The Effect of Pregabalin on Preoperative Anxiety and Sedation Levels: A Dose-Ranging Study

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BACKGROUND: Pregabalin is a gabapentinoid compound, which has been alleged to possess anxiolytic, analgesic, and anticonvulsant properties. We hypothesized that premedication with oral pregabalin would produce dose-related reductions in acute (state) anxiety and increases in sedation (sleepiness) before induction of general anesthesia. A secondary objective was to determine if premedication with pregabalin would reduce postoperative pain.

METHODS: One hundred eight ASA I–III outpatients undergoing elective surgery were randomly assigned to one of the four premedication treatment groups: 1) control group received placebo capsules, 2) pregabalin 75 group received pregabalin 75 mg, po, 3) pregabalin 150 group received pregabalin 150 mg, po, and 4) pregabalin 300 group received pregabalin 300 mg, po. The effects of the study drug on the patients' level of anxiety, sedation, and pain were assessed at baseline (immediately before study drug administration), at 30 and 60 min after drug administration, and immediately before induction of anesthesia, as well as at 30-min intervals in the postanesthesia care unit (PACU) using standardized 11-point verbal rating scales, with 0 = none to 10 = maximal effect. The need for postoperative opioid analgesic medication, incidence of nausea and vomiting, requirement for rescue antiemetics, and times to discharge from the PACU and hospital, as well as the patients' quality of recovery scores, and late recovery outcomes (e.g., resumption of dietary intake and recovery of bowel function) were assessed at a 7-day follow-up interview.

RESULTS: Demographic characteristics, times between study drug administration to anesthetic induction, type of surgical procedures, duration of anesthesia, PACU and hospital discharge time, as well as the requirement for fentanyl in the PACU, did not differ among the four study groups. Anxiety levels remained unchanged during the preoperative evaluation period, and did not differ among the four study groups. Sedation scores were significantly higher in the pregabalin 300 group at the preinduction assessment interval and at 90 and 120 min after surgery compared with the control group (5 ± 3 vs 3 ± 2, 7 ± 4 vs 5 ± 3, 8 ± 4 vs 4 ± 4, respectively, $P < 0.05$).

CONCLUSION: Preoperative pregabalin administration (75–300 mg po) increased perioperative sedation in a dose-related fashion, but failed to reduce preoperative state anxiety, postoperative pain, or to improve the recovery process after minor elective surgery procedures.

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Preoperative anxiety and postoperative pain remain problems for many outpatients during the perioperative period. Although benzodiazepines are effective in reducing preoperative anxiety in the ambulatory setting,[1] the anxiolytic effect is frequently accompanied by undesirable sedation. The prevention and treatment of postoperative pain with opioid analgesics contributes to postoperative nausea and vomiting and can delay recovery of bowel function, as well as adversely affect many other organ systems in the body.[2] Opioid-related side effects contribute to delayed discharge and recovery of activities of daily living after ambulatory surgery.[3]

Recently, an increasing emphasis has been placed on the use of non-opioid analgesic drugs as part of a multimodal regimen for preventing pain in the perioperative period.[3–5] Novel compounds (e.g., α-2 agonists, ketamine, esmolol, and capsaicin) are being examined as adjuvants for minimizing pain after surgery.[6–9] Oral gabapentin administered for premedication has been found to improve the quality of

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recovery in the early postoperative period comparable to a cyclooxygenase-2 inhibitor.[10–12] Pregabalin is an analog of gabapentin, which has been alleged to possess anxiolytic, analgesic, and antiepileptic activity.[13] Pregabalin has been approved for the treatment of neuropathic pain, and preliminary clinical studies suggest a possible role in the perioperative period.[14,15]

In this placebo-controlled, dose-ranging study, we hypothesized that patients receiving oral pregabalin for premedication would experience a decrease in their level of acute "state" anxiety before induction of general anesthesia. Secondary objectives of this study were to determine if premedication with pregabalin would increase sedation or reduce postoperative pain.

