
Comparison of oral triazolam and nitrous oxide with placebo and intravenous diazepam for outpatient premedication

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Triazolam was evaluated as an oral sedative agent for dental outpatients in two studies in the oral surgery model. The first study demonstrated that 0.25 mg of triazolam in combination with nitrous oxide provides therapeutic effects but with a more rapid recovery than a 0.50 mg dose in combination with nitrous oxide. In the second study, triazolam produced a significant anxiolytic effect that was comparable to the effects of diazepam titrated to the usual clinical endpoint (mean dose = 19.3 mg). Less impairment in cognitive-psychomotor impairment and ambulatory function was seen after triazolam in comparison with diazepam. Triazolam appears to be a safe, effective alternative to parenteral sedation with a benzodiazepine for dental outpatients.

(ORAL SURG ORAL MED ORAL PATHOL 1993;75:156-64)

Parenteral premedication has become a standard alternative to general anesthesia for apprehensive dental outpatients. The most widely used combination¹ is a benzodiazepine, either diazepam or midazolam, administered in conjunction with an opioid such as meperidine or fentanyl by titration. The limited data available suggest that parenteral premedication is much safer than general anesthesia.² General anesthesia and parenteral premedication, however, are used primarily by oral surgeons and only a limited number of other dentists³ with appropriate training. Thus the vast majority of patients who seek dental care for procedures other than oral surgery and who would benefit from pharmacologic methods of anxiety control do not have access to general anesthesia or parenteral premedication.

The use of oral premedication as an alternative to

the parenteral route of administration is limited by the prolonged onset of activity after oral administration, the inability to titrate the dose on the basis of the patient's response, limited efficacy because of lower blood levels (in comparison with a similar dose administered parenterally), and more delayed recovery. Clinicians have attempted to overcome some of these disadvantages by using higher than recommended doses of single agents or by combining two or more agents to achieve faster onset, greater peak effects, or longer duration. Although scientifically acceptable documentation of putative advantage for such strategies is often lacking, reports of clinical manifestations of toxicity have accumulated.⁴⁻⁷ The limitations of agents traditionally used for oral sedation and their potential clinical toxicity suggest that a therapeutic need exists for an oral agent or combination of agents that provides onset appropriate for an outpatient dental environment, effective anxiety reduction to permit performance of a dental procedure with local anesthesia, safety, and relatively rapid recovery.

Triazolam (Halcion) is a benzodiazepine hypnotic agent that is rapidly absorbed after oral administration. Peak plasma levels are reached within 1 to 2

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0030-4220/93/\$1.00 + .10 7/12/42062

hours after oral administration but decrease rapidly with the formation of inactive metabolites.⁸ Side effects are a direct extension of its pharmacologic properties and include drowsiness, dizziness, and incoordination.⁸ No respiratory depression has been detected at the highest doses that are used clinically (0.25 to 0.50 mg).⁹ The pharmacologic profile of triazolam suggests that it be evaluated as an oral premedication agent for use in dental outpatients. The present study sought to demonstrate that triazolam results in anxiety reduction in a dental outpatient setting and that greater efficacy can be achieved with the addition of nitrous oxide. Comparison was made with a placebo to demonstrate the independent effect of each agent alone and to intravenous (IV) diazepam as a prototypic parenterally administered benzodiazepine.

METHODS

Two studies were conducted in series first, to determine the triazolam dose to be evaluated in combination with nitrous oxide and, second, to compare the effects of triazolam plus nitrous oxide with placebo and IV diazepam. The subjects for both studies consisted of healthy dental outpatients who required the surgical removal of impacted third molars.

Study No. 1: Dose response study

All subjects completed a battery of psychomotor and subjective questionnaires approximately 75 minutes before the start of the procedure (baseline observation). One of four oral drugs was administered randomly to the subjects (N = 12/group) 60 minutes before the surgical procedure: a placebo, 0.125 mg triazolam, 0.25 mg triazolam, or 0.5 mg triazolam. A second set of psychomotor tests and subjective questionnaires were completed 45 minutes later to measure the effects of the oral medication (postdrug observation). A nasal hood was placed, and 50% nitrous oxide administered in combination with 50% oxygen for 10 minutes before the start of surgery and continued until the completion of the last extraction. Local anesthesia consisting of 2% lidocaine with 1:100,000 epinephrine was administered 5 minutes before the procedure. The efficacy of anesthesia was tested by the presence of lower lip paresthesia and nonresponsiveness to probing of the mucosa overlying each tooth with a probe. The surgical procedure was interrupted at 15 minutes for presentation of a picture to test postoperative recall, and subjective questionnaires were administered to patients to rate their pain and apprehension during the procedure (intraoperative observation). A different picture was presented, and set of questionnaires completed at the end of the pro-

