TITLE: COGNITIVE MECHANISM OF AMNESIA PRODUCED BY MIDAZOLAM.

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Midazolam produces anterograde amnesia. The mechanism of this effect has not been well described. We investigated the effects of I.V. midazolam on learning and short term memory (STM) using a word memorization/ recall task.

METHODS: This study was approved by the local IRB and informed consent was obtained in 10 healthy volunteers (4M, 6F) aged 25-36. Midazolam 0.07 mg/kg was infused I.V. at 0.5 mg/min. The Rey Auditory-Verbal Learning Test (AVLT) consists of a 15-word list presented 5 times to assess learning (L1-L5), followed by a new 15-item list to assess the effect of interference (INT), and immediate (IR) and delayed recall (DR) of the first list. Three AVLT's were performed: baseline(B), immediately after infusion(INF), and 80 minutes post-infusion(REC). Visual analog scales of sleepiness and concentration were obtained throughout. Repeated measures ANOVA ($P<0.05$) were used to determine significant effects.

RESULTS: Number of correct words:

	L1	L2	L3	L4	L5	INT	IR	DR
B	7.7	11.6	13.1	13.7	14.1	9.0	13.3	13.9
INF	4.4	5.4	7.4	7.7	8.5	4.1	4.5	2.1
REC	7.0	10.7	12.2	12.9	13.3	5.5	11.1	8.6

In all conditions learning of the word list occurred ($P<.001$). Midazolam reduced the number of words successfully acquired by 50% ($P<.002$). IR & DR following interference were reduced by midazolam ($P<.0001$). Delayed recognition of INF words was reduced by 2/3 compared to B and REC. VAS scores of sleepiness increased and concentration decreased markedly following drug infusion ($P<0.006$). VAS scores did not correlate well with memory task scores, indicating that the results of the AVLT were related to the cognitive rather than the sedative effects of midazolam.

CONCLUSIONS: Midazolam in these doses impairs the capacity to acquire new information. This may be due to a) reduced storage capacity of STM, or b) increased vulnerability to interference, or both. Words "learned" under the influence of midazolam are not transferred to permanent storage, and are not available for later recall or recognition. Amnesia from midazolam appears to be compatible with an encoding/consolidation impairment rather than a retrieval deficit.

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TITLE: DOES CHRONIC VERAPAMIL TREATMENT ALTER MALIGNANT HYPERTHERMIA DIAGNOSTIC SKELETAL MUSCLE CONTRACTURE TESTS?

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In vitro halothane (H) and caffeine contractures represent the current methodology for elective malignant hyperthermia (MH) diagnosis. There is evidence to suggest that in vitro and in vivo, calcium channel blockers acutely attenuate the responses to these agents (1,2,3). However the effect of chronic administration of calcium channel blockers on diagnostic muscle contracture responses is unknown.

To determine the in vitro consequences of chronic in vivo verapamil treatment (CVT); seven dogs (3 MH+, 4 MH-) received slow release verapamil 240mg bid for 10 days. This protocol was approved by the animal welfare committee of Univ. of Texas. Fascicles of gracilis muscle were biopsied prior to for control (C) and at the end of CVT. The following tests were performed on 2 fascicles for each: caffeine, 0.5-32 mM; halothane 1% (H1%) plus caffeine, 0.25-32 mM; halothane, 3% followed by succinylcholine, 50 mM (SCh). Contracture tension (CT) was measured for each test and the caffeine specific concentration in the absence (CSC) or in the presence (HCSC) of H% was calculated. Results are presented in Table 1.

Table 1: In Vitro Muscle Contracture Data

		CSC, mM	HCSC, mM	CTH3%, g	CTH3%+SCh, g
MH+	C	2.08 ± .57*	.48 ± .13*	1.33 ± .43*	1.58 ± .36*
	CVT	1.77 ± .45*	.43 ± .14*	2.08 ± .76*	1.74 ± 1.09*
MH-	C	7.93 ± 3.39	2.14 ± .5	0.13 ± .23	.68 ± .36
	CVT	7.90 ± 1.6	2.47 ± .87	0.19 ± .03	.29 ± .17

Mean ± Std, 2 ways ANOVA, * $p < 0.05$ vs MH-

Verapamil and norverapamil concentrations after 8 and 10 days of treatment were 110.2 ± 21.6 ng/ml and 641.7 ± 102.7, respectively.

This study provides original evidence that CVT does not alter in vitro contracture responses to caffeine with and without halothane or halothane with and without SCh in MH+ and MH- dogs. Consequently CVT in patients is not expected to affect MH diagnosis by contracture testing biopsied muscle.

References

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