

TITLE: INFLUENCE OF IMIPRAMINE AND PARGYLINE ON THE ARRHYTHMOGENICITY OF EPINEPHRINE DURING HALOTHANE, ENFLURANE OR METHOXYFLURANE ANESTHESIA IN DOGS

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Both monoamine oxidase (MAO) inhibitors and tricyclic anti-depressants are effective in treating psychiatric patients, although the mechanism of action is different. MAO inhibitors block oxidative deamination of endogenous monoamines but do not inhibit synthesis of biogenic amines (e.g. norepinephrine) which accumulate in adrenergic nerve terminals. Tricyclic anti-depressants block the reuptake of norepinephrine by adrenergic nerve terminals, while synthesis and release of norepinephrine are not affected. Both classes of drugs are expected to augment intraoperative exogenous administration of catecholamines. This study evaluates the influence of imipramine (a tricyclic antidepressant) and pargyline (a MAO inhibitor) on the arrhythmogenicity of epinephrine during general anesthesia in dogs. Comparisons were made during 1.2 MAC halothane, enflurane or methoxyflurane with 50% N₂-O₂ anesthesia.

METHOD: Eighteen male mongrel dogs weighing 15-20 kg were used in this study. Group One (6 dogs) was treated with oral pargyline 100 mg/day for at least 7 days, while Group Two (6 dogs) was treated with oral imipramine 25 mg/day for the same period. Group Three (6 dogs) served as untreated control. Anesthesia was induced with IV thiopental 15-20 mg/kg to facilitate endotracheal intubation and the lungs were ventilated mechanically to maintain a PaCO₂ of 35-40 torr. Each animal in all groups received 1.2 MAC halothane (1%), enflurane (2.6%) or methoxyflurane (0.28%) in 50% N₂O. The end tidal PCO₂, halothane and enflurane were measured continuously by Beckman Infra-red analyzers. Each animal was studied three times, but only one of the above anesthetic regimens per study, and the order of administration of the anesthetics was randomized. Groups One and Two were studied between day 8-14 during treatment.

Lead II of the ECG, esophageal temperature and arterial pressure were monitored continuously. Esophageal temperature was maintained at 37° ± 1° C. Five percent dextrose in lactated Ringer's solution was infused to maintain an MAP of 80 torr prior to the epinephrine challenge. The volume of crystalloid varied from 10-23 ml/kg with a mean of 15 ml/kg. When the preparation became stable in 30-45 minutes, epinephrine 5 ug/ml was infused at a rate of 1 ug/kg/min with a Harvard syringe pump. The occurrence of three or more consecutive dysrhythmic beats was used as the end point of the epinephrine arrhythmic dose. The epinephrine challenge was not further infused to determine threshold of ventricular tachycardia or fibrillation in order to preserve the animals through all three studies. Statistical comparisons were made using the Student's t-test. P values less than 0.05 were considered significant.

RESULTS: Arterial blood gases taken at 30 minute intervals showed minimal changes in all groups during the course of the experiment: PaO₂ - 190 ± 26 torr, PaCO₂ - 37 ± 2 torr and pH - 7.36 ± 0.07. Summary

of data are presented in tables.

Table 1. Effects of Epinephrine Infusion in the Untreated Group (Mean ± SD, N = 6)

	Control Pressure (torr)	Peak MAP after epi (torr)	PVC epi dose (ug/kg)
Halothane	95±23	147±32	3.8±1.8
Enflurane	90±18	168±30	3.6±1.5
Methoxyfl	97±27	176±42	4.2±1.7*

*3 out of 6 animals; the other 3 received 10 ug/kg without PVC's

Table 2. Effects of Imipramine Pretreatment During Epinephrine Infusion (Mean ± SD, N = 6)

	Control Pressure (torr)	Peak MAP after epi (torr)	PVC epi dose (ug/kg)
Halothane	102±25	180±20	1.43±0.51
Enflurane	101±31	177±22	2.35±0.52*
Methoxyfl	93±29	217±16	3.23±0.32*

*P < .05 from halothane
+P < .05 from enflurane and halothane

Table 3. Effects of Pargyline Pretreatment During Epinephrine Infusion (Mean ± SD, N = 6)

	Control Pressure (torr)	Peak MAP after epi (torr)	PVC epi dose (ug/kg)
Halothane	113±21	143±29	2.84±1.92+
Enflurane	82±19	154±19	5.44±1.17
Methoxyfl	107±34	204±20*	4.97±1.02

*P < 0.05 from enflurane and halothane
+P < 0.05 from enflurane and methoxyflurane

DISCUSSION: The arrhythmogenic dose of epinephrine is significantly lowered in the imipramine pretreated group in comparison with the pargyline pretreated and the control group. Imipramine, like cocaine, blocks the reuptake of norepinephrine by the adrenergic nerve endings. Since the reuptake of catecholamines is the principal mechanism by which catecholamine action is terminated, the results from the imipramine group are compatible with published data. The results also suggest that methoxyflurane > enflurane > halothane in protecting against epinephrine induced ventricular dysrhythmias. Pargyline pretreated dogs required higher doses of epinephrine for the development of PVC's in comparison with the imipramine group notably because pargyline has no effect on the neuronal uptake of catecholamines. The recommendation that discontinuance of MAO inhibitors for at least two weeks before elective surgery is not incompatible with our results. Avoidance of reflex or indirect stimulation of the sympathetic nervous system (i.e. hypotension, hypercarbia, indirect sympathomimetic agents, etc.) can minimize an exaggerated sympathetic response from the pargyline pretreated animals.