TITLE: MIDAZOLAM AND FENTANYL INTERACTION IN REDUCING ENFLURANE MAC

AUTHORS: Ian M. Schwieger, M.D., Richard I. Hall, M.D., FRCP (C) and Carl C. Hug, Jr., M.D., Ph.D.

AFFILIATION: Cardiothoracic Anesthesia Division, Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA 30322

Introduction: Although fentanyl (FEN) and midazolam (MID) are used in combination with inhaled anesthetics to produce anesthesia, the nature of their interaction remains unknown. Studies in man and dogs have demonstrated that neither FEN[1,2] nor MID[3] alone is a complete anesthetic. The purpose of this study was to examine the nature of the interaction between FEN and MID (i.e., additive, synergistic, antagonistic).

Methods: After determination of control enflurane MAC (EMAC) by the tail clamp method, 8 dogs were given a loading dose of FEN followed by a constant infusion of 0.05 $ug \cdot kg^{-1} \cdot min^{-1}$ to reduce EMAC by approximately 10%.[1] This infusion rate was maintained until the administration of naloxone (see below). Following a 60 min observation period, EMAC was determined and then MID was administered to each animal in a series of three incremental infusions (2.4, 9.6, 28.8 $ug \cdot kg^{-1} \cdot min^{-1}$) following appropriate loading doses. These infusion rates were expected to produce a 30%, 45%,and 60% reduction of EMAC, respectively.[3] EMAC was determined following a 60 min observation period for each new infusion rate. At the highest infusion rate associated with no movement, FEN was discontinued and naloxone (NOX) 1 mg/kg was administered every 10 min until EMAC was determined for the last time. Arterial blood was taken for analysis of FEN and MID 45 min after initiation of each infusion rate and every 15 min until EMAC was determined. FEN concentrations in plasma [FEN] were measured by radioimmunoassay, and MID concentrations [MID] by gas-liquid chromatography. Significant differences ($p<0.05$) between the degree of EMAC reduction observed and that predicted by extrapolation of the concentration vs EMAC reduction curves previously determined were identified by the t-test.[1,3] A one-way analysis of variance with replication was used to demonstrate concentration-related differences in the degree of MAC reduction produced by the sequential infusions. Values represent the mean ± SD.

Results: [FEN] remained stable throughout the experiment at 1.0 ± 0.3 ng/ml and, in the absence of MID, reduced EMAC by 28 ± 11% (predicted EMAC reduction 12 ± 3%, $p<0.01$). The addition of MID produced further significant reductions in EMAC (Table). When the further degree of EMAC reduction produced by any [MID] was compared to that predicted, no significant differences were observed. After discontinuation of FEN and administration of NOX, the degree of EMAC reduction returned to that expected to be produced by MID alone.

Discussion: The absence of significant differences between the EMAC produced by the FEN-MID combination and that obtained by extrapolating EMAC from seperate concentration vs EMAC curves for FEN and MID demonstrates the additive nature of the interaction between FEN and MID in the dog. In addition, acute tolerance to MID probably did not develop since the addition of NOX returned the EMAC to that attributed to MID alone. The initial EMAC reduction by FEN was greater than predicted probably because the variability is greater when measuring a relatively small degree of effect. These interpretations are supported by the finding that antagonism of the FEN effect resulted in an EMAC reduction predicted for MID alone. There was no evidence of the development of acute tolerance to midazolam in this study.

References: 1. Murphy MR, Hug CC Jr: The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 57:485-488, 1982.
2. Sprigge JS, Wynands JE, Whalley DG: Fentanyl infusion anesthesia for aortocoronary bypass surgery: Plasma levels and hemodynamic response. Anesth Analg 61:972-978, 1982.
3. Hall RI, Schwieger IM, Hug CC Jr: The anesthetic efficacy of midazolam in the enflurane anesthetized dog. Anesthesiology 68: in press, 1988.

Table. Reduction of enflurane MAC (control = 2.24±0.25%) by fentanyl, by midazolam, and by combinations of midazolam and fentanyl in the dog.

Infusion	% EMAC Reduction	ng/ml of plasma		% EMAC Reduction Predicted*			Observed Minus
ug/kg/min	Observed	[FEN]	[MID]	FEN	MID	FEN+MID	Predicted
FEN 0.05	28±11**	1.1±0.2	--	12±3	--	12±3	+16
FEN + MID 2.4	35±11	1.0±0.3	129±18	11±3	32±1	43±3	-8
FEN + MID 9.6	53±11[a,b]	0.9±0.3	530±75	10±3	46±1	56±2	-3
FEN + MID 28.8	70±9[a,b,c]	0.9±0.2	2139±358	10±2	61±2	71±3	-1
MID + NOX 1 mg/kg	59±10	-	1795±358	--	59±2	59±2	0

[a] $p<0.01$ vs FEN alone
[b] $p<0.01$ vs FEN + MID 2.4
[c] $p<0.01$ vs FEN + MID 9.6
Values = Mean ± SD
**$p<0.01$ vs predicted
*Reduction of EMAC due to (FEN) and (MID) as predicted from [FEN] vs EMAC and [MID] vs EMAC reduction curves obtained from previous experiments.[1,3]

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/69/3A/A559/640106/0000542-198809010-00559.pdf by guest on 18 April 2024