

TITLE: INHALATION ANESTHETICS AND DILTIAZEM ON SPECIALIZED INTRACARDIAC CONDUCTION: AWAKE STATE COMPARISONS IN DOGS

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Introduction. Diltiazem has cardiac electrophysiological actions similar to those of verapamil, and also is effective after intravenous administration against reentrant atrioventricular tachycardia [1]. In association with isoflurane, diltiazem may cause heart block or junctional escape rhythm in dogs [2]. Since knowledge of the exact location of impaired conduction - e.g., at or below the AV node - will determine specific management (pharmacologic vs. electrical) of arrhythmias involving impaired conduction, we determined the effects of diltiazem (DIL) on specialized intracardiac conduction in dogs anesthetized with enflurane (ENF), halothane (HAL) or isoflurane (ISO).

Methods. Mongrel dogs (N=22) were instrumented for chronic His bundle studies. Dogs were anesthetized on six weekly occasions with levels of ENF, HAL or ISO equivalent to 1.2 and 1.6 MAC (order randomized) for the dog. Awake testing preceded testing with the anesthetics. On one of two testing occasions with each anesthetic, after awake testing, the dogs received DIL (bolus = 140 mcg/kg, continuous infusion = 8.5 mcg/kg/min). Dogs were studied awake with DIL, and subsequently with DIL at the 1.2 and 1.6 MAC levels of anesthesia. Anesthesia was induced with the anesthetic in O₂ (F_{IO₂} = 1.0), and maintained at the desired end-tidal level (Beckman LB-2) for at least 20 min prior to measurements. No drugs were given other than DIL or anesthetic. Ventilation was controlled to keep end-tidal CO₂ between 33 and 38 mm Hg (Beckman LB-2). Esophageal temperature ranged between 37 and 39°C. No fluids other than vehicle for DIL (0.9 NaCl = 100 ml) were infused. Plasma DIL levels were determined by high performance liquid chromatography (Pharmaceutical and Toxicology Research Laboratory, Lexington, KY). The Wilcoxon test with an appropriate Bonferroni correction was used for statistical comparisons.

Results. Plasma DIL levels are listed in Table 1, and anesthetic and DIL effects on spontaneous heart rate (HR), AV nodal (AVN), His-Purkinje (HP) conduction times, and mean arterial pressure (MAP) in Table 2. DIL increased HR (ENF and HAL dogs only) and AVN in awake dogs. Anesthetics, with or without DIL had no effect on HR. AVN was prolonged by ENF and HAL, but not ISO. There was comparable prolongation of AVN with all three anesthetics and DIL. DIL did not affect HP. All anesthetics, alone or with DIL, produced similar prolongation of HP. Regardless of anesthetic, or the presence of DIL, no dogs exhibited second degree or higher AV block. Finally, all anesthetics reduced MAP. DIL alone (except ENF dogs) did not affect MAP. The reduction in MAP with anesthesia and DIL was greatest in dogs anesthetized with ENF.

Discussion. These data indicate that compared to awake, ENF and HAL (but not ISO) produce comparable prolongation of AVN. All anesthetics, alone, appear to increase HP. AVN, but not HP is prolonged

by DIL alone. With DIL, there is comparable and added prolongation of AVN by all three anesthetics. We also note that all anesthetics produce similar increases in plasma level of DIL, which may in part explain the similar action of all three anesthetics in combination with DIL at the AV node. Finally, there appears to be no added prolongation of HP with DIL over that caused by anesthesia alone. We conclude that DIL interacts with the ENF, HAL and ISO to produce the greatest impairment of conduction at the AV node. Furthermore, the observed plasma levels of DIL, which are said to be clinically useful [1,2], do not appear likely to cause heart block with any of the major inhalation anesthetics.

References.

1. Rowland E, McKenna WJ, Gulker H, et al: The comparative effects of diltiazem and verapamil on atrioventricular conduction and atrioventricular reentry tachycardia. *Circ Res* 52(Suppl I): 163-168, 1983.
2. Kapur PA, Campos JH, Tippitt SE: Influence of diltiazem on cardiovascular function and coronary hemodynamics during isoflurane anesthesia in the dog. *Anesth Analg* 65:81, 1986.

Table 1. Plasma DIL (ng/ml). All Values Mean ± SEM.

	ENF	HAL	ISO
AWAKE	109±11	94±13	124±9
1.2 MAC	171±32	169±5*	185±12*
1.6 MAC	201±25*	174±12*	235±19*

* P < 0.05 vs awake

Table 2. Heart Rate, Conduction Times and Blood Pressure. All Values are Mean ± SEM.

	HR	AVN	HP	MAP	
ENF (N=10)	AWAKE	112±9	90±5	38±1	101±3
	1.2 MAC	107±5	106±4*	42±2*	73±5*
	1.6 MAC	110±4	104±8	43±2*	68±4*
	DIL	123±7*	99±5*	38±1	94±3*
HAL (N=10)	1.2 DIL	90±3	133±8*	42±1*	59±4*
	1.6 DIL	95±4	133±9*	42±1*	47±4*
	AWAKE	104±3	86±5	34±1	104±6
	1.2 MAC	90±6	105±5*	37±1*	78±5*
ISO (N=10)	1.6 MAC	98±8	110±5*	37±1*	71±4*
	DIL	121±7*	117±9*	35±1	99±4
	1.2 MAC	101±6	134±9*	39±1*	70±5*
	1.6 MAC	106±6	129±4*	40±2*	65±5*
ISO (N=10)	AWAKE	116±6	89±5	37±2	102±3
	1.2 MAC	116±5	94±5	40±2*	67±3*
	1.6 MAC	112±5	97±5*	41±2*	60±3*
	DIL	113±7	116±6*	38±2	95±6
ISO (N=10)	1.2 MAC	103±6	130±8*	41±3*	63±4*
	1.6 MAC	99±6	131±9*	43±2*	59±2*

* < 0.05 compared to AWAKE without DIL