# ANALGESIC ACTION OF INTRAVENOUS DIAZEPAM

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## SUMMARY

Intravenous diazepam is commonly used in clinical dentistry to produce sedation for dental procedures. Its chief benefit seems to derive from its sedative and amnesic properties. The literature contains conflicting reports about the direct analgesic effects of the drug. In the present study, we observed significant increases for conventional pain threshold measures in response to electric tooth pulp stimulation and decreased sensitivity to a fixed painful stimulus when diazepam was administered intravenously using clinical criteria for conscious sedative dosages. The data support the possibility that intravenously administered diazepam in conscious sedative doses may have some analgesic action in addition to its better documented sedative and amnesic properties.

## INTRODUCTION

Intravenous administration of diazepam has proved useful for sedation of dental patients during oral surgery and restorative dental procedures. It is well recognized clinically that diazepam modifies anxiety and produces amnesia for painful dental procedures.[1] The exact mechanism through which intravenous diazepam provides these benefits is not completely understood and only a few studies have attempted to quantify possible analgesic affects of diazepam.

Experiments carried out by Brown and Dundee[2] demonstrated analgesic action following intravenous diazepam injection. However, the authors concluded that diazepam did not decrease sensitivity to somatic pain to the same extent as intravenous barbiturates. These findings are somewhat in contrast to those of Gracely, et al.[3] who found that reported sensory intensity in response to electrical tooth pulp stimulation was not reduced after the administration of diazepam with saline but was reduced following the administration of diazepam with fentanyl. Yang, et al.[4] evaluated the analgesic action of diazepam and morphine using thermal stimulation and sensory decision theory (SDT) analyses. They did not observe significant increases in pain threshold or pain tolerance for diazepam, while morphine significantly elevated these conventional thresholds. However, SDT analysis revealed a shift in response bias for both morphine and diazepam. Diazepam elicited a small shift towards report of less pain, but statistically significant decreases in pain report were not observed until 75 to 105 minutes after injection of intravenous diazepam. The authors suggest that diazepam may have a small analgesic effect but attribute decreases in pain report to drug induced distraction or other attitudinal changes caused by diazepam rather than to the drug's inducing specific sensory loss.

In light of these conflicting reports, the present study was designed as a straightforward measurement of the analgesic action of diazepam on painful tooth pulp stimulation delivered in a clinically relevant dental setting. Since SDT pain research has raised still unresolved questions concerning how best to interpret data from human pain experiments and since we chose to simulate a clinical dental treatment setting as much as possible, we measured conventional sensation and pain thresholds in response to increasing amounts of electrical current as might be encountered in clinical pulp testing. We also sought to observe whether the subjective perception of a fixed painful stimulus differed when the stimulus was delivered before and after intravenous administration of diazepam. Finally, we measured anxiety levels for their possible relation to pain report.

## METHODS AND PROCEDURES

**Subjects:** Ten healthy male paid volunteers (mean age = 28.9 ± 3.4), participated in a single session study, which was conducted in the Oral Medicine Clinic of the University of Washington. Volunteers were informed that they were participating in a study to observe the effects of a commonly used drug on responses to stimulation of the tooth by electricity, and institution approved human subject consent was obtained from each volunteer.

**Pain Stimulation:** Electrical tooth pulp stimulation was delivered to the incisal edge of a continu-

Received in final form March 29, 1984
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ously-dried, intact, healthy, upper central incisor. The stimulation was delivered through a hand held probe containing a 2mm diameter conductive rubber electrode. Square wave stimuli of 5 msec. duration were delivered at about one second intervals. Stimuli of continuously increasing electrical current were delivered according to the Method of Ascending Limits. This method and apparatus for delivering painful tooth pulp stimulation has been carefully described[5,6] and contains constant current and isolation circuitry for reliability and patient safety.

