Title: NEUROCOGNITIVE PROFILE OF MIDAZOLAM INDUCED AMNESIA

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Introduction. Episodic awareness is a problem during general anesthesia as well as during the pre- and postoperative periods. Patients are often subjected to pain and the noise of a busy postoperative recovery room. They also suffer from considerable anxiety. Certain premedications are known to minimize the unpleasant memories of the day of surgery. In general, clinical evaluation of sedation is performed subjectively. The object of the present study was to determine in a controlled fashion the ability of subhypnotic doses of midazolam to produce amnesia in relation to its sedative effects in healthy adult volunteers. A computer generated neurocognitive assessment battery, memory cards, EEG power spectral analysis, the late component of the auditory evoked potential (P300), and subjective rating scales were utilized.[1]

Methods. The study was approved by The Committee to Review Grants for Clinical Research and Investigation Involving Human Beings of the University of Michigan Medical Center. Young, healthy volunteers were randomly assigned to each group. Medicated and control groups (10 subjects each) consisted of an equal number of males and females. Each experiment was completed over a two day period. Midazolam HCl in a dose of 0.02 mg/kg was injected three times at 15 min intervals after obtaining baseline electrophysiological recordings and computerized cognitive memory test (CCT) results. One min following each dose of midazolam, EEG and auditory evoked potential recordings were repeated. A memory card was shown for a baseline and after each dose.[2] The CCT was repeated at the end of the session on Day 1 and day 2.

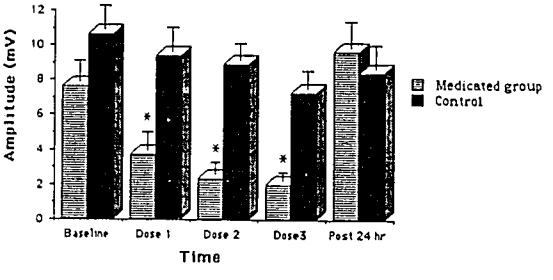
Four channels of EEG (F_3, C_Z, C_3, and O_1 referenced to linked A_1/A_2 leads) were monitored on a Grass 7C polygraph and recorded on FM tape. Absolute latencies and amplitudes of P300 data were then determined from C_Z and F_3. An automatic, non-invasive blood monitor (Dinamap) was used to record blood pressure and cardiac rate during the experiment. The CCT consisted of an IBM-XT associated touch screen hardware and consisted of three tasks: 1) Misplaced Objects, 2) Telephone Number and, 3) Concentration. Time, person, and place orientation were assessed by a standard 10 point self-rating scale. Sedation was rated as follows: 0-fully alert; 1-slightly sedated; 2-sleepy and/or very light sleep; 3-deep sleep, not easily awakened; 4-comatose. Amnesia was measured by the ability to recall or recognize the memory cards 24 hr after their presentation.

Results. Blood pressure, heart rate and rhythm were unaffected by midazolam. The relative EEG power was decreased for occipital and increased for frontal activities by midazolam in a dose dependent manner.

As illustrated in the figure below, the amplitude of the P300 component of the auditory evoked potential progressively decreased with increasing doses of midazolam as did the accuracy of counting the number of rare tones (*P < .05). One and 24 hr later the P300 amplitude recovered. Twenty four hr later following midazolam the treated subjects were impaired in their ability to recall the cards presented, particularly 10 min following the second and third midazolam dose (P < .05). The CCT was done 30 min after the last dose of midazolam and did not show any significant changes from the baseline test. Similarly, no amnesia was observed at this time for memory card recall.

Most of the subjects (80%) frequently could not recall the number of doses of midazolam administered. A progressive decrease in the level of sedation was rated from only 0 to 2 even after the third dose of midazolam.

P300 amplitude



PERCENT OF SUBJECTS RECALLING CARDS

	Pre	Dose1	Dose2	Dose3	Post10	Post35	Post45 min
CONTROL	90	90	70	80	80	80	60
TREATED	90	60	20*	10*	30*	30*	80

Conclusion. The results suggest that midazolam induced amnesia is better correlated with an attention deficit rather than gross sedation.

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References.

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