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Title : Cerebral Effects of Midazolam and Diazepam

Authors : Michael Nugent, M.D., Alan A. Artru, M.D., and John D. Michenfelder, M.D.

Affiliation: Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota 55901
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INTRODUCTION:

Midazolam maleate is a new water soluble benzodiazepine being evaluated for use as an induction agent in anesthesia. It has a shorter half life and causes less pain with intravenous injection than diazepam. The effects of midazolam compared to diazepam on cerebral metabolism and circulation were examined for each drug in 6 mongrel dogs. When it was found that midazolam produced a larger decrease in $CMRO_2$ than diazepam in the dog, the study was extended to evaluate the possibility that midazolam might provide greater cerebral protection from hypoxia than diazepam using a mouse model.

METHODS:

In the dog studies anesthesia was induced with halothane (1%) and nitrous oxide (60-70%) in oxygen. Succinylcholine (100 mg/h) provided muscle relaxation. $PaCO_2$ averaged 40 ± 1 mmHg (mean ± SEM), PaO_2 158 ± 3 mmHg, epidural temperature 36.9 ± 0.0°C, and buffer base 40 ± 1 mEq/L. Mean arterial pressure (MAP) and electroencephalographic activity (EEG) were monitored. The posterior sagittal sinus was cannulated for direct cerebral blood flow (CBF) measurement. $CMRO_2$ was determined as the product of CBF and the arterial-cerebral venous (sagittal sinus) blood oxygen content difference. Cerebral vascular resistance (CVR) was calculated as the ratio of MAP and CBF. At the completion of the surgical procedure halothane was discontinued. After stable base line measurements were established, midazolam was given in sequential intravenous doses of 0.2, 2.0, 5.0 and 10.0 mg/kg and diazepam in doses of 0.3, 3.0 and 7.5 mg/kg with a dosing interval fo 39 ± 1 min (mean ± SEM). Responses of cerebral and systemic variables were determined at 5, 15 and 30 min after each midazolam and diazepam administration. All doses were given as a bolus over 30 seconds. At the conclusion of the midazolam study brain biopsies were taken, and tissue extracts were analyzed by enzymatic fluorometric techniques for ATP, ADP, AMP, phosphocreatine (PCr), glucose, lactate, and pyruvate.

To test for protection against hypoxia 300 adult albino mice (26-40 gr) were injected intraperitoneally with normal saline (control) or increasing doses of midazolam or diazepam. Twenty minutes later the animals were placed alone in airtight chambers. Air was supplied at 4 L/min for 10 min of temperature equilibration (ambient temperature 35°C). Oxygen concentration was then rapidly decreased and maintained at 5% oxygen in nitrogen. Survival time, defined as the time from initiation of hypoxic gas delivery to cessation of respiration, was recorded for each animal.

RESULTS:

$CMRO_2$ did not decrease until after the second dose of midazolam (2.0 mg/kg) or diazepam (3.0 mg/kg) (Table 1). This reduction in $CMRO_2$ was associated with a change in the EEG pattern to a lower frequency and a higher amplitude. Further dose related reductions in $CMRO_2$ were seen after additional doses of diazepam and midazolam. Midazolam (0.2 mg/kg) and diazepam (0.3 mg/kg) decreased cerebral blood flow to about 55% of a 70% N_2O, 0.1% halothane control. In larger doses midazolam decreased CBF to a greater extent than diazepam. The dogs remained hemodynamically stable throughout the study. Assay of cerebral tissue taken at the end of the study from the midazolam treated dogs showed a normal metabolic profile.

In the mouse model for protection from hypoxia both diazepam and midazolam provided significant protection. Diazepam injected mice had a maximal survival time of 6.2 ± 0.1 min at 15 mg/kg compared to a control of 3.9 ± .1 min ($P < .01$). The midazolam treated mice had a survival time of 11.6 ± 1.1 min at a dose of 75 mg/kg vs. a control survival time of 4.0 ± 0.1 min ($P < .001$).

DISCUSSION:

In the dog midazolam at 0.2 mg/kg and diazepam at 0.3 mg/kg (the ED 100% for induction of anesthesia for each drug in man[1]) had similar cerebral metabolic and vascular effects. Both drugs reduced CBF to about 55% of control in this model.

Midazolam provides significantly greater protection from hypoxia (2.9 X control survival time) than diazepam (1.6 X control survival time) in the mouse model. By comparison barbiturates in this model provide a survival time which is 4.0 X control. Midazolam maleate, or a similar benzodiazepine, may be an alternative to the barbiturates in cerebral protection research.

REFERENCE:

1. Reves JG, Corssen G, Holcomb C: Comparison of two benzodiazepines for anaesthesia induction: Midazolam and diazepam. Can Anaesth Soc J 25:211-214, 1978.

TABLE 1. Cerebral metabolic and vascular effects of diazepam and midazolam maleate

Incremental Dose Administered mg/kg[+]		Time After Dose (min)	$CMRO_2$ ml/min/100 gr		CBF ml/min/100 gr	
			Diazepam	Midazolam Maleate	Diazepam	Midazolam Maleate
Control			5.50 ± 0.30[Δ]	5.29 ± 0.31[Δ]	119 ± 13	104 ± 8
Diazepam	Midazolam					
0.3	0.2	5	5.48 ± 0.29	4.74 ± 0.44	66 ± 7*	61 ± 3*
		30	5.42 ± 0.25	5.59 ± 0.50	59 ± 5*	55 ± 3*
3.0	2.0	5	4.46 ± 0.26*	4.08 ± 0.21*	55 ± 5*	37 ± 1*
		30	4.37 ± 0.29*	4.00 ± 0.11*	49 ± 6*	37 ± 0*
7.5	5.0	5	3.93 ± 0.30*	3.44 ± 0.11*	61 ± 8*	34 ± 1*
		30	4.00 ± 0.20*	3.62 ± 0.16*	46 ± 4*	31 ± 1*
--	10.0	5	---	2.90 ± 0.16*	---	32 ± 2*
		30	---	3.27 ± 0.09*	---	30 ± 2*

[+]Dosage interval 39 ± 1 min

[Δ]Mean ± SE for six dogs

*Significantly different from control (paired t, $P < 0.05$)