**Pain Measures:** As the intensity of electrical stimulation to the tooth continuously increased, subjects were asked to indicate: Absolute Sensation Threshold (AST) — defined as any initial sensation; Pain Threshold (PTH) — defined as the first report of pain perception; Pain Tolerance (PTO) — defined as the upper limit of painful stimulation the subject was willing to tolerate. The subjects indicated AST, PTH, and PTO levels by pressing buttons on a subject response panel. In addition to giving threshold responses to increasing amounts of tooth pulp stimulation, subjects also experienced a one minute train of 5 msec. painful impulses of intensity fixed midway between initial pain threshold and pain tolerance. (Fixed stimulus intensity = $\frac{PTO - PTH}{2} + PTH$).

Subjects rated the stimulus intensity (SI) and stimulus aversiveness (SA) of the fixed intensity painful stimulus by marking a 100mm visual analogue scale. SI was defined as the amount of intensity experienced; SA was defined as the unpleasantness or obnoxiousness of the fixed painful stimulus. Pain measures were recorded before and after administration of intravenous diazepam as described below. Finally, each time pain measures were obtained, state anxiety was also recorded, using the Spielberger State Anxiety Inventory.

**Intravenous Diazepam:** An intravenous infusion was started in the antecubital vein with 5% dextrose solution. Diazepam in a concentration of 0.5% was then injected slowly until the Verills eyelid ptosis sign was obtained and the patient appeared clinically sedated. Infusion of diazepam was then discontinued. This procedure for obtaining intravenous diazepam sedation is routinely used in the dental clinics of the School of Dentistry, University of Washington. The dosage range of diazepam administered was 12.5mg to 20mg. Five minutes after sedation was observed, all pain measures were repeated. Measures were again collected one hour after ptosis.

## RESULTS

Means and standard deviations for AST, PTH, and PTO were computed on the basis of 10 trials of ascending amounts of electrical tooth pulp stimulation. The mean values in microamps ($\mu$A) for each determination of AST, PTH and PTO are summarized in Table I. Paired t-tests were used to analyze the data for significant mean differences between measures of pain pre- and post-administration of intravenous diazepam. Statistically significant elevations of AST, PTH and PTO were observed five minutes after the infusion was completed. At the end of one hour AST, PTH and PTO were still significantly elevated but showed a trend to return to baseline.

Percentage changes from baseline in average threshold values revealed that five minutes of diazepam elevated AST by 26.3%, PTH by 26.5%, and PTO by 27.1%. One hour later, percentage elevations were 26.3% for AST, 20.6% for PTH and 25.0% for PTO. These changes are shown in Figure 1.

A statistically significant decrease, using paired t-tests, was found in the subjective perception of both the intensity and aversiveness of a fixed painful stimulus, when mean values for SI and SA were compared pre- and post-sedation (see Table I). Percentage changes from baseline for SI and SA were also examined. After 5 minutes of diazepam, SI was lowered on the average 36.7%; the mean decrease in SA was 40.0%. At the end of one hour, SI had decreased from baseline by 33.2% while SA had

**TABLE I.**

Mean (± s.d.) values for Absolute Sensation Threshold, Pain Threshold, Pain Tolerance; Stimulus Intensity and Stimulus Aversiveness; State Anxiety.

| | Baseline | 5 min. Post-Injection | 60 min. Post-Injection |
|---|---|---|---|
| Absolute Sensation Threshold ($\mu$A) | 19.0 ± 8.7 | 24.0* ± 8.2 | 24.0* ± 12.2 |
| Pain Threshold ($\mu$A) | 34.0 ± 8.2 | 43.0* ± 13.9 | 41.0* ± 16.7 |
| Pain Tolerance ($\mu$A) | 48.0 ± 9.6 | 61.0* ± 13.1 | 60.0* ± 18.4 |
| Perceived Stimulus Intensity (mm) | 69.0 ± 14.8 | 43.7* ± 15.4 | 46.1* ± 20.0 |
| Perceived Stimulus Aversiveness (mm) | 63.7 ± 17.1 | 38.2* ± 25.0 | 41.6* ± 19.8 |
| Anxiety State (Spielberger) | 40.1 ± 8.7 | 29.2 ± 5.1 | 32.2* ± 8.0 |

*Significant differences from baseline, paired t-tests, two-tailed, $p < 0.05$.