Table I. Allocation of drug treatments for factorial comparison of triazolam and nitrous oxide to parenteral premedication

| Drug group | Oral drug | Inhalational drug | Intravenous drug |
|--------------------------------|-------------------|----------------------|------------------|
| Placebo | Placebo | 100% O ₂ | Placebo |
| Triazolam | 0.25 mg triazolam | 100% O ₂ | Placebo |
| N ₂ O | Placebo | 40% N ₂ O | Placebo |
| Triazolam and N ₂ O | 0.25 mg triazolam | 40% N ₂ O | Placebo |
| Diazepam | Placebo | 100% O ₂ | Diazepam |

cedure (end of surgery observation). Subjects remained at the clinic for 120 minutes after surgery to test recovery of psychomotor skills and ambulatory function (postoperative observations). Before dismissal, subjects completed a questionnaire of their recall of intraoperative events, circled the pictures that they recalled from a composite figure, and completed a global evaluation of the sedative medication. Recall and the global evaluation were reexamined by phone 24 hours later (24-hour observation).

Study No. 2: Comparison of triazolam and nitrous oxide with placebo and diazepam

The second study was similar in design to study No. 1 with the addition of intravenous (IV) drug administration. Five groups of subjects (N = 15/group) were randomly allocated to receive either 0.25 mg of triazolam orally, 40% nitrous oxide, 0.25 mg of triazolam plus 40% nitrous oxide, IV diazepam (Valium), or a placebo. All subjects received oral drug or a matching placebo 60 minutes before surgery (Table I). Nitrous oxide 40% with 60% oxygen or 100% oxygen was administered starting 10 minutes before the procedure. IV diazepam was titrated to the usual clinical endpoint of drooping eyelids (Verrill's sign), slurring of speech, and patient subjective report of relaxation starting 8 minutes before the procedure by an investigator who was not a part of the double-blind procedure and who did not participate in the subjective data collection. A saline solution placebo was administered in a similar fashion in an attempt to maintain the patients' ignorance of the IV drug. All other aspects of the experimental design, data collection, and surgical procedure were identical to the first study.

Dependent measures

Dental anxiety trait was quantified before surgery with Corah's dental anxiety scale.¹⁰ The subjects' subjective report of anxiety state before and during

Table II. Subjective measures of drug efficacy for dose-response study

| Treatment group | Anxiety* | Pain | Global evaluation | Efficacy of sedation | Patient cooperation |
|-----------------|------------|-----------|-------------------|----------------------|---------------------|
| Placebo | 1.7 ± 4.8 | 0.8 ± 0.8 | 2.5 ± 1.3 | 1.4 ± 0.6 | 2.9 ± 1.6 |
| Triazolam | | | | | |
| 0.125 mg | 0.3 ± 7.3 | 0.3 ± 0.7 | 2.9 ± 1.2 | 1.8 ± 0.7 | 1.5 ± 1.8 |
| 0.25 mg | -0.1 ± 4.9 | 0.7 ± 0.7 | 3.4 ± 0.9 | 2.0 ± 0.6† | 1.5 ± 1.3† |
| 0.50 mg | -0.2 ± 5.7 | 0.9 ± 0.7 | 3.2 ± 0.8 | 1.8 ± 0.9 | 2.2 ± 1.5 |

*Change in anxiety report from baseline observation to intraoperative observation as measured by Corah's Interval Scale of Anxiety Responses.

†P < 0.05 in comparison with placebo.

the procedure were measured with Corah's interval scale of anxiety response.¹¹ At the intraoperative observation, subjects were instructed "to select the term that best describes how nervous you were during surgery." In the second study, a similar scale was used to evaluate nervousness that represented anxiety on a vertical continuum that ranged through 12 categories from "not nervous" to "extremely nervous." Intermediate categories were represented by the word "nervous" preceded by other adverb modifiers such as slightly, moderately, or very. Numerical values for each adverb modifier were determined previously and found to be independent of the word modified (for example, painful, unpleasant). These categories were spaced along the line at intervals that represented the mean value derived from these previous psychophysical measurements.^{12,13} Subjects were instructed to "mark on the scale how nervous you are now."

