprising. All patients were allowed additional analgesia on request using a standardized regimen, which is not only mandated by ethical considerations but is also consistent with prevailing clinical practice. The resulting measurements of pain intensity were therefore "contaminated" by the additional analgesic medication. Since the least effective premedication group was remedicated most frequently, the resulting "equalizing effect" tended to reduce the sensitivity of pain intensity as an outcome measure. Similarly, both patient and observer global impressions, being based on the overall pain experience and not solely on premedication received, were also subject to this attenuation of sensitivity.

Examination of our results would suggest that a larger sample size may have allowed the differential analgesic effects of the premedication regimens to be assessed in terms of postoperative pain intensities. Calculation of sample size,¹³ accepting α

and β errors of 0.05 and 0.10 respectively, and assuming a clinically significant difference of 1.5 cm on the VAS scale and a population variance of 2.60, as estimated from this study, would indicate that 32 patients per group would be required. Therefore, 40 patients per group, commonly used in postoperative pain studies to compare effective analgesics, should provide adequate sensitivity for the assessment of analgesic premedications. Validation of this model with formal establishment of sensitivity must await further trials in which placebo and graded doses of standard premedications are included.

In summary, when the interval between premedication and induction of anaesthesia was held constant at approximately 60 minutes, 200 mg zomepirac was superior to 100 mg, and also resulted in significantly higher plasma levels at termination of anaesthesia. Similarly, when the dose was held constant at 100 mg, zomepirac was more effective clinically when administered 30 minutes rather than 60 minutes preoperatively, and the former regimen also produced a significantly higher plasma level at termination of anaesthesia.

Acknowledgements

We are grateful to Dr. R. K. Nayak, McNeil Pharmaceutical, Springhouse, Pennsylvania, who performed the plasma zomepirac assays. We also wish to thank Ms. J. Kasperski for her assistance in the performance of the study.

References

- 1 Forrest WH, Brown CR, Brown BW. Subjective responses to six common preoperative medications. *Anesthesiology* 1977; 47: 241-7.
- 2 Booker PD, Chapman DH. Premedication in children undergoing day-care surgery. *Br J Anaesth* 1979; 51: 1083-7.
- 3 Fragen RJ, Caldwell N. Acute intravenous premedication with nalbuphine. *Anesth Analg* 1977; 56: 808-12.
- 4 Prescott RJ, Espley AJ, Davie IT, Slawson KB, Ruckley CV. Double-blind clinical trial of anaesthetic premedication for use in major day surgery. *The Lancet* 1976; 1148-50.
- 5 Forrest WH. Orally administered zomepirac and parenterally administered morphine. *JAMA* 1980; 244: 2298-2302.
- 6 Wallenstein SL, Rogers A, Kaiko RF, Heidrich G, Houde RW. Relative analgesic potency of oral zomepirac and intramuscular morphine in cancer patients with postoperative pain. *J Clin Pharmacol* 1980; 20: 250-8.
- 7 Fay MR. Nursing process in recovery room. *AORN J* 1976; 24: 1069-75.
- 8 Ng KT, Synderman T. Determination of zomepirac in plasma by high-pressure liquid chromatography. *J Chromatography* 1979; 178: 241-7.
- 9 Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: John Wiley and Sons, 1980.
- 10 Weiner BJ. *Statistical Principles in Experimental Design*, 2nd ed. New York: McGraw-Hill Book Co. Inc., 1971, pp. 514-99.
- 11 Nyak RK, Ng KT, Gottlieb S, Plostnieks J. Zomepirac kinetics in healthy males. *Clin Pharmacol Ther* 1980; 27: 395-401.
- 12 Dionne RA, Cooper SA. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. *Oral Surg* 1978; 45: 851-6.
- 13 Dundee JW. Clinical evaluation of mild analgesics. *Br J Clin Pharmacol* 1980; 10: 329S-34S.
- 14 Lasagna L. Double-blind evaluation of butorphanol and meperidine given intramuscularly before anaesthesia. *Curr Ther Res* 1976; 20: 763-71.
- 15 Armitage P. *Statistical Methods in Medical Research*. 4th ed. New York: John Wiley and Sons, 1971.

Résumé

On a comparé trois modes d'administration du zomépirac en tant que prémédication en regard du soulagement post-opératoire de la douleur. On a administré 100 mg ou 200 mg une heure avant l'intervention ou 100 mg trente minutes avant l'intervention. Les facteurs étudiés comprenaient les besoins post-opératoires en analgésiques, l'intensité de la douleur et les effets secondaires. Soixante patientes ayant à subir une ligature tubaire par laparoscopie ont été réparties de façon aléatoire dans un protocole à double insu. Toutes ont reçu une anesthésie générale sans morphinique. La dose de 100 mg administrée ½ heure avant l'intervention a été la plus efficace quant à la fréquence des doses analgésiques nécessaires après l'opération, à l'intensité de la douleur et aux effets secondaires. Cependant, dans tous les groupes le recours à l'analgésie post-opératoire a été fréquent, probablement en raison de la vive douleur rencontrée dans ce type de chirurgie au début de la période post-opératoire. Les différences dans les profils d'analgésie post-opératoires étaient en relation avec les concentrations plasmatiques de zomépirac à la fin de l'intervention; ainsi, on a pu démontrer une corrélation significative avec l'intensité de la douleur, classer selon une échelle descriptive ($r = 0.431$, $p = 0.025$), et le temps écoulé avant le besoin d'analgésie supplémentaire ($r = 0.541$, $p = 0.004$).