Gabapentin premedication: assessment of preoperative anxiolysis and postoperative patient satisfaction

M. TiraULT, L. FouCAN, B. DeBAENE, D. F RasCA, T. LeBRUN, J.-C. BernARD, I. SanDEFo and A. C. Van ElSTRAE T e

Abstract: Background: Gabapentin reduces anxiety in psychiatric patients. In this prospective, randomized, double-blinded, placebo-controlled study, we investigated whether a single dose of gabapentin as a premedicant reduces preoperative anxiety, and improves patient satisfaction.

Materials and methods: After Institutional Review Board approval and written consent, 210 patients were randomly allocated into 3 groups of oral premedication: placebo, hydroxyzine 75 mg, or gabapentin 1200 mg. Anxiety level was assessed 3 times, using a 100-mm visual analogue scale: before premedication, in the preoperative holding area, and just before induction of general anaesthesia. In the postoperative period, patients were asked about their satisfaction with their premedicant. Data were presented as mean ± SD. VAS scores were analyzed by repeated-measures analysis of variance followed by a Bonferroni test as appropriate. The chi-square test was used to analyze categorical data. All p values less than 0.05 was considered statistically significant.

Results: Baseline anxiety was not statistically different among the 3 groups. Anxiety level in the gabapentin group was significantly lower in the holding area, and before induction of anaesthesia (20 mm ± 21), than in the hydroxyzine group (33 mm ± 26; p = 0.023) and in the placebo group (36 mm ± 28; p = 0.004). Anxiety decreased significantly overtime only in the gabapentin group. The gabapentin and hydroxyzine groups had a higher proportion of “satisfied or extremely satisfied” patients (73% and 70% respectively) as compared to the placebo group (48%, p = 0.006).

Conclusion: A single dose of gabapentin has proven to be an effective premedication to reduce preoperative anxiety.

Key words: Premedication; gabapentin; hydroxyzine; preoperative anxiety.

Introduction

Most patients waiting for elective surgery experience preoperative anxiety (1-3). Preoperative anxiety may be increased through ignorance of anesthetic and surgical procedures, given past experience and patients’ psychological profile (4). Anxiety may adversely influence induction of anesthesia and patient recovery (5) and may decrease patient satisfaction of the perioperative experience. Additionally, preoperative anxiety also influences postoperative anxiety, pain and analgesic requirements in the postoperative period, and length of hospital stay (6).

Prevention of anxiety is therefore a major issue during the perioperative care. However, anxiolytic premedication is often determined by habit rather than on a scientific evidence basis (7).

Gabapentin, an analogue of γ-aminobutyric acid has been shown to have anxiolytic properties (8,9). Additionally, the effects of 1200 mg of gabapentin on preoperative anxiety was previously assessed as a secondary outcome in a recent clinical trial of 40 patients undergoing elective knee surgery (10). Maximal active knee flexion was considered the primary endpoint. The secondary endpoints were pain scores, morphine consumption, and preoperative anxiety scores. In this study, patients’ preoperative anxiety scores were significantly reduced by as much as 57%. Our study was then designed to evaluate preoperative anxiety as primary outcome measurement in a large sample of patients undergoing varied surgeries, and therefore the sample size was powered according to that endpoint. The secondary outcome was patient satisfaction. The

Myriam TiraULT, M.D.; Lydia FouCAN, M.D.; Bertrand DeBAene, M.D.; Denis F RasCA, M.D.; Thierry LeBRUN, M.D.; Jean-Christophe BernARD, M.D.; Ignace SanDEFo, M.D.; Alain C. Van ElSTRAE T e, M.D.

(*) Department of Anesthesiology, Clinique Saint-Paul, 97 200 Fort-de-France, Martinique, France.

(**) Research Group Clinical Epidemiology and Medicine, EA 4097, University of Antilles-Guyane, 97 159 Pointe-à-Pitre, Guadeloupe, France.

(***) Department of Anesthesiology and Intensive Care, INSERM ERI 23, University Hospital, 86 000 Poitiers, France.

Correspondence address: Myriam TiraULT, Department of Anesthesiology, Clinique Saint-Paul, 97 200 Fort-de-France, Martinique, France.
purpose of our prospective, randomized, double-blinded, placebo-controlled study was to assess the effect of a single preoperative dose of gabapentin on patient preoperative anxiety, compared to placebo and to hydroxyzine that is commonly used for premedication at our institution.