Pain was measured with a four-point category scale (none, slight, moderate, or severe pain) and with eight words that described pain intensity on the basis of a previously validated graphic rating scale.¹⁴ The digit symbol substitution test¹⁵ measured cognitive-psychomotor impairment. Ambulatory function was quantified on a six-point scale as: able to sit for 10 seconds (1), stands with support for 10 seconds (2), stands without support for 10 seconds (3), walks with support for 6 feet (4), walks without support for 6 feet (5), or line-walks for 6 feet (6). Alertness was rated on a five-point scale as: does not respond (1), responds only after mild prodding (2), responds only after name is called loudly and repeatedly (3), responds lethargically (4), or responds readily (5).

At the completion of oral surgery, the observer and surgeon rated the efficacy of sedation on a four-point category scale as: poor (0), fair (1), good (2), or excellent (3). The surgeon and observer also rated patients' cooperation during the procedure on the basis of movements and verbalizations, which ranged from totally cooperative (0) to major interference with the procedure (9).

Blood pressure and pulse were recorded at each observation as well as every 5 minutes during the pro-

cedure with an automatic blood pressure device (Sentron, Bard Biomedical, Lombard, Ill.). Chest movements were observed over 20 seconds to estimate respiration rate. Concurrent administration of oxygen with the nitrous oxide prevented meaningful assessment with pulse oximetry; monitoring of carbon dioxide (capnography) was not available. A global evaluation of the sedative medication was categorized by the patient before discharge from the clinic at 120 minutes as: poor (0), fair (1), good (2), very good (3), or excellent (4). The type and severity of side effects were recorded before dismissal and at 24 hours later.

Statistical analyses

Categoric data were analysed by Kruskal-Wallis analysis of variance followed by pair-wise comparisons with the Mann-Whitney test. The incidence of recall of picture cards shown and clinical events was evaluated with Chi-square tests. The area under the curve was estimated by time-weighted totals of scores for alertness, digit symbol substitution test, and recovery of ambulatory function, and tested for linearity by regression analyses. Two-way analysis of variance was used to evaluate the drug effects of triazolam and nitrous oxide and their interaction in the second study. Comparisons between treatment groups were made by one-way analysis of variance followed by Duncan's Multiple Range Test.

RESULTS

Study No. 1: Dose response study.

Triazolam differed from the placebo on several measures of drug efficacy (Table II). The mean rating of the efficacy of sedation by the surgeon and observer was significantly better for the 0.25 mg dose of triazolam than the placebo (P < 0.05). The mean rating for this dose was equivalent to a rating of "good" with individual patient responses ranging from "fair" to "excellent." Both of the other doses of triazolam and the placebo group had lower mean ratings as well as individual scores equivalent to "poor" sedation. Patient cooperation was also significantly

