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Effectiveness of Triazolam, Diazepam, and Placebo as Preanesthetic Medications

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Eighty-three ASA Physical Status 1-2 patients were orally premedicated with triazolam (0.125, 0.25, or 0.5 mg), diazepam (5, 10, or 15 mg), or placebo to evaluate the effectiveness of these drugs and doses in reducing preoperative anxiety, providing sedation, and producing amnesia. The drug treatments were administered in a randomized, double-blind manner. The results obtained with each drug (dose) group were compared against those of the placebo group as a control. Changes in anxiety at 60 min after drug administration were evaluated: 1) by a trained anesthesia nurse clinician using an analog scale, 2) by the patient using the same analog scale, and 3) by the patient with the Multiple Affect Adjective Check List (MAACL). Changes in sedation at 60 min were also evaluated by the patient and nurse clinician using an analog scale. Amnesia was assessed by postoperative recall of picture cards shown to the patient 1 h after receiving preanesthetic medication. There were no significant differences between any drug (dose) and placebo for changes in patient-evaluated anxiety or sedation on the analog scale. With the other measures of anxiety, only triazolam (0.5 mg) reduced anxiety more than did placebo on both the patient (MAACL) and the nurse (analog) scales. With the nurse (analog) measure of sedation, only the highest doses of triazolam and diazepam were more sedating than placebo. Triazolam (0.5 mg) was the only drug dose that produced significant amnesia. The authors conclude that drug effects on anxiety, sedation, or amnesia that are statistically significant *versus* placebo effect are seen at only the highest doses of triazolam (0.5 mg) and diazepam (15 mg). (Key words: Hypnotics: diazepam; triazolam. Premedication: amnesia; anxiety; sedation.)

A SUPPORTIVE PREANESTHETIC visit by the anesthesiologist effectively reduces apprehension.[1] In addition, preanesthetic medication is frequently ordered to provide amnesia, sedation, and additional anxiolysis.[2,3] Preanesthetic medication can also decrease the physiologic concomitants of stress and anxiety (tachycardia, hypertension, elevated serum catecholamine levels) which may lead to a more hemodynamically stable induction of anesthesia.[4,5]

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Currently, benzodiazepines are popular preanesthetic medications because their anxiolytic, sedative, and amnestic properties are combined with minimal cardiovascular and respiratory depression.[4,6] Although some studies have questioned the efficacy of benzodiazepines, particularly diazepam, in reducing anxiety,[7–9] differences in experimental design and methodology may well account for differences in outcome. In the present work, we examined the effectiveness of diazepam and triazolam as preanesthetic medications. Using a randomized, double-blind treatment protocol, we compared three different doses of each drug with placebo for anxiolysis, sedation, and amnesia. We evaluated the effects of these drug doses 60 min after oral administration, as this is a commonly employed time interval from drug ingestion to arrival in the preoperative area. Levels of anxiety and sedation were evaluated both by an anesthesia nurse clinician and by the patient. Amnesia was evaluated by recall of picture cards shown to the patient 1 h after receiving their preanesthetic medication.

Methods

Eighty-three adult patients (ASA PS 1–2) scheduled for elective surgery were studied according to a protocol approved by our institutional review board. The surgical procedures were classified as abdominal (hysterectomy, bowel resection, lysis of adhesions, cholecystectomy, ovarian cystectomy) or peripheral (mastectomy, inguinal herniorrhaphy, resection of hidradenitis, orthopedic surgery, or ENT procedures). The evening prior to surgery the anesthesiologist assigned to the case performed a history and physical exam. If the patient satisfied admission criteria for the study (18–55 yr old, ASA physical status 1–2, 55–100 kg, no history of habitual CNS stimulant/depressant use, no CNS disease), a member of the study team explained the aims of the study to the patient and obtained informed consent. The following morning, approximately 1½ h prior to surgery, the anesthesia nurse clinician evaluated the patient's level of anxiety and sedation (see below). Concurrently, the patients evaluated their own levels of anxiety and sedation. The oral preanesthetic medication specified by the randomization code was then administered to the patient by a staff nurse not otherwise involved in the study. One hour later, anxiety and sedation evaluations were repeated by both the patient and the nurse clinician. This time period was chosen

for evaluation of drug effect, since this is a common time interval between oral preanesthetic medication administration on the ward and arrival of the patient in the preoperative area. At this time, the patient was also shown two different picture cards for recall testing. Anesthesia consisted of thiopental, fentanyl, droperidol, isoflurane or enflurane, N_2O, oxygen, and muscle relaxation, none of which has been shown to produce retrograde amnesia. The day following surgery, the patient was asked to recall the two picture cards shown 1 h after receiving the preanesthetic medication.