METHODS

Patient Selection

This prospective, randomized, double-blinded, placebo-controlled study was carried out following Institutional Review Board approval. Written informed consent was obtained from 210 inpatients undergoing elective surgery requiring general anesthesia. All patients were between 18 and 65 years of age and had an American Society of Anesthesiologists (ASA) physical status score of I-III.

The exclusion criteria were ASA physical status score of IV-V, history of chronic anxiety, use of antidepressant or anticonvulsant drugs, use of anxiolytic drugs on a regular basis, drug or alcohol addiction, Body Mass Index (BMI) > 35, pregnancy, breast-feeding, presence of hepatic, renal or pulmonary dysfunction, contraindications to any drug used in the study, inability to provide informed consent, and participation in another research project within the preceding 30 days. The evening before surgery, neither anxiolytic nor sedative drugs were administered to the included patients.

Premedication protocol and anxiety measurements

Patients were randomly allocated in a double-blinded fashion to 1 out of 3 possible groups of premedication: gabapentin group, or hydroxyzine group, or placebo group. A physician not involved in data collection created a computerized random number list for use in patient allocation. This list was given to the pharmacist at our institution (who did not participate in patient care) who prepared and delivered the designated drug to each patient according to the randomized allocation. Two hours before surgery, the premedication was administrated orally to the patients: gabapentin group received 1200 mg gabapentin and hydroxyzine’s placebo; hydroxyzine group received 75 mg hydroxyzine and gabapentin’s placebo; and placebo group received hydroxyzine’s placebo and gabapentin’s placebo. The most common dose of gabapentin is 1200 mg in the trials performed on post-operative pain, and this dose has been found to be effective in systematic reviews (11-13). We therefore chose to administer 1200 mg of gabapentin as a premedicant. Group allocation was maintained in opaque envelopes. Patients, anesthesiologists, surgeons, and nurses involved in the study were blinded to the premedication administered to each patient.

The patients were taught how to use a 100-mm visual analogue scale (VAS) with 0-mm representing no anxiety and 100-mm being defined as extreme anxiety. Anxiety level was assessed 3 times: firstly, in the patient’s bedroom before premedication; secondly, when entering the preoperative holding area; and thirdly, in the operating theatre just before induction of anesthesia. The nurse in charge of the patient in the holding area recorded sedation scores and adverse effects due to premedication.

From a methodological standpoint, the gold standard for anxiety evaluation is the Spielberger State-Trait Anxiety Inventory (STAI) (14). However, the STAI’s format that includes 20 multiple-choice questions for the anxiety state alone limits its use as a bedside instrument. On the other hand, the VAS anxiety score has been shown to be as effective as the STAI to measure preoperative anxiety and to be easier to use in clinical practice (4,15). We therefore chose the VAS anxiety score to assess anxiety level. As all included patients were hospitalized the evening before surgery, we were able to teach them calmly how to use the 100-mm visual analogue scale to evaluate their anxiety.

Sedation was measured on a 4-point categorical scale derived from the Ramsay Score as follows: 0 = alert, aware; 1 = somnolent, arousable by verbal contact; 2 = somnolent, arousable by tactile stimulation; and 3 = asleep, arousable by painful stimulation. Adverse effects included dizziness, blurred vision, headache, nystagmus, nausea, vomiting, and respiratory depression.

Patient’s satisfaction

In the operating theatre, standard intraoperative monitoring was performed, and general anesthesia was induced at the discretion of the anesthesiologist in charge of the patient. The day following surgery, patients were asked about their satisfaction concerning the drug they received to reduce their preoperative anxiety: “How satisfied are you with the drugs that were used before the operation to make you feel comfortable? Satisfied to extremely satisfied, or ambivalent to dissatisfied?".
**Statistical Analysis**

The primary endpoint was the level of preoperative anxiety experienced by the patient as measured by the VAS score. Our sample size estimate was based on the expected differences in VAS anxiety scores between the value obtained before premedication and the value obtained upon entering the operating theatre. An open study of VAS anxiety scores before premedication in 50 patients at our institution revealed a mean VAS score of 31 mm ± 25 (mean value ± standard deviation). A sample size estimate indicated that including 55 patients per group would be needed to give a power of 90% with a a level of 0.05 for detecting a 50% decrease in anxiety levels after receiving the study drug. A study size of 165 patients (n = 55 per group) was therefore required to give our study adequate power.