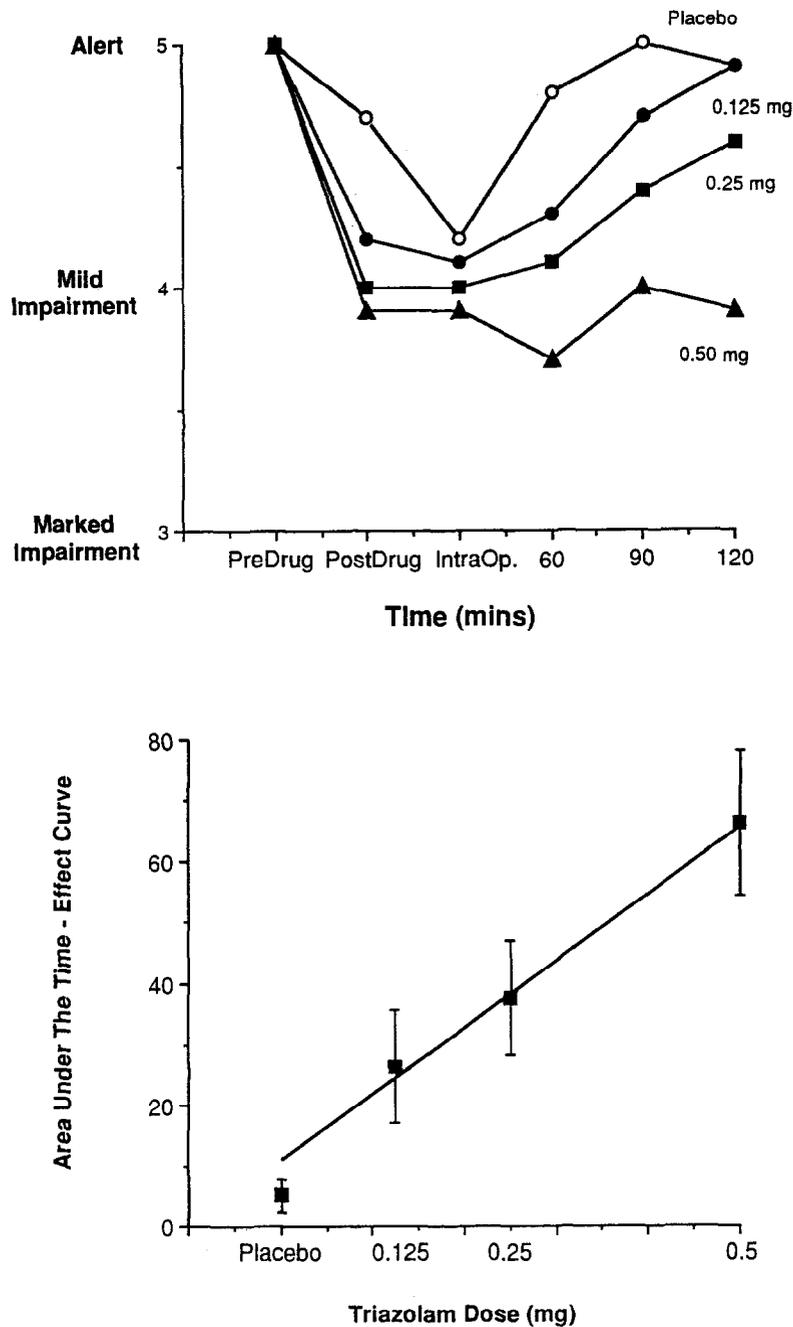


Fig. 1. Decrease in alertness. Top, Effect on alertness over time of 0.125 mg, 0.25 mg, and 0.5 mg of triazolam in comparison with placebo. Bottom, Linear decrease in alertness with increasing triazolam dose.

better after 0.25 mg of triazolam than the placebo ($P < 0.05$) with little or no interference with the procedure. A similar mean level of cooperation was produced by the 0.125 mg dose but with greater variability between patients; the 0.5 mg dose produced somewhat worse patient cooperation. Patients who received the placebo exhibited the greatest amounts of disruption in the procedure, although the average rating for

this group was equivalent to "minor" interfering movements and "some" verbalizations.

Patient self-report of anxiety was decreased after all three doses of triazolam; reaction to the three doses did not differ significantly from reaction to the placebo nor was a dose response relationship seen. Patients reported "slight" pain during the procedure with no difference between groups. Subjects' global

