TITLE: DOSE RELATED AMNESIC AND SEDATIVE PROPERTIES OF INTRAVENOUS MIDAZOLAM.

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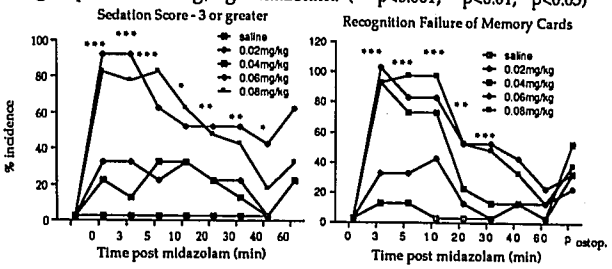
INTRODUCTION: Midazolam 5mg intravenously produces sedation and anterograde amnesia within 2-5 minutes, and of approximately 30 minutes duration.(1) This study assesses the effects of a range of midazolam doses.

METHODS: After Research Ethical Committee approval and informed consent, 60 patients for elective minor gynaecological surgery in a double blind study, received as premedication, intravenous saline, 0.02, 0.04, 0.06 or 0.08mg/kg midazolam in a volume of 10 mls (10,10,10,10, and 20 patients respectively). A blinded observer who evaluated sedation clinically, asked each patient to identify a visual memory card, and to perform ascending and descending frequency tasks (CFFT) on a Leeds Flicker Fusion Tester, before, and at 3,5,10,20,30,40 and 60 minutes after the test drug. Following a standard anaesthetic 10 patients in the 0.08mg/kg midazolam group, randomly received 0.01mg/kg flumazenil or saline in 10mls. The same tests were repeated 30 minutes postoperatively. A 5-point scoring system was used to assess sedation: (1) no sedation, (2) not sleepy but relaxed, (3) asleep, but aroused by verbal stimulus, (4) asleep, but aroused by physical stimulus, (5) not rousable. Twenty four hours postoperatively, each patient was asked to recall and then to identify the pictures previously shown from 20 visual memory cards. The data was analysed using X2, X2 for trend, analysis of variance, Mann Whitney U test, Student's T test and Method of Contrasts.

RESULTS: There was a statistically significant dose-related trend for sedation score and incidence of recall or recognition failure amongst the groups. Both sedation and anterograde amnesia were most marked during the initial 3-20 minutes. One patient was unrousable for 20 minutes after 0.08mg/kg, midazolam but had minimal respiratory embarrassment. All other patients were rousable by physical or verbal stimulus.Duration of recall failure was significantly longer after 0.06 or 0.08mg/kg compared to 0.02mg/kg midazolam ($p<.01$). The changes in descending (but not ascending) frequency of CFFT differed significantly between the groups ($p=.0001$). Throughout the 60 minute preoperative period, there was a statistically significant dose related trend in descending frequency CFFT scores. Postoperative sedation, recall/recognition and CFFT scores did not differ between the flumazenil and non flumazenil subgroups after 0.08mg/kg midazolam. (*** $p<0.001$; ** $p<0.01$; * $p<0.05$)



DISCUSSION: Dose-related differences in sedation, psychomotor function, and incidence of amnesia were demonstrable following 0.02-0.08mg/kg midazolam. Intravenous flumazenil 0.01mg/kg, given at least 60 minutes after 0.08mg/kg midazolam, did not alter postoperative sedation or amnesia. Changes in descending but not ascending frequency of CFFT with time were dose-related.

REFERENCES:

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MID-LATENCY AUDITORY EVOKED POTENTIALS (MLAEP) AND INTRAOPERATIVE WAKEFULNESS DURING GENERAL ANESTHESIA (GA) WITH PROPOFOL, ISOFLURANE AND FLUNITRAZEPAM/FENTANYL

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During combined local and general anesthesia clinical signs of adequate suppression of consciousness are difficult to evaluate. In the present study we combined epidural analgesia with 3 techniques of GA. Intraoperative wakefulness was documented and correlated with cardiocirculatory parameters as well as with MLAEP and their frequency analysis. After institional approval and informed consent 30 patients undergoing elective laparatomia were studied as follows: First continuous epidural analgesia was instituted in all patients to eliminate nociceptive stimuli. Then GA was induced with propofol (2,5 mg/kg) (group I, n=10), thiopentone (5 mg/kg) (group II, n=10) or etomidate (0,2 mg/kg) (group III, n=10) and maintained with propofol (3-5 mg/kg/n) (gr I), isoflurane (0,4-0,8 Vol%) (gr II) or flunitrazepam (0,005-0,01 mg/kg) and fentanyl (0,0025-0.005 mg/kg) bolus injection every 20 to 30' (gr III). Succinylcholine (1 mg/kg) was given for endotracheal intubation. No other muscle relaxants were employed. Heartrate and arterial pressure were registered continuously. Reflectory reactions (coughing) and more complex motoric reactions (movements of limbs and head, mimics) were documented as signs of intraoperative.wakefulness. Auditory evoked potentials were recorded in the awake state, after induction and during maintenance of GA on vertex (positive) and mastoides (negative). Auditory clicks were presented binaurally at 70 dBnHL with 9.3 Hz. 1000 successive stimuli were averaged over a 100 ms poststimulus period. Latencies of the peaks V, Na, Pa were measured. By Fast-Fourier Transformation corresponding powerspectra were calculated to analyse energy portions of the AEP frequency components. Duration of GA and dosages of local anesthetics were comparable in the 3 groups. Reflectory reactions were identically in the 3 groups, whereas more complex motoric reactions were 6 to 7 times more often in group III. There was no correlation between motoric reactions and cardiocirculatory parameters. Latencies of the peaks V, Na, Pa of the awake patients were in the normal range, corresponding power spectra showed energetically dominant frequencies in the 30-40 Hz range. After induction of GA with propofol, thiopentone and etomidate as well as during maintenance of GA with propofol and isoflurane peak latencies Na, Pa increased, frequencies in the 30-40 Hz range became suppressed and MLAEP energy maxima shifted to the low frequency range. In contrast during maintenance of GA with flunitrazepam/fentanyl peak latencies Na, Pa returned to the awake value, frequencies in the range of 30 Hz regained energy dominance in the corresponding powerspectra. These results indicate that auditory stimuli processing in the awake coincides with an auditory evoked 30-40 Hz oscillatory brain mechanism. It becomes suppressed during GA with propofol, thiopentone, etomidate, isoflurane, whereas it persists using flunitrazepam/fentanyl bolus injections for maintenance of GA. This correlates well with the high incidence of complex motor reactions in this group. Auditory evoked potentials could be an useful tool for monitoring sensory stimuli processing during general anesthesia and quantifying what we call up to now "depth of anesthesia".