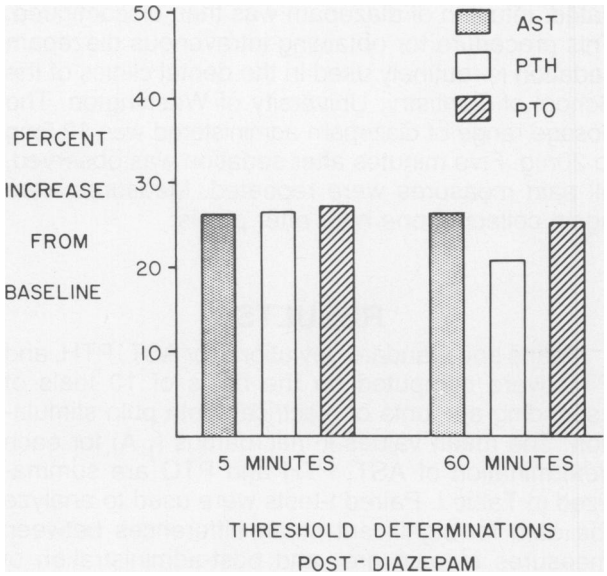


**Fig. 1** — Mean percentage increase from baseline for Absolute Sensation Threshold (AST), Pain Threshold (PTH) and Pain Tolerance (PTO) 5 minutes and 60 minutes post-diazepam injection.

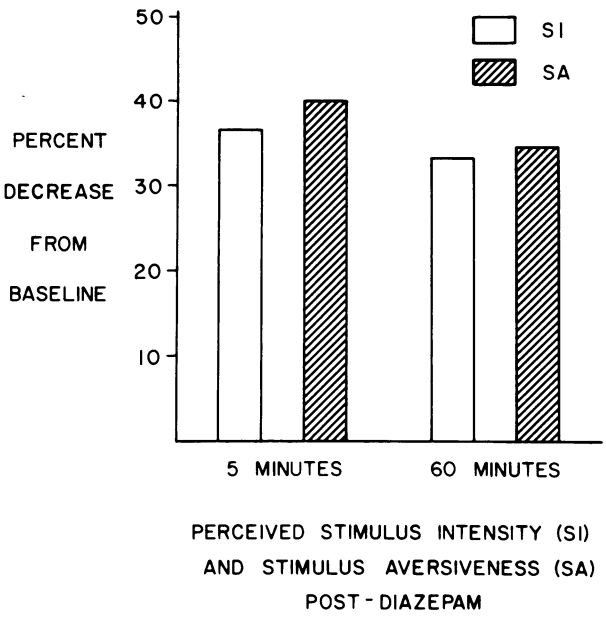


**Fig. 2** — Mean percentage decrease from baseline for perceived Stimulus Intensity (SI) and Stimulus Aversiveness (SA) 5 minutes and 60 minutes post-diazepam injection.

decreased by 34.7%. Figure 2 depicts these percentage change findings for SI and SA.

State anxiety levels also showed significant change, indicating that the subjective experience of anxiety, as measured by the Spielberger State Anxiety Inventory, was significantly reduced from baseline five minutes after infusion of diazepam (mean anxiety levels = 40.1 vs. 29.2 respectively) and also one hour later (mean anxiety levels = 40.1 vs. 32.2, respectively). These findings are also summarized in Table I.

## DISCUSSION

The data reported here demonstrate the intravenous diazepam administered to produce clinical sedation as defined by clinical signs of ptosis, significantly elevated thresholds for sensation, pain, and pain tolerance. The perceived intensity (SI) and aversiveness (SA) of a constant painful stimulus were also significantly lowered under the drug conditions. These results support the possibility that commonly used sedative dosages of diazepam provide an analgesic effect.

