TITLE: AGING INCREASES PATIENT SENSITIVITY TO THE HYPNOTIC EFFECTS OF MIDAZOLAM

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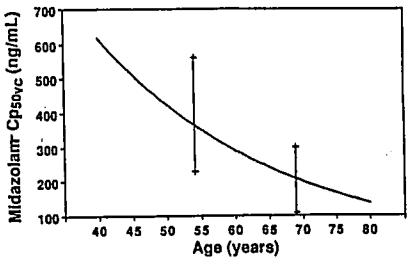
INTRODUCTION: This study was designed to characterize the effects of aging on patient sensitivity to the hypnotic effects of midazolam by determining the Cp50: analogous to MAC. Cp50 is the plasma drug concentration (Cp) at which fifty percent of patients will not respond to a specific stimulus.

METHODS: Thirty-six CABG patients were premedicated with midazolam 1-4 mg: Midazolam was infused for 10 min using a pharmacokinetic model-driven drug infusion device (CACI). A single setpoint concentration of midazolam was used for each patient in this study, and a wide range of setpoints was used across the study population. Plasma midazolam concentration was measured in samples taken from the radial artery catheter at 5 (Cp(t=5)) and 10 min (Cp(t=10)) into the 10 min midazolam infusion. At end of midazolam infusion, the presence or absence of a response to verbal command was established. Cp(t=10), age, and the observed probability of a response to command from each patient were grouped and fit to the logistic model $P=(1+\exp(\beta_0+\beta_1 Cp(t=10)+\beta_2 Age))^{-1}$. With the coefficients, the $Cp50 = -(\beta_0/\beta_1) - (\beta_2/\beta_1)Age$ for response to verbal command ($Cp50_{VC}$).

RESULTS: Ages ranged from 39 to 77. The Cp(t=10) in these patients ranged from 64 to 796 with a median value of 308 ng/mL. Age was found to be a significant (p=0.0228) predictor of $Cp50_{VC}$, which could be calculated for various ages from $Ln(Cp50_{VC}) = 7.934 - (0.037)Age$.(Figure)



DISCUSSION: Sensitivity to midazolam increases as age increases between 40 and 80 years. This work differs from other studies in that the observations were not obfuscated by the use of premedicants other than the study drug, age was considered as a continuous variable, and the assessment of patient responsiveness was made while the plasma concentration of the study drug was stable. Midazolam dosages should be reduced in elderly patients because of increased age related sensitivity.

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TITLE: RELATIONSHIP BETWEEN SERUM F^- AND CYTOCHROME P-450 AFTER SEVOFLURANE ANESTHESIA IN ETHANOL TREATED RATS

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Introduction: Sevoflurane, a newly developed inhalation anesthetic, is the ether containing seven fluoride atoms. It has been shown that inorganic fluoride (F^-) is released when this agent is metabolized in the body. On the other hand, it was demonstrated that liver cytochrome P-450 isozymes appear to exclusively catalyze ether cleavage of the halogenated anesthetics. In the study of the normal liver function, the serum concentration of F^- during sevoflurane anesthesia do not reach the level which cause renal dysfunction. However, metabolism of sevoflurane in cytochrome P-450 induced liver was not examined. Therefor we investigated the relationship between cytochrome P-450 content and serum concentration of F^- in ethanol treated rats which is considered to be induced cytochrome P-450.

Methods: Twenty male Sprague-Dawley rats (200 grs) were randomly divided into 2 groups of 10 rats each: treatment with standard diet and ethanol diet. The conposition of the standard and ethanol diets was as follows: fat, 5%; protein, 8%; carbohydrate, 87% of the total calories and adequate vitamins and minerals; in the standard diet. In the ethanol formula, carbohydrate was isocalorically replaced ethanol to the extent of 42% of the total calories. The two gruops of rats were paired fed isocalorically for 4 weeks. 2.5% sevoflurane was administered in a 30 liter plastic chamber with 30% oxygen and 70% nitrous oxide. The average gas flow through chamber was 3 liter/min. After 2 hours anesthesia, blood sampling was performed from vena cava inferior. The liver was excised and immediately placed in ice-cold 100mM potassium phosphate buffer (pH=7.4), and microsomes prepared in standard fashion. Serum was analyzed for F^- concentration. Cytochrome P-450 content and cytochrome b_5 content were measured by the method of Omura [1]. Data were analyzed for statical significance by using a Student's paired t-test.

Results and Discussion: As shown in table 1, cythchrome P-450 and cytochrome b_5 was induced by the treatment of ethanol diet. And in ethanol diet group serum concentration of F^- was significantly higher than that of standard diet group. This results suggest that cytochrome P-450 and b_5 which were induced by ethanol enhanced sevoflurane defluorination. Previous study suggestd that serum concentration of F^- did not increased in phenobarbital treated rats[2]. Therefore the metabolism of sevoflurane might be associated with cytochrome P-450 and b_5 which were induced by ethanol. In conclusion, it may be as well to avoid sevoflurane anesthesia in the patient of alcoholic liver damage.

Reference
1. J. Biol. Chem. 239:2370-2378, 1964
2. Anesth & Analg 54:829-835, 1975

Table 1 Effect of ethanol treatment of rats on contents of hepatic cytochrome P-450, b_5 and serum F^-

	standard	ethanol
Cytochrome P-450		
n moles/mg protein	1.16 ± 0.35	1.46 ± 0.38
n moles/g liver	14.7 ± 4.61	21.8 ± 2.31**
Cytochrome b_5		
n moles/mg protein	0.48 ± 0.10	0.55 ± 0.14
n moles/g liver	6.09 ± 1.31	8.27 ± 1.11**
Serum F^-		
μM	4.21 ± 1.05	9.99 ± 1.89***

Values are mean ± SD. n=10
** p<0.01, *** p<0.001 vs standard