Test Groups

Patients were randomly assigned to one of seven test groups—triazolam (0.125, 0.25, 0.5 mg), diazepam (5, 10, 15 mg), or placebo. There were 11 or 12 patients per test group.

Anxiety Evaluation

Patients evaluated their own level of anxiety using the Multiple Affect Adjective Check List (MAACL) test developed by Zuckerman.[10] This test has been shown to be a sensitive measure of the anxiolytic effects of preanesthetic medication.[11,12] Patients selected words describing their mental/emotional state from a list containing 11 anxiety-present and 10 anxiety-absent words. Anxiety level was scored as the sum of anxiety-present words selected plus anxiety-absent words *not* selected. The possible range of scores is from 0–21, with the higher scores reflecting greater anxiety.

A second method of anxiety evaluation was performed separately by both the patient and the nurse clinician before and 1 h after receiving medication. Both the patient and the nurse clinician independently rated the level of anxiety on an analog scale from 1–10 (*e.g.*, 1 = calm and smiling; 5 = verbally expressing anxiety; 10 = crying, wringing hands).

These tests were performed immediately before (at 0 min) and again at 60 min after administration of the preanesthetic medication. The 60 min scores were compared to the 0 min scores as a measure of drug effect on an absolute basis. The difference (Δ) between the 60 min and 0 min scores, representing the change in anxiety level for patients within each treatment group, was then compared to the change obtained with placebo to measure drug effect relative to placebo effect.

Sedation Evaluation

Sedation was measured by both the patient and nurse clinician on an analog scale from 1–10 (*e.g.*, 1 = wide awake and alert; 5 = beginning to lose interest in remaining awake; 10 = cannot be kept awake for further evaluation). Both the patient and the nurse clinician independently evaluated the patient's level of sedation before and 60 min after medication. Within each group, the 60 min score was compared to the 0 min sedation score to assess the absolute drug effect. The Δ in sedation for each group was then compared to the Δ produced by placebo to measure the effectiveness of the drug *versus* placebo.

Recall Evaluation

Each patient was shown two picture cards at the 60 min postmedication evaluation. The patient was asked to remember these pictures and told that he or she would be asked to recall the picture cards the next morning.

Statistical Analysis

Uniformity among the seven treatment groups with regard to age, weight, PACU (recovery room) time, as well as for baseline (premedication) values of anxiety and sedation, was examined by analysis of variance. The distributions of sex, ASA physical status, and type of surgery were compared using the chi-squared test. For anxiety and sedation, the 0 min *versus* 60 min comparisons within each treatment group were done using the sign test (nonparametric equivalent of the paired *t* test), with significance ($P < 0.05$) denoted by (*) in the 60 min column of tables 2 and 3. The difference (Δ) between the 0 and 60 min values for each treatment group was compared against the Δ for the placebo group using the Mann Whitney U test, with significance ($P < 0.05$) denoted by (†) in the Δ column. The proportion of correctly recalled pictures was compared between drug treatment and placebo groups *via* Fisher's exact test.

Results

All seven treatment groups were comparable with respect to age, sex, weight, ASA physical status, PACU (recovery room) time, type of surgery (see table 1), and baseline anxiety and sedation scores (see tables 2 and 3).

Anxiety (table 2) as measured by the nurse clinician on the analog scale was significantly reduced at 60 min by all treatments except two—placebo and the lowest diazepam dose (* in 60 min column). However, only the highest triazolam dose (0.5 mg) reduced anxiety more than did placebo († in Δ column). Anxiety measured by the patient on the analog scale was significantly reduced only with the highest diazepam dose and highest and lowest triazolam doses; no treatment proved superior to placebo. Patient-evaluated anxiety measured with the MAACL showed significant anxiolysis in all treatment groups except placebo and triazolam 0.25 mg (* in 60 min column), while the highest doses of both triazolam and diazepam were also significantly better than placebo († in Δ column).