Conflicting reports regarding effects of intravenous diazepam show wide variability in dosage, route of administration, type of painful stimulus and time of measurement following intravenous administration. Using intravenous dosages of diazepam as high as 35-60mg (approximately .8mg/kg) Brown and Dundee[2] found moderate analgesic effects in response to a painful tibial pressure technique. Their interest, however, was in pursuing the efficacy of intravenous diazepam to induce general anesthesia. In contrast, Gracely et al.[3] used dosages of .11mg/kg of diazepam. At this concentration, subjects weighing 54-91kg (approximately 120-200 lbs.) would receive approximately 6-10mg of intravenous diazepam. They found that intensity of sensations produced by tooth pulp stimulations were unaltered by diazepam and concluded that diazepam has little, if any, effect on the intensity of pain sensations. Yang, et al.[4] used similar doses of 0.14mg/kg and reported no early significant analgesic effects on traditional pain thresholds, but observed significant changes in pain perception beginning 75 minutes after injection. Our dosage range for producing clinical ptosis was 12.5-20mg of diazepam administered intravenously. This range, which was associated with analgesic effects, was intermediate between the often anesthetic dosages of Brown and Dundee[2] which produced analgesia and the much lower dosages of Gracely, et al. and Yang, et al. which produced no immediate significant changes in pain responsivity. Using a different route of administration, Chapman and Feather[7] reported that 10mg of oral diazepam significantly increased tolerance to tourniquet pain but not radiant heat. Taken together these data imply a dose-response relationship for analgesia induced by diazepam.

To our surprise, appreciable effects on thresholds and perceived intensity and aversiveness were observed one hour after intravenous diazepam was administered in our study. In effect, we were unable, in the present experiment, to observe a true return to baseline. Serum levels following intravenous diazepam are reported to peak from 5 to 15 minutes following injection, followed by an approximate 60% reduction of peak values after one hour.[2,8] Effects on

memory following intravenous diazepam administration have been carefully measured for up to thirty minutes by Gregg, et al.[1] and Clark, et al.[8] who presented evidence that amnesic effects are dose related and that higher doses (e.g., .3mg/kg) can be associated with approximately 80% memory loss thirty minutes post-injection. Unfortunately, these studies focusing on the amnesic effects of intravenous diazepam did not include pain measures as well. Our findings of analgesic effects one-hour post-injection and the more indirect findings of Yang, et al. of a significant analgesic effect of diazepam 75-105 minutes post-injection may not be so surprising, after all, given the data from studies investigating longer-lasting amnesic action of intravenous diazepam. These findings of long-lasting analgesic and amnesic effects, if confirmed, could have important clinical and even medico-legal implications regarding patient safety after clinical dental treatment with intravenous diazepam.

Our experimental design lacked a control group for the effects of repeated pain measures without benefit of diazepam and we were also not able to calculate dose relationships to body weight. Had we included both these considerations, our own data analyses could have answered some questions implicit in the conflicting reports regarding analgesic action of diazepam. Nevertheless, we were able to observe significant analgesic effects in response to intravenous diazepam, both when subjects responded to a continuously increasing stimulus and when they judged the intensity and aversiveness of a fixed painful stimulus.

Our findings that anxiety levels, within normal limits at baseline for this age group were lowered significantly after diazepam administration, and the related findings of others[3,4,7] suggest that the drug's anxiolytic properties may be related to its ability to modulate pain. Direct studies of diazepam's action on the neurophysiologic basis of pain have not been reported and the underlying mechanism of the drug's modulation of brain activities is not known. Further studies which focus specifically on the affective dimension of pain experience may help to clairfy these relationships.

Clearly, before definite conclusions can be made about the analgesic effects of intravenous diazepam, studies are also needed to examine in greater detail the interaction between dosage, route of administration, nature of the painful stimulus, and subjective perception of pain over time.

## ACKNOWLEDGEMENTS

This research was supported, in part, by Grant No. DE05130 from the National Institutes of Health (NIDR).

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