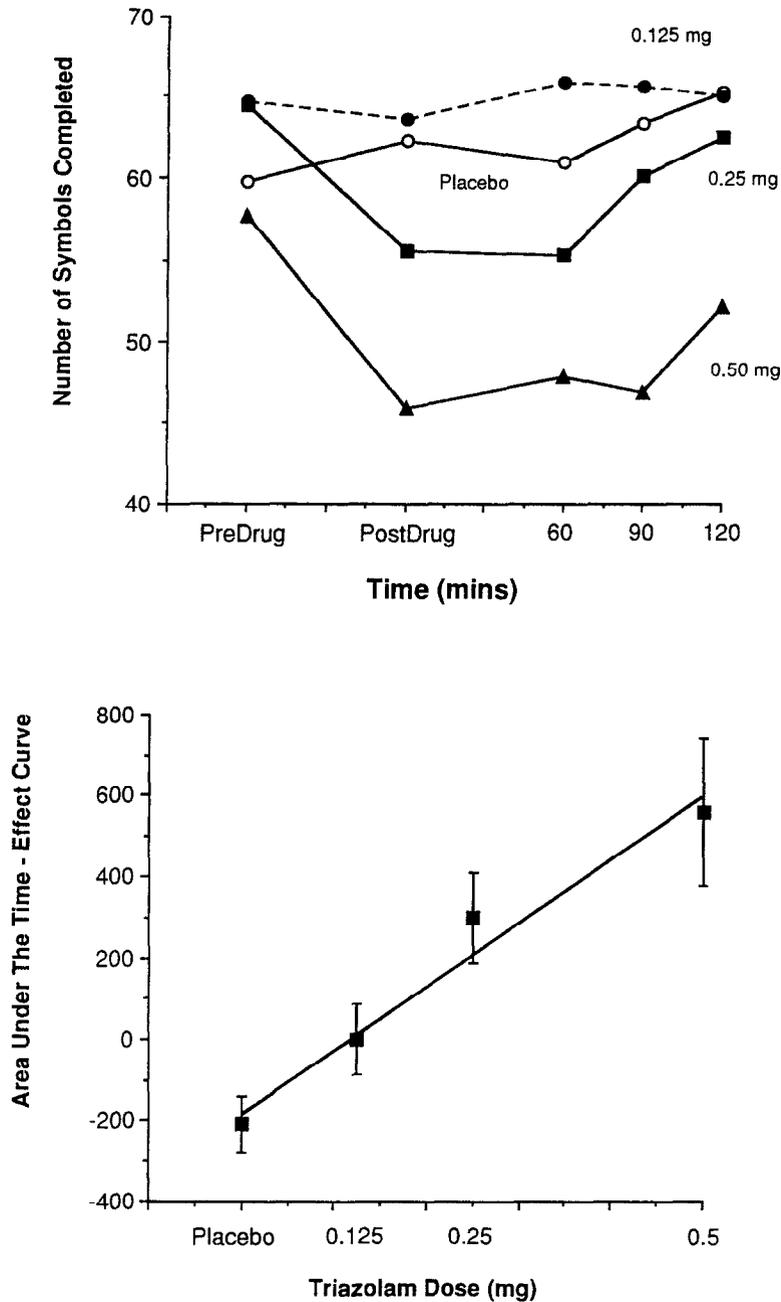


Fig. 2. Impairment of cognitive-psycomotor function as measured by digit symbol substitution test. Top, Effect over time for 0.125 mg, 0.25 mg, and 0.5 mg of triazolam in comparison with placebo. Bottom, Linear decrease in cognitive-psycomotor impairment with increasing triazolam dose.

evaluation of the efficacy of sedation did not differ significantly among treatments; the mean rating for the 0.25 mg triazolam dose was equivalent to "very good."

No significant amnesia to clinical events such as local anesthesia administration and extractions was detected at the two lower triazolam doses; 0.5 mg resulted in amnesia to the extractions in one third of the

sample (Chi-square = 11.9, $P < 0.01$). Only 20% of subjects could recall the picture card shown at the end of surgery for both the 0.25 and 0.5 mg doses ($P < 0.01$).

Triazolam differed from the placebo in a dose-related manner for all three measures of drug impairment. Patients' subjective rating of alertness (Fig. 1) was impaired significantly by triazolam in a dose-re-

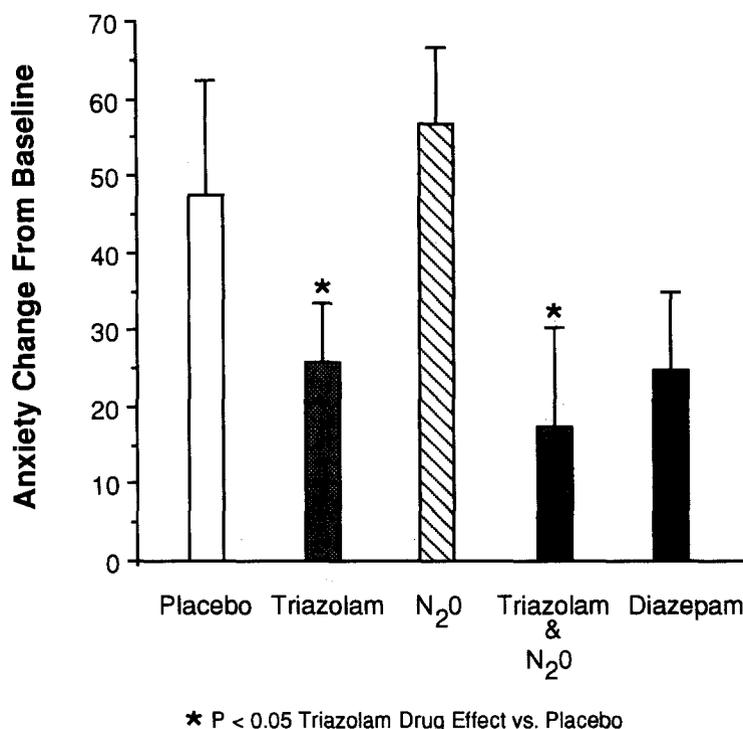


Fig. 3. Change in patient self-report of anxiety from baseline observation to intraoperative observation for placebo, triazolam, nitrous oxide, combination of triazolam plus nitrous oxide, and IV diazepam.