METHODS

After obtaining institutional review board approval at the University of Texas Southwestern Medical Center at Dallas and written informed consent, 108 ($n = 27$ per group) ASA I–III patients, aged 18–70 yr, scheduled for elective ambulatory and short-stay (<24 h) surgical procedures (e.g., ear–nose–throat, laparoscopic, urologic, and plastic surgery) were enrolled in this randomized, double-blind, placebo-controlled clinical study. Patients were excluded if they were known to be allergic to gabapentin or pregabalin, had any clinically significant medical or psychiatric conditions, were pregnant or lactating, had a history of alcohol or drug abuse within the past 6 mo, or were taking opioid-containing pain or sedative medications on a long-term basis.

The patients were randomly assigned using a computer-generated random numbers table to one of the following four treatment groups: 1) control group received an oral placebo, 2) pregabalin 75 group received pregabalin 75 mg, po, 3) pregabalin 150 group received pregabalin 150 mg, po, and 4) pregabalin 300 group received pregabalin 300 mg, po. The study medication was prepared in identical-appearing capsules by the manufacturer of pregabalin (Pfizer, New York, NY). The study medication capsules were put in numbered envelopes containing two placebo capsules (control), one pregabalin 75 mg with one placebo capsule (pregabalin 75), one pregabalin 150 mg with one placebo capsule (pregabalin 150), or two pregabalin 150 mg capsules (pregabalin 300). The patients received the study medication by mouth 60–90 min before induction of general anesthesia. The patients, clinical investigators, attending anesthesiologists, and nurses in the recovery room who were involved in the patients' care were all blinded as to the content of the study medication capsules.

In the preoperative holding area, the patients assessed their level of pain, anxiety, and sedation (or sleepiness) using an 11-point verbal rating scale (VRS), with 0 = none to 10 = maximum effect before receiving the study medication, subsequently at 30 and 60 min after study drug administration, and immediately before induction of anesthesia. Anesthesia was induced with fentanyl (100 μg IV) and propofol (1.5 mg/kg IV). Rocuronium, 0.6 mg/kg IV was administered to facilitate tracheal intubation. Anesthesia was maintained with desflurane (4%–6% inspired concentration) in combination with air (1 L/min) and oxygen (1 L/min). A remifentanil infusion, 0.075–0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was administered for intraoperative analgesia. In addition, a combination of ondansetron, 4 mg IV, and dexamethasone, 8 mg IV, was administered intraoperatively for the prevention of postoperative nausea and vomiting. At the end of the surgical procedure, desflurane was discontinued and the inspired oxygen flow was increased to 5 L/min. Residual neuromuscular block was reversed with neostigmine, 40 μg/kg IV, and glycopyrrolate, 5 μg/kg IV. Tracheal extubation was performed when the patients could open their eyes and obey simple commands.

In the postanesthesia care unit (PACU), fentanyl, 25–50 μg IV, boluses were administered to control acute postoperative pain when the patient complained of moderate-to-severe pain. The patients were asked to assess the level of their drowsiness/sleepiness (sedation) and incisional pain using the VRS at 30-min intervals for the first 2 h in the postoperative period. Pain was also assessed on the first, third, and seventh postoperative day (POD). If the patients complained of moderate-to-severe nausea, or experienced one or more episodes of vomiting (or retching) they were administered metoclopramide, 10 mg IV (or phenergan, 12.5 mg IV, if their emetic symptoms persisted after receiving metoclopramide). The requirement for postoperative "rescue" pain medication and antiemetic drugs, as well as the times to discharge from the PACU and hospital, were recorded. Side effects recorded by the PACU nursing staff were also analyzed. Difficulty in arousing patients when assessing their postoperative vital signs was recorded as excessive somnolence by the PACU staff. Quality of recovery scores (using a validated nine-item questionnaire[16]) were assessed on PODs 1, 3, and 7. Patient satisfaction with their pain management was assessed on POD 7 using a 100-point VRS scale, with 1 = completely dissatisfied to 100 = completely satisfied. Recovery times to resumption of oral fluid and normal dietary intake, as well as first bowel movement, were recorded.