To minimize the effects of data loss, we recruited 70 patients per group. The sample size was thus prospectively set at 210 patients (n = 70 per group).

Quantitative variables (age, weight, height) were reported as mean values ± standard deviation. Normality was assessed using the Kolmogorov-Smirnov test. Repeated-measures analysis of variance (ANOVA) was used to analyze continuous variables (VAS scores). Analysis of variance for paired data and a Bonferroni test were used to study the evolution of the anxiety level overtime in each group. The chi-square test was used to analyze categorical data (gender, ASA physical status score, patient satisfaction, incidence of adverse effects). Spearman test was used to estimate correlation coefficient between preoperative degree of anxiety and the effect of gabapentin. Statistical analysis was performed using SPSS, version 16.0 (SPSS Inc, Chicago, IL). All p values less than 0.05 were considered statistically significant.

**Results**

A total of 210 patients (70 per group) were enrolled in the study. No patient refused to participate. Nine patients were withdrawn from the study, 7 due to protocol violation (4 in the gabapentin group and 3 in the hydroxyzine group) and 2 because surgery was cancelled (1 in the hydroxyzine group and 1 in the placebo group). The final statistical analysis included 201 patients: 66 in the gabapentin group, 66 in the hydroxyzine group, and 69 in the placebo group. Six different types of surgical procedures were performed: ear, nose, and throat surgery (22.4%), orthopaedic surgery (21.9%), spinal surgery (19.4%), gastrointestinal surgery (18.9%), gynaecologic surgery (10.9%), and gastrointestinal endoscopic procedures (6.5%). There was no statistical difference between the groups for different types of surgical procedures.

Patient characteristics (age, BMI, ASA score), negative memories of previous surgical experiences, and the time between premedication administration and arrival in the operating theatre were similar among the three groups (Table 1).

Patients’ anxiety level (as measured by the VAS score) before premedication did not differ according to the type of surgery and was not statistically different among the 3 groups (29 mm ± 24 in the gabapentin group, 27 mm ± 23 in the hydroxyzine group, and 30 mm ± 22 in the placebo group).

However, in the preoperative holding area, gabapentin significantly reduced anxiety as compared to placebo (22 mm ± 22 and 36 mm ± 25 respectively; p = 0.004). At this time, anxiety level in the gabapentin group was not significantly different from the anxiety level in the hydroxyzine group (28 mm ± 21; p > 0.05). Likewise, at the time of induction of anesthesia in the operating theatre, the anxiety level in the gabapentin group (20 mm ± 21) was significantly lower than the anxiety level in the hydroxyzine group (32 mm ± 26; p = 0.023) and in the placebo group (36 mm ± 28; p = 0.004) (Table 2). However, no significant difference in anxiety level was observed between patients receiving placebo and hydroxyzine, all over the study.

The evolution of anxiety level overtime differed among the 3 groups: as early as the arrival in the holding area, anxiety scores in the gabapentin group decreased significantly (p < 0.001), while anxiety scores never changed significantly overtime in the hydroxyzine group and in the placebo group (Fig. 1). There was a high correlation between preoperative degree of anxiety and the effect of gabapentin (r = + 0.65) on Spearman’s analysis. Incidence of adverse effects due to premedication was similar among the three treatment groups (Table 3). Sedation was the most prevalent adverse event in this context, but no patient entered the holding area with a sedation score rated as 2 or 3. No significant differences concerning sedation scores were found among the three groups (p < 0.05) (Table 3).

The gabapentin and hydroxyzine groups had a significantly higher proportion of “satisfied or extremely satisfied” patients (73% and 70% respectively) as compared to the placebo group (48%; p = 0.006).
DISCUSSION

This prospective, randomized, double-blinded, placebo-controlled study confirmed that preoperative anxiolysis produced by a single dose of oral gabapentin was significantly more effective than that produced by hydroxyzine or placebo. No excessive preoperative sedation and no significant preoperative adverse effects were observed. Additionally, patient satisfaction was higher in the gabapentin and the hydroxyzine groups as compared to the placebo group.