Table III. Dependent measures of drug efficacy for comparison of triazolam and nitrous oxide to placebo and IV diazepam

| Treatment Group | Anxiety* | Pain | Global evaluation | Efficacy of sedation | Patient cooperation |
|-----------------------------|---------------|-----------|-------------------|----------------------|---------------------|
| Placebo | 47.4 ± 58.2 | 0.8 ± 0.7 | 1.9 ± 1.5 | 1.3 ± 0.8 | 1.9 ± 2.2 |
| Triazolam | 26.0 ± 28.9† | 0.9 ± 0.8 | 2.1 ± 1.5 | 1.5 ± 0.9 | 2.3 ± 2.1 |
| Nitrous oxide | 56.9 ± 37.6 | 0.9 ± 0.8 | 2.5 ± 1.6 | 1.0 ± 0.7 | 2.5 ± 1.9 |
| Triazolam and nitrous oxide | 17.3 ± 51.2†‡ | 0.8 ± 0.9 | 2.7 ± 1.1 | 1.6 ± 0.9 | 1.9 ± 2.3 |
| IV diazepam | 24.8 ± 38.8 | 1.5 ± 0.5 | 2.8 ± 0.8 | 2.1 ± 0.7 | 1.9 ± 1.9 |

*Change in anxiety from baseline to intraoperative observation as measured by graphic rating scale for anxiety.

†Triazolam drug effect $F = 6.77$, $P < 0.01$.

‡ $P < 0.05$ vs. N₂O.

lated manner ($R = 0.44$, $F = 8.35$, $P < 0.01$) with the subjects who received 0.5 mg of triazolam still being rated as mildly impaired at the time of dismissal 120 minutes after surgery (Fig. 1). Psychomotor performance, as measured by the digit symbol substitution test, was also significantly impaired ($R = 0.47$, $F = 9.87$, $P < 0.01$) with higher doses (Fig. 2), substantial impairment was still measurable at 120 minutes for the 0.5 mg dose (Fig. 2) Ambulatory function was also impaired in a dose-related manner ($r = 0.53$, $F = 13.1$, $P < 0.001$) but with almost complete recovery by 120 minutes (data not shown). No significant differences in the incidence of side effects were seen between groups.

Study No. 2: Comparison of triazolam and nitrous oxide to placebo and diazepam

Patient self-report of intraoperative anxiety increased from baseline to intraoperatively in all groups (Fig. 3), but was significantly attenuated by triazolam ($F = 6.77$, $P < 0.01$) when analyzed by two-way analysis of variance. No drug effect was seen for nitrous oxide alone nor was there any interaction between triazolam and nitrous oxide. The mean level of intraoperative anxiety for the two groups who receive triazolam was similar to the mean effect for diazepam. The triazolam plus nitrous oxide group reported anxiety levels that were significantly less ($P < 0.05$) than the nitrous oxide only group (Fig. 3).

