TITLE: AMIODARONE AND HALOTHANE: EFFECTS ON CANINE PURKINJE FIBER ACTION POTENTIALS
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Introduction Amiodarone (A) may produce serious adverse interactions with anesthetics. We used blood cross-perfusion[1] to study the interaction between chronic A therapy and halothane (H) on canine Purkinje fiber (PF) action potentials (AP).

Methods Dogs received 3 wks of oral A therapy (25mg/kg/d x 7d; then 15mg/kg/d x 14-18d). PF were excised from the heart of one dog, and placed into a tissue bath. A second A treated (support) dog, after pentobarbital 30mg/kg, was ventilated (F_iO_2=1.0, PCO_2 35-40 mmHg) and heparinized. A femoral arteriovenous bypass circuit was established to superfuse the excised PF with arterial blood (37°C). APs were recorded from cells impaled with glass microelectrodes. Resting membrane potential (RMP), AP amplitude (AP_{amp}), AP duration to 50% and 90% repolarization ($APD_{50,90}$), and V_{max} were measured. H 0% to 2% (random order) was administered to the support dog and (via the blood perfusate) to the PF. After 40 min, AP measurements were recorded. A control group in which neither PF donor nor support dog had received A was subjected to the same blood cross perfusion protocol. Data were analyzed using ANOVA. ($P<0.05$ was considered significant)

Results 24 PF from 20 A treated dogs superfused with blood from A treated dogs (Serum A = 0.91 µ/ml) were compared with 6 untreated controls. Compared with control fibers, A treated fibers displayed reduced RMP and increased APD_{90}. In the A group, AP_{amp} was reduced by H1% and H2%, and V_{max} was decreased by H2%. APD_{50} was reduced by H2% in both groups and H2% shortened APD_{90} in the A group only. (Table 1)

Discussion The combination of H and A reduced RMP, AP_{amp} and V_{max}. Since conduction depends upon these properties, patients are potentially at risk when these agents are combined. Clinically, this could manifest as heart block or increased susceptibility to reentrant dysrhythmias, especially if the decrease in APD_{90} caused by H2% in group A decreased refractoriness.

References: 1. Circ Res 30:575-587, 1972.

		H0%	H0.5%	H1.0%	H2.0%
RMP	C	-93 ± 3.4	-97 ± 1.9	-97 ± 2.4	-95 ± 3.8
(mV)	A	-87 + 1.2*	-88 ± 1.1	-85 ± 1.0	-85 ± 1.3
AP_{amp}	C	118 ± 1.4	122 ± 3.7	120 ± 2.8	118 ± 2.0
(mV)	A	119 ± 1.3	118 ± 1.0	114 + 1.3*	114 ± 1*
APD_{50}	C	154 ± 17.9	156 ± 16	156 ± 20	141 ± 16*
(ms)	A	147 ± 4.4	149 ± 3.8	144 ± 3.8	132 ± 3*
APD_{90}	C	223 ± 19	233 ± 12	233 ± 17	255 ± 14
(ms)	A	243 ± 4.3*	246 ± 5.2	240 ± 4.7	235 ± 5*
V_{max}	C	363 ± 32	412 ± 24	421 ± 29	425 ± 32
(V/s)	A	478 ± 24	473 ± 23	444 ± 23	434 ± 22*

C = Control group (n=6); A = Amiodarone group (n=24);
*p<0.05: Group A *vs* C; or H1%,2% *vs* H0%; Paced at 2Hz

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TITLE: MECHANISMS MEDIATING THE MODULATION OF BAROREFLEX REGULATION OF CORONARY CONDUCTANCE BY FENTANYL IN CHRONICALLY INSTRUMENTED DOGS

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The present study examines the postulate that opioid receptor activation by fentanyl modulates resting and baroreflex control systems regulating coronary vascular tone. The data obtained is expected to provide insights into the role of neural mechanisms and their disturbances as possible mechanisms for transient myocardial ischemia during the perioperative period.

Methods. Studies were conducted in conscious chronically instrumented mixed breed dogs after prior approval from the Animal Care and Ethics Committee of the University of Newcastle. A chronically implanted cw Doppler flow transducer measured circumflex coronary flow (CF); atrioventricular block was induced by a closed heart technique using 0.05 mL formaldehyde (37%) and ventricles paced at 100 beats min^{-1}. Baroreceptor-coronary dilator responses were evoked by inflation of an intra-aortic balloon which caused an acute rise in aortic (AoP) and carotid pressures. Studies were conducted in 7 dogs prior to and during fentanyl i.v.i. (138, 275, 550, 1100 ng kg^{-1} min^{-1}). Studies were repeated at fentanyl 550 ng kg^{-1} min^{-1} i.v.i. following either: (i) µ-opioid blockade (naloxone, 10 µg kg^{-1} bolus + 1 µg kg^{-1} min^{-1}), (n=5); (ii) total autonomic blockade (TAB; i.v.i. methscopolamine 270 µg kg^{-1}, guanethidine 4 mg kg^{-1}, propranolol 1 mg kg^{-1}, phentolamine 4 mg bolus + 0.1-0.2 mg min^{-1}), (n=5); or (iii) arginine vasopressin (AVP) blockade ($d(CH_2)_5TYR(Me)AVP$, 10 µg kg^{-1}), (n=3).

Results. Low dose (138) fentanyl caused a fall in mean AoP to 92% of pre-infusion control. At higher doses (550, 1100), AoP rose to 119% and 133%, respectively, of control after 20 min infusion. Resting mean CF rose to 111% of control at 5 min at 1100 ng kg^{-1} min^{-1} dosage, and subsequently fell to 89% at 20 min during continued infusion. Low dose (138) fentanyl evoked a rise in coronary conductance (CC) of 112% and falls in CC with higher dosages reaching 67% of control at 20 min after 1100 ng kg^{-1} min^{-1}. The gain of the baroreceptor-coronary dilator response (i.e. δCC%/δAoP%) increased at the lowest dosage (138) to 139% of control and fell to 53% and 43% of control values at 550 and 1100 ng kg^{-1} min^{-1}, respectively. Naloxone abolished the rise in AoP and falls in CF and CC whereas TAB blocked the fall in CC but small rises in AoP to 112% and CF to 111% of post-TAB control values persisted. AVP blockade failed to block the rise in AoP and falls in CF and CC in 2 of 3 dogs.

Discussion. At low opioid stimulation, the balance between competing vasoconstrictor and vasodilator mechanisms activated by fentanyl favors facilitation of baroreflex-coronary dilator responses to improve blood flow to the myocardium. On the other hand, at higher opioid stimulation, resting systemic and coronary vasoconstriction predominate to inhibit reflex blood flow rises evoked through blood pressure rises. Coronary vasoconstriction is primarily neurally mediated and AVP plays a role in the systemic vasoconstriction evoked by fentanyl, but not coronary vasoconstrictor responses at the dosage levels used in the present study. The coronary constriction induced by fentanyl occurring in the face of rises in systemic arterial pressure and the inhibition of baroreceptor-mediated vasodilator responses may contribute to an imbalance between myocardial oxygen supply and demand, particularly in obstructive coronary artery disease.[1]

Reference
1. Thompson et al, Anesthesiology 61:385-393, 1984