Although preoperative anxiety levels have previously been found to be related to gender, age and surgical procedure (16), there was no statistically significant difference noted among the groups in our study, with respect to gender, age, BMI, and surgical procedure (Table 1).

Preclinical data have shown that gabapentin possesses anxiolytic properties (17,18), and clinical evidence has demonstrated the potential anxiolytic effect of gabapentin in psychiatric patients (8,9) and in individuals placed in an anxiogenic situation such as simulated public speaking (19). Gabapentin might therefore be an effective anxiolytic premedicant before surgery. Since after oral administration, peak plasma concentrations of gabapentin are achieved within 2-3 h (17), the premedication was administered two hours before surgery. The most common dose of gabapentin is 1200 mg in the trials performed on post-operative pain, and this dose has been found to be effective in systematic reviews (11-13). We therefore chose to administer 1200 mg of gabapentin as a premedicant. The effects of 1200 mg of gabapentin on preoperative anxiety was previously assessed as a secondary outcome in a recent clinical trial of 40 patients undergoing elective knee surgery (10). In this study, patients’ preoperative anxiety scores were significantly reduced by as much as 57%. Our findings were consistent with the results of this previous study (10). Anxiety level was reduced by as much

---

Table 1

Demographic characteristics, negative memories of previous surgical experiences, and time between premedication and arrival in the OR of included patients

<table>
<thead>
<tr>
<th></th>
<th>Group Placebo (n = 69)</th>
<th>Group Hydroxyzine (n = 66)</th>
<th>Group Gabapentin (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F) (n)</td>
<td>20 / 49</td>
<td>25 / 41</td>
<td>28 / 38</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44 ± 13</td>
<td>47 ± 12</td>
<td>46 ± 12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 3</td>
<td>25 ± 3</td>
<td>25 ± 3</td>
</tr>
<tr>
<td>ASA score of I, II, or III (n)</td>
<td>49, 18, 0</td>
<td>41, 19, 4</td>
<td>42, 20, 3</td>
</tr>
<tr>
<td>Bad memories of previous surgery (n)</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Time between premedication and arrival in OR (min)</td>
<td>200 ± 103</td>
<td>212 ± 89</td>
<td>191 ± 104</td>
</tr>
<tr>
<td>Time between arrival in OR and induction (min)</td>
<td>44 ± 26</td>
<td>36 ± 22</td>
<td>39 ± 24</td>
</tr>
</tbody>
</table>

* Data are presented as mean values ± standard deviation or numbers (n).
  M = male ; F = female ; BMI = Body Mass Index ; ASA = American Society of Anesthesiology.
  No significant differences were found among the three treatment groups.

Table 2

Patients’ anxiety level measured by VAS score overtime: before premedication, when entering the preoperative holding area, and just before induction of anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Group Placebo (n = 69)</th>
<th>Group Hydroxyzine (n = 66)</th>
<th>Group Gabapentin (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival in the holding area</td>
<td>36 ± 25 [29-42†]</td>
<td>28 ± 21 [23-34]</td>
<td>22 ± 22 [17-28]*</td>
</tr>
<tr>
<td>At induction of anesthesia</td>
<td>36 ± 28 [29-43†]</td>
<td>32 ± 26 [26-39]#</td>
<td>20 ± 21 [15-26]*</td>
</tr>
</tbody>
</table>

* Data are (mm), presented as mean values ± standard deviation [95% Confidence Interval].
  Comparison among the 3 groups:
  † Significantly different compared with the gabapentin group (p = 0.004)
  # Significantly different compared with the gabapentin group (p = 0.023)
  Evolution over time inside a group:
  * Significantly different compared with anxiety level before premedication in the gabapentin group only (p < 0.001).
as 30% by gabapentin premedication, and patients’ satisfaction was improved.

The lower decrease of the VAS anxiety score in the present study (30%) as compared with the decrease in the preceding study of Ménigaux (57%) (10) can be explained by the fact that our study was designed to look at preoperative anxiety as primary outcome measurement and, therefore, was powered according to that endpoint.