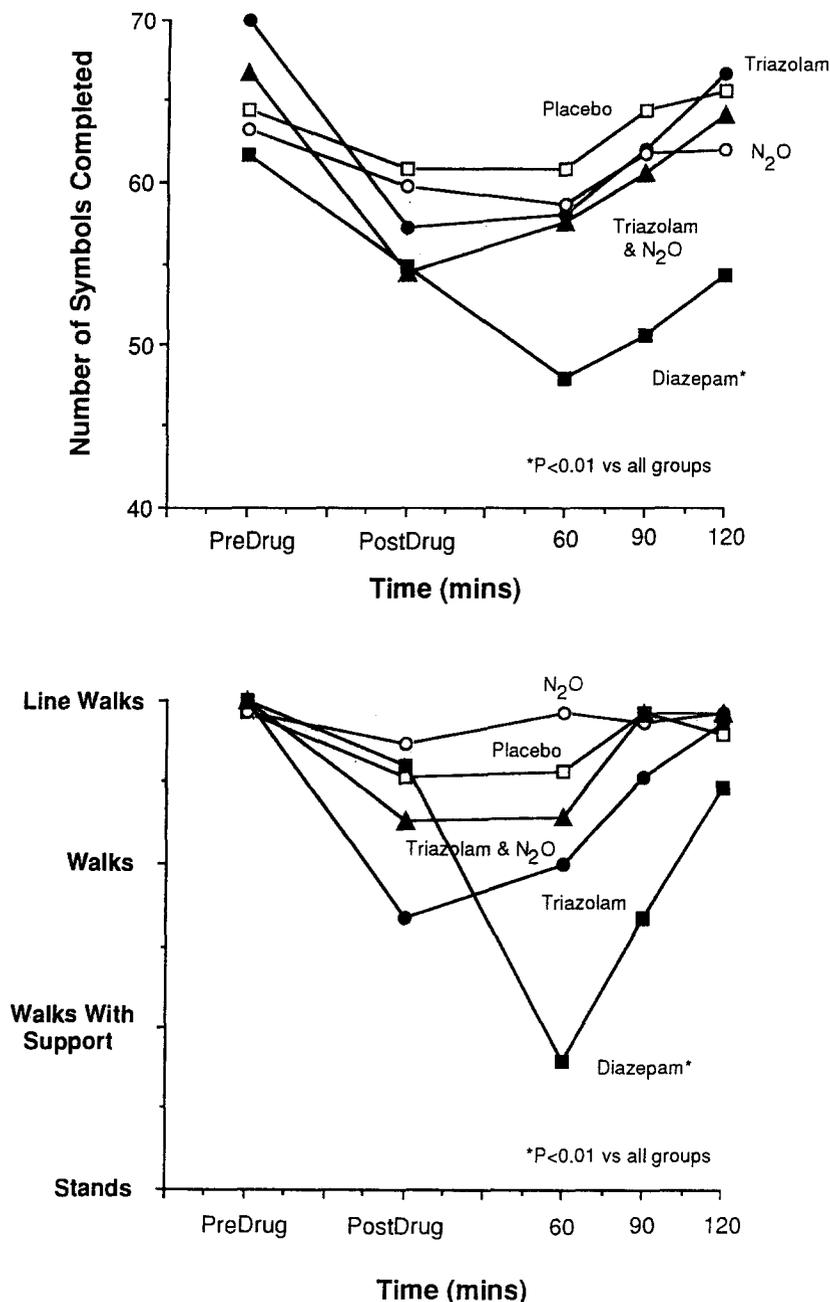


Fig. 4. Postoperative recovery after placebo, triazolam, nitrous oxide, combination of triazolam plus nitrous oxide, and IV diazepam. Top, Cognitive-psycomotor recovery as measured by digit symbol substitution test. Bottom, Recovery of ambulatory function over time.

Pain report in all groups was "slight" as a result of the concurrent use of local anesthetic (Table III). The patients' global evaluation resulted in the lowest ratings for the placebo, intermediate ratings for the groups that received triazolam, nitrous oxide, and triazolam plus nitrous oxide, and highest ratings for IV diazepam (Table III).

The rating of sedation by the surgeon and observer

did not differ significantly among treatments although the IV diazepam group had the highest mean rating (Table III). Patient cooperation was also similar among groups, with the mean ratings indicative of minor interfering movements during the procedure.

Triazolam and nitrous oxide alone or in combination did not significantly suppress alertness ratings (data not shown). In contrast, IV diazepam resulted

in impaired alertness ($p < 0.01$). Both groups that received triazolam demonstrated decrements in cognitive-psychomotor skills, as measured by the digit symbol substitution test, but recovery was nearly complete by 120 minutes (Fig. 4). Diazepam also produced significant impairment in comparison with the placebo ($P < 0.01$) but with incomplete recovery by the 120 minute observation. Ambulatory function was also markedly impaired by diazepam (Fig. 4) in comparison with all groups ($P < 0.01$). In comparison, both groups that received triazolam were less impaired initially and demonstrated recovery to baseline performance by 120 minutes.

Respiration rate, blood pressure, and pulse were similar among treatments (data not shown). The incidence of side effects was too low (0 to 3 per group) to differentiate between treatment groups.

DISCUSSION

Oral administration of triazolam in combination with nitrous oxide to dental outpatients attenuates intraoperative anxiety produced by oral surgery. This anxiolytic effect appears to be largely due to the pharmacologic effect of triazolam, as a significant drug effect was demonstrated in the second study for triazolam with little apparent activity for nitrous oxide either alone or in combination with triazolam. The magnitude of the triazolam anxiolytic effect is comparable to intravenous administration of a substantial dose of diazepam (mean = 19.3 mg in study No. 2). These findings suggest that a dentist who is not trained in the use of parenteral sedation can achieve an anxiolytic effect comparable to a moderate dose of IV diazepam.

The pharmacologic effects of triazolam in the first study were not dose related for most dependent efficacy measures: anxiety relief, analgesia, patients' rating of global evaluation, patient cooperation, and efficacy of sedation. Conversely, many of the undesirable properties of triazolam that limit its clinical use such as delayed postoperative recovery and decreased alertness were dose related. The 0.125 mg dose resulted in variable subjective effects, suggestive of a borderline dose that resulted in therapeutic effects in some patients and subtherapeutic effects in others. The middle dose of triazolam (0.25 mg) was selected for further evaluation in the second study on the basis of its efficacy and recovery in comparison with the higher and lower dose. The higher dose (0.5 mg) did not offer any greater efficacy in terms of anxiolytic activity, patient cooperation, or observers' ratings of sedation although it did produce longer recovery of cognitive-psychomotor impairment and ambulatory

function. It is likely that adjustment of the dose of triazolam on the basis of body weight and preoperative anxiety would result in greater clinical efficacy in a higher percentage of patients. The results of the present study, however, do not provide a basis for calculating a variable dose on the basis of these or other prognostic factors.

