Title: THE INTERACTIONS OF TIMOLOL WITH NEOSTIGMINE AND ATROPINE IN DOGS

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Introduction. Timolol is a non-selective beta adrenergic antagonist commonly used as a topical agent in the treatment of glaucoma. Case reports of untoward reactions during anesthesia in patients treated with timolol have been published(1-3). These reactions have included profound hypotension, atropine-resistant bradycardia, and cyanosis. Anticholinesterase drugs used to reverse neuromuscular blockade may exacerbate bradycardia and hypotension associated with the long-acting beta blocking agents. The purpose of this study was to evaluate the interaction of timolol with neostigmine and compare it with the interaction between propranolol and neostigmine.

Methods. Two groups of mongrel dogs (n=6) were anesthetized with thiopental (20 mg/kg) followed by intubation of the tracheal and controlled ventilation with 1% isoflurane and 70% nitrous oxide in oxygen. The electrocardiogram was continuously recorded. A femoral arterial catheter was placed to allow direct continuous blood pressure recording and blood sampling for measurement of arterial blood gas tensions and pH. A pulmonary artery catheter was placed via the right internal jugular vein to allow the measurement of cardiac output. The ventilator was adjusted to maintain partial pressure of carbon dioxide at 33-40 torr. Body temperature was maintained at 36.5 ± 1°C by the use of heating pads. Intravenous fluid replacement was with normal saline at a rate sufficient to keep urine output>1 ml/kg/hr. Vecuronium (0.15 mg/kg) was administered. The heart rate, blood pressure, and cardiac output were measured before and after the administration of isoproterenol (0.1 ug/kg) 30 min after the induction of anesthesia to determine the baseline beta adrenergic response prior to beta blockade. Propranolol or timolol was titrated intravenously in a double blinded fashion; the adequacy of beta blockade was evaluated with isoproterenol. A lack of chronotropic effect was considered evidence of beta blockade. Neostigmine (70 ug/kg) and atropine (30 ug/kg) were administered rapidly 10 min after the establishment of beta blockade. Heart rate, blood pressure, and cardiac output were recorded for 60 min after administration of neostigmine/atropine. An isoproterenol challenge was administered at the end of the 60 min observation period. Data was analyzed using an unpaired Student's t-test. A p value< 0.05 was considered statistically significant.

Results. Intravenous propranolol (0.39 mg/kg) or timolol (0.08 mg/kg) produced beta blockade as evidenced by lack of response to isoproterenol challenge. The response of heart rate, blood pressure, and cardiac output are shown in the table. The administration of neostigmine and atropine in the presence of beta blockade did not result in a decrease in any of the measured parameters.

Discussion. The possibility that timolol produces a more intense blockade than propranolol at lower serum levels is suggested by the fact that published case reports relating intraoperative complications have all occurred in patients using timolol eye drops. One of the cited advantages of topical therapy for glaucoma is the relative lack of side effects. Systemic absorption of timolol does occur, however, and the low serum timolol levels necessary for beta blockade can be achieved. For this reason it is currently believed that patients with any contraindication to beta blockade should not be on timolol eye drops. Plasma levels of 0-5 ng/ml are not unusual in patients treated with topical timolol and have been associated with systemic effects.(2,3)

The administration of anticholinesterase agents in the presence of beta blockade produced by propranolol has been shown to be acceptable by Wagner et al.(4). They achieved beta blockade with propranolol 0.25 mg/kg as compared with 0.39 mg/kg in our study. This may have been due to the fact that we titrated the drug to effect rather than administering a single, large bolus and some of the drug effect could have dissipated with time. Neostigmine was chosen for this study because it may have more muscarinic side effects than either edrophonium or pyridostigmine.

This study suggests that the administration of neostigmine and atropine will not produce adverse reactions with beta blockade and that the reversal of non-depolarizing muscular blockade with this combination seems acceptable in the presence of timolol.

Time	T HR	P	T MAP	P	T	CO P
Baseline	126±7	143±10	78±11	90±11	5.0±.4	5.1±.4
ISO	166±12*	166±15*	52±8	71±7	4.9±.5	5.2±.3
Beta Blockade						
Baseline	112±8	126±7	84±8	85±11	5.1±.5	5.1±.4
ISO	112±8	126±8	84±8	86±11	5.3±.5	5.1±.4
Time after Neo/Atr						
1 Min	114±8	125±7	87±6	84±11	5.6±.8	5.6±.7
3 Min	114±8	124±7	90±7	82±11	5.7±.8	5.5±.7
5 Min	114±8	124±7	92±5	81±10	5.4±.7	5.4±.5
15Min	114±8	124±6	98±9	81±10	5.4±.6	5.6±.6
30Min	113±7	125±6	91±7	84±9	5.4±.6	5.4±.6
60Min	113±7	125±6	94±10	90±7	5.5±.5	5.9±.7
ISO	116±7	132±6	97±11	89±8	5.3±.6	5.7±.7

HR=heart rate, MAP=mean arterial pressure, CO=cardiac output, T=timolol, P=propranolol, ISO=isoproterenol, Neo/Atr=neostigmine/atropine.
*p<0.05 as compared with control. Values=mean±SEM

References.
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