Statistical Analysis

Data were expressed as mean values ± SD, medians (and interquartile ranges), percentages (%), and numbers (n). The statistical analysis was performed using a standard SPSS software package (Chicago, IL). One-way analysis of variance was used to analyze continuous variables. Changes in VRS scores over time were analyzed using repeated-measures analysis of variance. Student's t-test was used to analyze the parametric data, and discrete (categorical) variables were

Table 1. Demographic Characteristics, Time from Study Drug Administration Until Induction of Anesthesia, Types of Surgical Procedures, Duration of Anesthesia, Length of Stay in the PACU and Hospital, Intraoperative Fentanyl and Remifentanil Dosages, and the Amount of "Rescue" Fentanyl in the PACU[a]

	Control ($n = 27$)	Pregabalin 75 ($n = 27$)	Pregabalin 150 ($n = 27$)	Pregabalin 300 ($n = 27$)
Age (yr)	48 ± 15	43 ± 14	48 ± 16	46 ± 13
Sex (M/F) (*n*)	11/15	12/15	18/8	11/15
Weight (kg)	84 ± 22	78 ± 18	82 ± 16	89 ± 30
Height (cm)	170 ± 10	169 ± 10	173 ± 13	174 ± 10
ASA (I/II/III) (*n*)	5/17/4	8/13/4	5/18/3	2/18/4
Time before anesthesia induction (study drug)	79 ± 51	79 ± 38	83 ± 41	85 ± 54
Types of surgical procedures (*n*)				
Otolarygologic	9	11	12	13
General surgery	9	5	8	8
Plastic surgery	4	5	3	3
Urologic surgery	5	6	4	3
Time of anesthesia (min)	154 ± 114	133 ± 71	138 ± 51	151 ± 89
PACU stay (min)	72 ± 29	72 ± 31	71 ± 43	90 ± 36
Discharge time (min)	164 ± 77	164 ± 81	153 ± 76	181 ± 95
Intraoperative opioids				
Fentanyl (μg)	145 ± 70	149 ± 87	144 ± 105	112 ± 71
Remifentanil (μg)	1480 ± 1180	1000 ± 540	820 ± 540	1400 ± 1120
Rescue fentanyl in PACU (μg)	93 ± 76	84 ± 71	92 ± 109	81 ± 132

No significant differences were noted among the four treatment groups.

M = male; F = female; ASA = American Society of Anesthesiology; PACU = postanesthesia care unit.

[a] Data are presented as mean values ± standard deviation, numbers (*n*).

analyzed using the χ^2 test, with P values <0.05 considered statistically significant. The primary end point for this study was a reduction in the patient's preoperative level of anxiety as assessed using the VRS. Based on a predicted 26% reduction from the patient's pretreatment (baseline) VRS anxiety score (mean value of 5 and a SD of 3[1]), a minimum of 25 subjects was required in each of the four study groups under the assumptions of an α level of 0.05 and power of 80% using a two-sided t-test.

RESULTS

One hundred forty patients were screened for eligibility to participate in this study, and 108 patients were subsequently consented and enrolled ($n = 27$ per group). There were no significant differences among the four groups with respect to age, gender, weight, height, ASA physical status, time intervals between study drug administration and induction of anesthesia, classification of the surgical procedures, and duration of anesthesia (Table 1).

The preoperative VRS anxiety scores were unchanged from the baseline values in all four groups during the preoperative evaluation period. Furthermore, there were no significant differences among the four groups (Table 2). The sedation ("sleepiness") scores were also unchanged in the control, pregabalin 75 and 150 groups. However, VRS sedation scores were significantly higher in the pregabalin 300 group at induction of anesthesia, and at 90 and 120 min after surgery compared with the control group. A higher percentage of patients in the high-dose pregabalin group complained of dizziness (or light-headedness) and were reported to be "difficult to arouse" by the nurses in the PACU (Table 3). Although the length of the PACU stay and the times to hospital discharge were longer in the pregabalin 300 (versus control) group (90 ± 36 vs 72 ± 29 min, 181 ± 95 vs 164 ± 77 min, respectively), these differences failed to achieve statistical significance (Table 1).

Pain score reported in the PACU and the amount of rescue fentanyl administered in PACU did not differ significantly among the four groups (Tables 1 and 2). Similarly, the pain scores on PODs 1, 3, and 7 did not differ among the four groups. Finally, quality of recovery scores, patient satisfaction with their pain management, as well as times to tolerating a normal diet and resumption of bowel activity did not differ among the four treatment groups (Table 3).