TABLE 1. Characteristics of Patients Receiving Preanesthetic Medication

Drug	N	Age (yr)	Sex (M:F)	Weight (lb)	ASA Status (1:2)	PACU Time (min)	Type of Surgery (abd:periph)
Placebo	12	39 ± 3	3:9	154 ± 5	10:2	141 ± 11	9:3
Triazolam							
0.125 mg	12	34 ± 2	2:10	149 ± 8	8:4	157 ± 14	9:3
0.25 mg	12	39 ± 4	2:10	153 ± 10	7:5	129 ± 14	8:4
0.5 mg	12	40 ± 4	2:10	154 ± 4	8:4	121 ± 9	8:4
Diazepam							
5 mg	11	36 ± 3	1:10	162 ± 11	7:4	135 ± 17	7:4
10 mg	12	40 ± 3	3:9	161 ± 9	8:4	143 ± 8	9:3
15 mg	12	34 ± 2	3:9	147 ± 8	10:2	137 ± 9	7:5

Ages, weights, and PACU times are given as group means ± SEM. There are no statistically significant differences among groups for any of the variables shown.

Sedation (table 3) evaluation by the nurse clinician on the analog scale showed significant increases in sleepiness with all treatments except placebo and the lowest dose of diazepam (5 mg). The highest dose of both triazolam and diazepam also produced significantly more sedation than did placebo. Sedation evaluated by the patients on the analog scale increased significantly in all treatment groups except placebo, although in no group did patient-evaluated sedation attain a level significantly greater than with placebo.

Recall of picture cards 24 h after surgery (table 4) was significantly impaired only at the highest triazolam dose. There was 100% recall with placebo and diazepam (5 mg, 10 mg).

Discussion

This study was designed to evaluate triazolam and diazepam as preanesthetic medication while avoiding certain methodological limitations of previous studies. Our study was randomized and double-blinded to reduce bias in both the selection of patients and the evaluation of drug treatment. We tested triazolam and diazepam over a range of commonly used doses rather than comparing a single dose of one benzodiazepine to a single dose of another. By looking at several doses of each drug, we avoided assumptions concerning relative potencies between drugs and doses, which are difficult to measure precisely and which may vary with the pharmacological effect being studied.[8] Finally, inclusion of placebo controls has not been a consistent feature of previous work. The importance of placebo treatment is illustrated by the results of this study and others[7,9,13,14] in that effects of specific drug treatment may be significantly different from those of no treatment at all but fail to attain statistical significance when compared with effects of placebo treatment.

We evaluated the effects of triazolam and diazepam at

TABLE 2. Anxiety Scores in Patients Receiving Preanesthetic Medication

Drug	Nurse/Analog			Patient/Analog			Patient/MAACL		
	0 min	60 min	Δ	0 min	60 min	Δ	0 min	60 min	Δ
Placebo	3.9	3.4	−0.5	4.1	3.2	−0.9	8.6	8.8	+0.3
	(0.3)	(0.4)	(0.5)	(0.8)	(0.7)	(1.0)	(0.9)	(1.0)	(0.4)
Triazolam									
.125 mg	3.9	2.7*	−1.3	4.1	3.0*	−1.2	10.5	8.8*	−1.7
	(0.3)	(0.6)	(0.4)	(0.9)	(0.8)	(0.5)	(1.1)	(1.0)	(0.6)
.250 mg	3.8	2.7*	−1.1	3.8	3.4	−0.4	8.5	8.1	−0.4
	(0.2)	(0.3)	(0.3)	(0.6)	(0.5)	(0.7)	(0.9)	(0.8)	(0.5)
.500 mg	4.6	2.7*	−2.0†	5.5	4.2*	−1.3	11.3	8.7*	−2.7†
	(0.3)	(0.4)	(0.4)	(0.6)	(0.8)	(0.6)	(0.8)	(0.9)	(0.8)
Diazepam									
5 mg	4.2	3.1	−1.1	4.2	3.2	−1.0	10.2	8.8*	−1.4
	(0.4)	(0.6)	(0.6)	(0.6)	(0.8)	(0.8)	(0.7)	(0.8)	(1.0)
10 mg	3.6	2.3*	−1.3	2.8	2.0	−0.8	8.3	6.9*	−1.4
	(0.3)	(0.3)	(0.4)	(0.5)	(0.5)	(0.3)	(1.3)	(1.0)	(0.7)
15 mg	4.2	3.1*	−1.1	3.8	3.1*	−0.7	11.5	9.0*	−2.6†
	(0.4)	(0.6)	(0.4)	(0.4)	(0.5)	(0.4)	(0.9)	(0.7)	(0.9)

