

Title: INCREASED ANXIETY AFTER INTRAVENOUS MIDAZOLAM

Authors: J. L. Lichtor, M.D., K. Korttila, M.D., Ph.D., H. deWit, Ph.D., J. Ward, M.B., B. ch., B. S. Lane, B.A.

Affiliation: Department of Anesthesia and Critical Care, and Department of Psychiatry, the University of Chicago, Chicago, IL 60637

Introduction: Frequently, patients presenting for outpatient surgery have not been seen by an anesthesiologist before they have come to the operating room. If anxiety in these patients is to be treated pharmacologically, a drug with a rapid onset of action would be desirable. We designed the following experiment to compare the use of the premedicant midazolam to no premedicant, and correlate the effects with the patient's level of preoperative anxiety.

Methods: Ambulatory patients scheduled to undergo laparoscopy for tubal ligation were asked to volunteer for a study analyzing moods after receiving the anxiolytic midazolam or placebo. The study protocol and consent procedures were approved by our clinical investigation committee. Fifty-two consecutive consenting patients met the following criteria for study inclusion: i) they were not currently receiving narcotics, anxiolytics, or antihypertensives; ii) they were not hypertensive (systolic BP < 140); and iii) they weighed less than 100 kg. Initially, patients completed the Hopkins Symptom Checklist (HSCL)¹ and six visual analogue scales (VAS) (0-10 scale) with the words "stimulated," "high," "anxious," "sedated," "down" and "hungry." An IV was then inserted, and the patients again completed the six VAS's. Patients then randomly received either midazolam 0.05 mg/kg (5mg/ml) or an equal volume of placebo. The patient and investigator were both unaware of the identity of the drug being administered. Fifteen minutes later, the patients were again asked to complete the six VAS's. The HSCL is a sensitive measure of psychiatric symptomatology and mood states, including trait anxiety. The VAS's were used to quantify momentary mood states and they could be completed by the patients in a relatively short period of time. Seven patients who were initially randomized to midazolam (2 patients) or placebo (5 patients) had to be excluded because they could not finish the study before the operating room was ready for them.

After completion of the study, the mean value of the anxiety scale of the HSCL for the remaining 45 patients was determined and was used to divide the patients into a low anxiety or a high anxiety group. Repeated measures analysis of variance was then used to compare the changes in mood factors, as measured by the VAS's, at the three times the scales were administered, with patients divided according to anxiety measured by the HSCL (low or high trait anxiety) and according to premedicant.

Results: Fifteen low anxiety patients each received placebo or midazolam; nine highly anxious patients received placebo and six highly anxious patients received midazolam. Three non-anxious patients who received

midazolam were too drowsy to arouse fifteen minutes after receiving midazolam to complete the VAS's and were excluded from further analysis.

Patients with high trait anxiety reported higher momentary anxiety levels; the association between trait anxiety and the visual analogue scale rating of "anxious" was significant ($p=0.008$). After patients received midazolam they became more anxious; if they received placebo, anxiety either stayed the same or decreased; the increased anxiety after midazolam was significant ($p=0.007$).

The interaction between trait anxiety and the visual analogue scale rating of "stimulated" was significant ($p=0.03$). Regardless of whether drug or placebo was injected, patients felt more "high" after injection ($p<0.001$); after patients received midazolam, they rated the feeling "high" greater than patients who received placebo ($p=0.003$). Regardless of whether drug or placebo was injected, patients felt more sedated after injection ($p < 0.001$); sedation increased more after midazolam than after placebo ($p < 0.001$). Patients who were anxious and received midazolam reported a greater increase in sedation than patients who were not anxious ($p=0.004$); as stated above, though, 3 of 15 nonanxious patients who received midazolam fell asleep and could not complete the study.

Discussion: Surprisingly, midazolam increased self-reported anxiety in both non-anxious and anxious subjects. The dose used in our study, 0.05 mg/kg, was smaller than that used in other studies and may have been too low to observe an anxiolytic effect. However, three of our patients who did receive midazolam were too somnolent to arouse to complete the VAS's. In addition, because of reports of respiratory depression and respiratory arrest, especially when the drug is used for conscious sedation, smaller doses are recommended. The dose we used is within the range recommended by the manufacturer for intravenous administration in normal healthy adults.

This report is the first to show a significant increased level of anxiety after midazolam when compared to control. Further testing of a wider range of doses with other objective measures of anxiety would seem warranted to insure that this increased anxiety is not just dose specific.

References:

1. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L: The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral Sciences* 19:1-15, 1974