DISCUSSION

Pregabalin is alleged to modulate the release of excitatory neurotransmitters, leading to a reduction in levels of anxiety and pain.[13] A study in patients with generalized anxiety disorders found that chronic use of pregabalin was significantly more effective than the benzodiazepine alprazolam in improving somatic anxiety symptoms.[17] However, our study suggests that a single dose of pregabalin for preoperative medication in doses ranging from 75 to 300 mg was ineffective in reducing acute preoperative (state) anxiety. The highest dose of pregabalin (300 mg) produced increased levels of sedation both before and after ambulatory surgery.

Hill et al.[13] were the first to report on the use of pregabalin for treating pain after surgery. In this preliminary study involving patients undergoing

Table 2. Preoperative Anxiety and Sedation, and Postoperative Pain Scores Recorded Using a 11-Point Verbal Rating Scale at Specific Time Intervals Before and After Surgery, Respectively[a]

	Control ($n = 27$)	Pregabalin 75 ($n = 27$)	Pregabalin 150 ($n = 27$)	Pregabalin 300 ($n = 27$)
Anxiety[b]				
Preoperative period				
0 min (baseline)	4 ± 3	4 ± 3	4 ± 2	3 ± 3
30 min	3 ± 3	4 ± 3	3 ± 2	3 ± 3
60 min	3 ± 3	3 ± 3	3 ± 2	3 ± 3
Preinduction	3 ± 3	3 ± 3	3 ± 3	3 ± 3
Sedation[b]				
Preoperative period				
0 min (baseline)	2 ± 2	2 ± 2	2 ± 2	2 ± 2
30 min	3 ± 3	2 ± 2	3 ± 2	3 ± 3
60 min	3 ± 3	2 ± 2	3 ± 3	4 ± 3
Preinduction	3 ± 2	3 ± 3	4 ± 3	5 ± 3*†
Postoperative period				
0 min (in PACU)	6 ± 3	7 ± 3	7 ± 3	7 ± 4
30 min	6 ± 3	5 ± 3	5 ± 3	6 ± 3
60 min	5 ± 3	5 ± 3	5 ± 3	6 ± 4
90 min	5 ± 3	5 ± 2	5 ± 3	7 ± 4*
120 min	4 ± 4	6 ± 3	6 ± 4	8 ± 4*
Pain after surgery[b]				
0 min (in PACU)	3 ± 4	3 ± 3	3 ± 3	4 ± 4
30 min	4 ± 3	4 ± 3	4 ± 3	5 ± 3
60 min	4 ± 3	3 ± 2	5 ± 3	5 ± 3
90 min	4 ± 2	3 ± 2	4 ± 2	5 ± 3
120 min	4 ± 3	4 ± 3	4 ± 2	4 ± 4
POD 1	2 ± 2	3 ± 2	3 ± 2	4 ± 3
POD 3	2 ± 3	2 ± 2	2 ± 2	3 ± 2
POD 7	1 ± 2	1 ± 1	1 ± 1	2 ± 2

POD = postoperative day; PACU = postanesthesia care unit.

[a] Data are presented as mean ± standard deviation.

[b] Verbal rating scale: 0 = no anxiety, sedation ("sleepiness") or pain to 10 = maximal anxiety, sedation ("sleepiness") or pain.

* $P < 0.05$ vs control group.

† $P < 0.05$ vs "0 min" (preoperative baseline or postoperative in PACU).

Table 3. Adverse Side Effects in the PACU, Quality of Recovery Scores, Patient Satisfaction with Pain Management, Times to Oral Intake, Normal Diet, and Bowel Movement[a]

	Control ($n = 27$)	Pregabalin 75 ($n = 27$)	Pregabalin 150 ($n = 27$)	Pregabalin 300 ($n = 27$)
Rescue antiemetic (n, %)	6, 22	6, 22	4, 15	8, 30
Difficult to arouse (n, %)	2, 7	2, 7	3, 11	7, 26*
Dizzy or lightheaded (n, %)	1, 4	3, 11	6, 22	8, 30*
Quality of recovery score[b]				
POD 1	14 ± 3	15 ± 2	16 ± 2	16 ± 2
POD 2	16 ± 2	16 ± 2	17 ± 2	17 ± 2
POD 7	17 ± 1	16 ± 1	17 ± 1	17 ± 2
Patient satisfaction with pain management (0–100)	86 ± 21	82 ± 23	91 ± 7	83 ± 26
Time to oral intake (h)	8 ± 8	7 ± 8	6 ± 8	8 ± 8
Resumption of normal diet (h)	18 ± 17	23 ± 39	20 ± 24	20 ± 18
Time to first bowel movement (h)	35 ± 30	30 ± 26	33 ± 25	32 ± 24

PACU = postanesthesia care unit; POD = postoperative day.