Values given are group means, with 1 SEM in parenthesis below.
Δ = 60 min value minus 0 min value.
* $P < 0.05$ *vs.* 0 min value for the same group.
† $P < 0.05$ *vs.* Δ value for placebo group.

60 min after oral administration, as this is a typical elapsed time between preanesthetic medication and arrival in the operating room[2] both in practice and in previous research studies. At physiologic *p*H, all benzodiazepines are highly lipid soluble and rapidly absorbed following oral ingestion.[15] Both diazepam and triazolam have similar onset times. Following oral administration, plateau drug concentrations are achieved in 30 min for both diazepam and triazolam and maintained for 120 min for diazepam[16] and 180 min for triazolam.[17] Based on these pharmacokinetic data, we feel that our evaluation of anxiety and sedation, 1 h after oral administration of the drug, occurred during the plateau drug concentration. However, it is possible that due to individual patient variation, an adequate drug level may not yet have been attained at the time of patient evaluation and that additional drug effect may have appeared at a later time. It is also possible that additional drug significance may have appeared if the group sizes were increased. However, the use of each patient as his or her own control reduced baseline variability and added statistical significance to these numbers. More importantly, if large numbers of patients are needed in each group to prove statistical significance, this would probably not translate into a consistent and important clinical effect in any individual patient.

We also employed several measures of anxiety to assess treatment efficacy. Our rationale for this was that anxiolysis may be perceived and evaluated differently by the anesthesiologist and the patient. This concept is supported by Forrest *et al.*[7] and by Male *et al.*[8], who reported that patient evaluations varied significantly from physician evaluations when benzodiazepines were administered as preanesthetic medication. The difference between self- and non-self evaluations, also observed in our study, may be explained in several ways. It is possible that evaluation criteria used by patients were more heterogeneous, since each patient has his or her personal definition of, and tolerance for, anxiety. Another factor which could have limited the discriminative power of patient evaluation is that each patient performed only a single pair of evaluations, so that practice and consistency in use of the analog scale was limited. Additionally, it was possible that the patients' perception of the evaluation system was altered by the effect of the preanesthetic medication on mental status. The MAACL system of anxiety evaluation requires less explanation and is easier for patients to understand and perform. The amnestic and sedative actions of the medication are more likely to have impaired the patient's ability to perform a reliable and consistent analog self evaluation. The nurse clinician, on the other hand, was not subject to any of these limitations on the accuracy and consistency of her performance. Interestingly, no drug attained significance *versus* placebo when the patient used an analog scale.

TABLE 3. Sedation Scores in Patients Receiving Preanesthetic Medication

Drug	Nurse/Analog			Patient/Analog		
	0 min	60 min	Δ	0 min	60 min	Δ
Placebo	1.2 (0.2)	2.4 (0.6)	+1.2 (0.7)	1.6 (0.3)	2.3 (0.4)	+0.7 (0.6)
Triazolam						
.125 mg	1.2 (0.2)	3.5* (0.5)	+2.3 (0.5)	2.2 (0.3)	4.0* (0.6)	+1.8 (0.7)
.250 mg	1.4 (0.2)	4.3* (0.8)	+2.8 (0.7)	2.3 (0.5)	4.4* (0.7)	+1.8 (0.6)
.500 mg	1.5 (0.3)	5.4* (0.8)	+3.9† (0.7)	2.4 (0.8)	4.6* (0.7)	+2.2 (0.7)
Diazepam						
5 mg	1.7 (0.3)	2.1 (0.4)	+0.4 (0.5)	2.3 (0.3)	3.4* (0.4)	+1.1 (0.6)
10 mg	1.2 (0.1)	2.8* (0.3)	+1.6 (0.3)	1.9 (0.4)	3.6* (0.7)	+1.8 (0.8)
15 mg	1.3 (0.1)	5.4* (0.9)	+4.1† (1.0)	1.9 (0.6)	4.7* (0.8)	+2.4 (1.0)

Values given are group means, with 1 SEM in parenthesis below.
Δ = 60 min value minus 0 min value.
* $P < 0.05$ *vs.* 0 min value for the same group.
† $P < 0.05$ *vs.* Δ value for placebo group.