Interestingly, preoperative anxiety level decreased significantly overtime only in the gabapentin group whereas anxiety score did not significantly vary in the hydroxyzine group and in the placebo group from time of premedication to induction of anaesthesia. Moreover, this declining anxiety level in the gabapentin group was observed since the first measurement after premedication.

The basal anxiety level in the population studied was low, and consequently even a significant decrease in anxiety after premedication might be considered of limited clinical interest. This relatively low preoperative anxiety might be due to the population studied. It is well admitted that anxiety is linked to several factors like education, religion, ancestral beliefs, confidence, fatalism... The population studied in the present study is a population from Caribbean countries for whom obviously apprehension and fear of surgery and anaesthesia is minimal, and confidence in medical teams is high. The study might have possibly gained in power in other countries like European countries where the basal preoperative anxiety is probably much higher (10).

In our study, in spite of the rather high dose of gabapentin used (1200 mg), no significant or
serious adverse effects were found to be associated with gabapentin in the preoperative period, as compared to hydroxyzine or to placebo. However, powering the study on occurrence of adverse effects would have probably needed a much larger population of patients. Therefore, because of the small number of patients studied, we are unable to draw any definite conclusion about occurrence of adverse effects. On the other hand, a limitation of the study could be that adverse effects were not assessed in the postoperative period. As a result, the occurrence of adverse effects and the optimal anxiolytic dosing of gabapentin need to be estimated (11), and further powered investigations are warranted in obese patients, in elderly patients, or in case of renal dysfunction. Another limitation of the study is that the length of stay in the Post-Anesthesia-Care-Unit has not been assessed, impeding estimation of a potential increased cost.

We chose to use hydroxyzine 75 mg as an active comparator in the control groups, as we wanted to compare gabapentin with our routine premedication. Hydroxyzine is an unique non-phenothiazine drug that has bronchodilator and antihistaminic effects, possesses anticholinergic properties, and is useful in the treatment of motion sickness-induced nausea, insomnia, as well as notably for the treatment of mild anxiety. Hydroxyzine is an effective sedative, hypnotic, and tranquilizer. However, abuse, dependence, addiction, and toxicity potential are minimal. Hydroxyzine has been found to be an effective surgical premedicant in several studies (20-22). In our study, hydroxyzine failed to decrease anxiety scores from time of premedication to induction of anaesthesia. However the day following surgery, patients’ satisfaction concerning premedication was high and nearly the same in the hydroxyzine group as in the gabapentin group. At the opposite, our results did not demonstrate that hydroxyzine provided better anxiolysis than placebo, but patients’ satisfaction in the hydroxyzine group was significantly higher than in the placebo group. This surprising result could lie in the fact that the effect of light somnolence provided by hydroxyzine premedication should conferred to the patient a certain degree of “comfort” when waiting for surgery.

It is noteworthy that nearly 50% of patients in the placebo group reported being satisfied or extremely satisfied with their premedicant. Therefore, clinicians should try to maximize patients’ awareness of their treatment and attempt to modulate patients’ expectations regarding the efficacy of the treatment they receive (23).

Our results emphasize that research regarding placebo use and anxiolysis that explores both psychological and neurobiological mechanisms is needed to improve the efficacy of preoperative anxiolysis. However, comparing gabapentin with an effective anti-anxiolytic drug like benzodiazepine would be valuable.

Interestingly, it has been recently reported that pregabalin, a new analog of gabapentin, possesses an early onset anxiolytic efficacy after a single dose (24). However, pregabalin failed in a recent clinical study to reduce preoperative anxiety despite an increase in preoperative sedation at the administered dose (25). Clearly, subsequent studies would be valuable to confirm the results of this study.
In summary, our findings confirmed that gabapentin might improve preoperative anxiolysis and patient satisfaction. We suggest that gabapentin may therefore be considered as a possible premedicant in patients undergoing elective surgery. However, further powered clinical investigations should define the appropriate dosing of gabapentin, and occurrence of adverse effects.

References

22. Herr G. P., Conner J. T., Schehl D., Dorey F., Comparison of i.m. diazepam and hydroxyzine as premedicants, Br. J. ANAESTH., 54, 3-9, 1982.

© Acta Anaesthesiologica Belgica, 2010, n° 4