POSTER SESSION IV

A45

TITLE: ASSESSING AND CHARACTERIZING THE HYPNOTIC AND ANALGESIC EFFECTS OF ANESTHETIC DRUGS

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We have previously described a method of measuring hemodynamic responses to electrical tail stimulation (ETS) in the rabbit (1). We realized that the use of ETS was not only a viable alternative method to tail-clamping, but also it offered a method of applying noxious stimuli gradually in a quantifiable manner. By changing the intensity of ETS, two distinct behavioral responses were noted: a) Head Lift (HL), an arousal response by opening the eyes and lifting the head; and b) Escape Movement (EM) away from the noxious stimulus. Thus we could obtain the responses and plot the threshold voltage (V) versus the drug dosage (Dose) at which HL and EM occurred. The aim of the present study was to characterize the conventional volatile anesthetics (Halothane, Isoflurane, Enflurane) and opioid analgesics (Morphine, Fentanyl, Sufentanil) using the ETS in the rabbit model.

This study was approved by the institutional Animal Care and Use Committee. Previously tracheotomized and cannulated adult rabbits were placed in a hammock that allowed the animal's head and legs to be free to move. Baseline sedation was maintained with a gas mixture of 60% N_2O in O_2 breathed via endotracheal tube throughout the experiment. A pair of needle electrodes were placed in the shaved tail, and electrical current (1 ms, 5 Hz) was delivered gradually from a Grass S48 nerve stimulator.

The responses were consistent and in good agreement with the clinical notion that volatile (halogenated) anesthetics have indeed both hypnotic and anal gesic effects; whereas the narcotic opioids have more analgesic characteristics. All the volatile anesthetics elevated thresholds for both HL (hypnotic) and EM (analgesic) in a dose related manner. In contrast, opioids raised more the EM response, dissociating EM and HL lines divergently (Fig. 1).

The results of animal behavioral responses indicate that our method of using electrical stimulation in characterizing the hypnotic and analgesic anesthetic drugs may be useful. It is simple, quantifiable and reproducible, and it may be applicable to animal and human studies.

Reference: 1. Fukunaga AF, Taniguchi Y, Kikuta Y. Cardiovascular responses to noxious stimuli in experimental animals: "pressor or depressor"? Anesthesiology 72:969-71, 1990.

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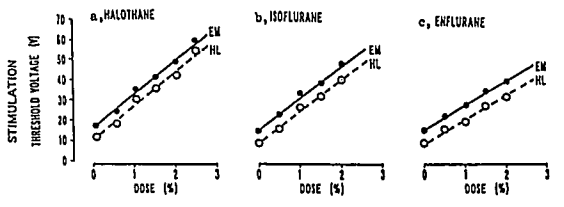

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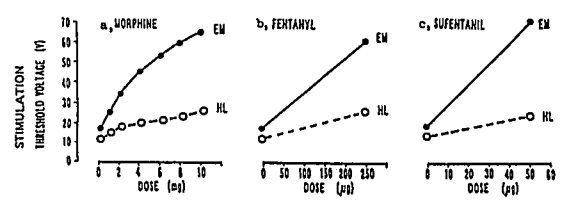

A46

TITLE: Evaluation of the Incomplete Response to Flumazenil

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Flumazenil (RO-15-1788) is a specific benzodiazepine receptor antagonist. In prior studies of flumazenil, using 0.2-1.0 mg to antagonize midazolam-based general anesthesia, only 82% had complete arousal.(1) This study was performed to evaluate whether: 1)there are demographic factors for failure to fully respond; 2) if larger doses of flumazenil (1-8mg) are effective.

This study was part of a multicenter trial. After receiving informed consent, 68 patients (pts) undergoing day surgery were given: midazolam and fentanyl iv (see Table for doses), N2O 60% and isoflurane *via* face mask. Pts alertness/sedation (OAA/S scores 1-5) was assessed on entry to the PACU by a trained observer. Part I: all pts received flumazenil in 0.2 mg increments q 1 min until the OAA/S was ≥ 4. If after 1.0 mg of flumazenil the OAA/S was ≤3, they entered part II (double-blind, randomized, unbalanced): Pts were given test solution (flumazenil 0.1mg/ml or placebo) over 6 min until they achieved an OAA/S ≥ 4 or 70 ml of test solution had been given. Pts alert after ≤1mg flumazenil were compared to those still sedated for differences in demographics, anesthetic conditions, or OAA/S at time of entry into the PACU by unpaired t-test and Mann-Whitney U. Pts in part II were compared for differences in amount of test solution to achieve OAA/S ≥ 4. $P < 0.05$ was considered significant.

Part I:	Responders	Non-Responders	P
n	57	11	
age yrs	45 (15)	54 (12)	.08
kgs	68 (15)	83 (18)	*.002
midaz mg/kg	0.35 (.14)	0.28 (.1)	.11
fent μg/kg	1.2 (.5)	0.98 (.3)	.15
flumaz mg/kg	0.0105 (.003)	0.0125 (.003)	.05
isofl ET%	0.39 (.2)	0.48 (.3)	.20
surgery min	34 (25)	48 (36)	.14
1st OAA/S	1.6	1.18	.11

Values are mean (SD)

Part II: Non-Responders added titration

	Placebo	Flumazenil	P
n	4	7	
+Response	3	6	
add'l ml	36 (29)	25 (25)	.51

+Response means OAA/S ≥ 4 was attained. No major side effects were noted in either part of the study.

Despite giving an ave of 24 mg midazolam over a 36 min anesthetic, 84% of the pts were easily awakened with flumazenil ≤1 mg. The only predictor of non-responder in part I was weight. Interestingly, 3/4 pts who did not initially respond to 1mg flumazenil and received placebo in part II, did respond during the subsequent 6 min of placebo treatment, indicating an ongoing or emerging antagonism of midazolam by flumazenil after the initial titration in part I. Thus, the time from injection to peak effect for flumazenil may be longer than previously expected.

Reference: (1) Anesth Analg 70:S340,1990