In our study, anxiety evaluations done by the nurse clinician demonstrated decreases in anxiety with all triazolam doses; however, only the highest triazolam dose was significantly better than placebo in treating anxiety. These data correlate with Pinnock *et al.*[18], who also showed no significant decrease in anxiety *versus* placebo with triazolam (0.25 mg) using a similar scale. Diazepam (10, 15 mg) also showed an anxiolytic effect in our study that was not significantly different from placebo. These results are consistent with those from other studies[8,9] showing little reduction in anxiety compared to placebo when oral diazepam was used as a preanesthetic medication. When our patients assessed their own anxiety level using the analog scale, no treatment group showed an advantage over placebo. We are unable to explain why the middle dose of triazolam (0.25 mg) showed no effect using patient self evaluations. However, using the

TABLE 4. Recall Following Preanesthetic Medication

Drug	Dose	% Recall
Placebo		100
Triazolam	0.125 mg	95
	0.25 mg	82
	0.5 mg	63*
Diazepam	5 mg	100
	10 mg	100
	15 mg	82

Data are given as the proportion recalled (in %) out of the total number of cards shown to patients in each group.
* $P < 0.05$ *vs.* placebo.

MAACL evaluation, the highest doses of both triazolam and diazepam were significantly anxiolytic compared to placebo. This agrees with work by Jakobson *et al.*[14]

Similar to the work by Waserman *et al.*[12] we found that the nurse clinician's analog evaluation paralleled the patient's MAACL evaluation in demonstrating significant anxiolysis *versus* placebo. The patient's self evaluation using the analog scale was less consistent, especially in the measurement of sedation. Not infrequently, when the evaluator had to wake the patient so he or she could perform the analog sedation evaluation, the patient marked the scale as "not sleepy" or "wide awake." Our data using the nurse clinician's analog evaluation of sedation are consistent with those of Longbottom and Pleurry,[6] who showed significant increase in sedation with triazolam (0.25, 0.5 mg), and of Kothary *et al.*,[19] who showed increasing sedation with diazepam. Conversely, Forrest *et al.*[7] showed no sedative effect with diazepam *versus* placebo. This last result does not necessarily conflict with ours: Forrest used intramuscular diazepam administration, which has erratic absorption;[20] whereas we used oral administration, which produces predictable blood levels in 30 min.[16,20]

Amnesia is classically tested by showing picture cards and asking the patient to recall them at a later time. Using this method we showed that only high-dose triazolam (0.5 mg) produced significant amnesia. It has been questioned whether testing for amnesia using picture cards shown to patients prior to anesthesia is valid. Anesthetic drugs can produce antegrade amnesia; however, anesthesia has not been shown to have any retrograde amnestic qualities.[21] Additionally, 100% of placebo-treated patients remembered all picture cards, further confirming the inability of an anesthetic to produce retrograde amnesia. Our results are consistent with those of Male *et al.*,[8] Pinnock *et al.*,[18] and Kothary *et al.*[19] It should be mentioned that amnesia attained with emotionally neutral picture cards may not be equivalent to providing amnesia for "emotionally significant events"[4,8] (including perioperative events) and that not all patients want to be amnestic during the preoperative period.

In summary, our study demonstrates that triazolam (0.5 mg) is the only drug (dose) tested that provides significant anxiolysis, sedation, and amnesia when compared to the placebo effect, while diazepam (15 mg) produced significant anxiolysis and sedation. Lower doses of triazolam (0.125, 0.25 mg) and diazepam (10 mg) reduced anxiety and sedation but did not differ from placebo. However, we cannot necessarily conclude that triazolam 0.5 mg is the preanesthetic medication of choice for all patients, since the needs for anxiolysis, sedation, and amnesia are not uniform.

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