[a] Data are presented as mean ± standard deviation, percentages, and number.

[b] Quality of recovery score: 0 = worst to 18 = best.

* $P < 0.05$ compared with control group.

third molar extractions, pregabalin 300 mg was significantly more effective than a placebo in reducing postoperative pain. They also suggested that pregabalin 300 mg po had a longer duration of analgesia than ibuprofen 400 mg po in this acute pain model. Analogous to the findings in our current study, patients receiving pregabalin 300 mg po in this preliminary study reported more frequent adverse effects (e.g., excessive sleepiness and dizziness).

Reuben et al.[18] evaluated the comparative analgesic efficacy of pregabalin 150 mg po and celecoxib 200 mg when administered both before and after spinal fusion surgery. Analogous to celecoxib, pregabalin reduced postoperative opioid usage compared with a placebo.

However, neither drug was found to reduce opioid-related side effects in the postoperative period. More recent studies by Paech et al.[19] and Jokela et al.[20] reported that preoperative administration of pregabalin 100 or 300 mg po was ineffective in reducing postoperative pain and the need for opioid analgesic rescue medication. Although pregabalin 600 mg po decreased the requirement for oxycodone after surgery,[20] its use was associated with a significant increase in adverse side effects (e.g., dizziness and blurred vision). In the study by Paech et al.,[19] even a 100-mg dose of pregabalin was associated with an increased incidence of light-headedness and difficulty in ambulating at 24 h after surgery (59% vs 33% in the placebo group). Our findings are consistent with these more recent studies and suggest that premedication with pregabalin lacks significant postoperative analgesic efficacy even when administered in doses associated with clinically significant side effects (e.g., dizziness and sleepiness).

The inconsistent finding with respect to the ability of pregabalin to improve the management of postoperative pain[14,15,18,19] may be related to a variety of potentially confounding factors. The most likely explanation relates to the type of surgical procedures and the use of multimodal analgesic regimens, as well as the timing of the drugs administration (e.g., preoperative versus postoperative). The pain scores on arrival into the PACU in our surgical population were relatively low (VRS scores of 3–4) because of the fact that these were superficial (noncavitary) procedures and local anesthetics were injected at the incision sites as part of a multimodal analgesic regimens. The severity of pain in our surgical population was significantly less than the pain typically associated with spinal fusion surgery.[18]

There are some deficiencies in our study design, which should be taken into consideration when interpreting these findings. First, only a single dose of the medication was administered before surgery, and the maximum dose in our study was 300 mg. However, when we attempted to use higher doses (e.g., 600 mg) in a pilot study, the occurrence of profound somnolence leading to prolonged PACU stays and delayed discharge necessitated that we eliminate this dosage group from this dose-ranging study. Second, the short time interval from administration of the study medication to induction of anesthesia (namely, 60–90 min) and relatively low baseline levels of anxiety may have limited our ability to detect an acute anxiolytic effect. Fortunately, pregabalin is rapidly (peak level <1 h) and completely ($>90\%$ bioavailability) absorbed after oral administration.[21,22] Third, we used a simple but well-validated measure of acute state anxiety, namely the VRS score, because of the limited time available to perform the preoperative assessments. Clearly, more sophisticated psychological testing procedures may have been able to ascertain subtle effects of the drug on the patients' level of acute anxiety. Finally, the variety of superficial surgical procedures with relatively low levels of pain in the postoperative period may have limited our ability to detect a significant effect on postoperative pain and the need for opioid analgesic medication.

In conclusion, pregabalin (75–300 mg po) failed to produce a significant anxiolytic effect when administered for preoperative medication despite the fact that the 300-mg dose produced a significant increase in the level of sedation before induction of anesthesia and in the early postoperative period. This study would suggest that pregabalin is not a useful drug for preoperative medication in patients undergoing ambulatory surgery.

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