Amnesia to clinically significant events, such as local anesthesia administration and extractions, was minimal at the 0.25 mg dose whereas 0.5 mg resulted in amnesia to extractions in one third of the sample. The relationship between amnesia to clinical procedures and future dental anxiety has not been demonstrated. Total amnesia to dental procedures in a phobic population that uses general anesthesia has proven less effective in the improvement of long-term dental care than behavioral measures with total recall of the event.¹⁶ This observation suggests that recall of previous clinical events is not the only factor that contributes to dental anxiety and subsequent aversion to dental care. Thus triazolam may serve as a useful adjunct to manage patient anxiety even though it does not produce amnesia to clinical events at lower doses.

Triazolam results in a transient deficit in alertness, cognitive-psychomotor impairment, and motor incoordination during ambulatory testing. The magnitude and duration of these manifestations of central nervous system impairment is less than the effects of IV diazepam, and recovery is virtually complete by the end of 2 hours. These findings indicate that comparable anxiolytic activity can be produced by triazolam in comparison with diazepam but with a more rapid recovery and earlier discharge after a dental procedure. Residual impairment in complex cognitive-psychomotor functions can exist for up to 6 hours after triazolam,^{9,17} which indicates that patients should follow the usual precaution of refraining from driving a motor vehicle or operating power tools on a day that they received triazolam for a dental procedure.

Triazolam did not result in any respiratory or cardiovascular impairment over the dose range of 0.125 to 0.50 in combination with nitrous oxide. Controlled evaluations in a greater number of subjects are needed before generalizing to debilitated patients who may be more susceptible to the effects of benzodiazepines, to the very young or old, and to patients taking other central nervous system depressants. Although subjects in this investigation were monitored for data collection, further research is needed to determine what level and frequency of monitoring would be needed for the use of triazolam in clinical practice.

No effect of nitrous oxide, either alone or in combination with triazolam, could be detected in this pa-

tient sample. The generally well-accepted clinical efficacy of nitrous oxide in dental practice suggests that the conditions of the second study were not sensitive enough to detect its anxiolytic effect at the dose evaluated. In the first study, subjects who received an oral placebo and 50% nitrous oxide served as a comparison group for the three doses of triazolam. Inclusion of a group that received both an oral and inhalational placebo might have permitted demonstration of a clinical effect for nitrous oxide. A subsequent double-blind study clearly separated 60% nitrous oxide from oxygen (Dionne RA, unpublished data, 1990), which indicated that at higher doses, the subjective effects of nitrous oxide can be detected in the oral surgery model. Thus the failure to detect an effect of 40% nitrous oxide in combination with 0.25 mg of triazolam may reflect a lack of assay sensitivity.

Oral administration is generally preferable to IV administration, especially if a patient's apprehension toward dental treatment is in part related to administration via injection. Oral administration is very likely to be more acceptable in the young or emotionally disturbed patient who will resist drug administration by a painful injection. Absorption of drugs after oral administration is slower and generally results in lower circulating drug levels.¹⁸ This minimizes the possibility of drug toxicity as a result of administration of a IV drug in too high a dose or at too rapid a rate. Conversely, oral administration eliminates the ability to titrate incremental doses of the drug on the basis of the patient's subjective response as the drug is administered. Use of an effective dose of nitrous oxide in combination with a fixed, basal dose of triazolam should allow the nitrous oxide to be titrated on the basis of the patient's verbal report of relaxation or readily reversed in the event of over sedation.

The results of these two studies indicate that oral triazolam is an effective anxiolytic agent for use in dental outpatients comparable in efficacy to intravenously administered diazepam. Use of this agent by general dentists and nonoral surgeon specialists provides a pharmacologic modality for anxiety control in a much greater patient population than is currently treatable with general anesthesia or parenteral sedation. Although reliable morbidity and mortality statistics do not exist for the use of anesthesia and sedation in dentistry,¹⁹ it appears reasonable to assume that use of a single orally administered agent should result in minimal morbidity. The availability of a benzodiazepine antagonist²⁰ would permit selective management of toxicity associated with an inadvertent overdose or an exaggerated response in a susceptible patient. The use of oral premedication with tri-

azolam provides many of the therapeutic advantages of IV diazepam sedation at the same time that it avoids the potential toxicity of parenteral drug administration.

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