β_1- OR β_2-BLOCKERS TO IMPROVE HEMODYNAMICS FOLLOWING ENDOTRACHEAL ADRENALINE ADMINISTRATION

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SUMMARY

Background: The recommended dose for endotracheal adrenaline (0.02 mg/kg) causes a pronounced initial decrease in diastolic blood pressure which is detrimental at the initial phase of cardiopulmonary resuscitation. This effect was previously attributed to an early and preferential stimulation of the β-adrenergic receptors causing vasodilatation unopposed by an α-adrenergic vasoconstriction. We hypothesized that inhibition of the β_2-adrenoreceptors is responsible for prevention of the deleterious initial decrease in blood pressure that takes place following endotracheal administration of adrenaline.

Methods: Adrenaline (0.02 mg/kg) diluted with normal saline (5 ml) was injected into the endobronchial tree of anesthetized dogs 3 min following pretreatment with the non-selective β-blocker propranolol, selective β_1-blocker metoprolol (0.1 mg/kg, i.v.), or without pre-

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treatment. Heart rate, blood pressure and arterial blood gases were monitored.
Results: The selective β_1-blocker metoprolol was almost as effective as the non-selective β-blocker propranolol in attenuating the initial decrease in blood pressure following endotracheally administered adrenaline, a phenomenon that was previously attributed to inhibition of β-adrenoreceptors.
Conclusions: The outcome of this study might be explained by a dose-related loss of cardioselectivity of metoprolol. Further studies are warranted to refine the pharmacological means to abort the initial blood pressure-lowering effect of endotracheally administered adrenaline.

KEY WORDS

adrenaline, beta-adrenergic antagonist, tracheal, cardiopulmonary resuscitation, dog

INTRODUCTION

In the emergency setting, rapid delivery of resuscitative drugs aiming for prompt effect is crucial. The endotracheal (ET) route is recommended by the American Academy of Pediatrics and the American Heart Association as an alternative method for the administration of drugs, whenever it is impossible to obtain intravenous access /1,2/. The European Committee for Resuscitation recommends that when the endotracheal route is used, the adrenaline (epinephrine) dosage should be 0.02-0.03 mg/kg /3/. We have previously shown that ET adrenaline administration at doses of 0.02 mg/kg /4/ or 0.05 mg/kg /5,6/ produces prompt peripheral vasodilatatory and hypotensive effects that were attributed to β-adrenoreceptor activation. These effects, that are counterproductive in the early phase of the resuscitation due to their ability to lower aortic pressure and to reduce myocardial perfusion pressure, were abrogated by pretreatment with the non-selective β-blocker propranolol /5/.

We hypothesized that inhibition of the β_2-adrenoreceptors is responsible for prevention of the deleterious initial decrease in blood pressure that takes place following endotracheal administration of

adrenaline. To test this hypothesis, we compared the effects of pretreatment with the selective β_1-blocker metoprolol and the non-selective β-blocker propranolol on changes in blood pressure induced by endotracheal adrenaline administration in a dog model.

METHODS

The study was approved by the Animal Care and Users Committee of Tel Aviv University, and the animals were cared for in accordance with national and institutional guidelines.

Five adult mongrel dogs of both sexes, weighing 6-19 kg, were anesthetized with i.v. sodium pentobarbital (25 mg/kg) and intubated orally with a low-pressure cuffed endotracheal tube. Endotracheal tube position was verified by bilateral lung inflation. The animals were ventilated (Harvard Apparatus Dual Phase Control Respirator Pump, South Natick, MA, USA) (FIO_2 = 21) at a respiratory rate of 20 to 24 breaths/min to maintain a $PaCO_2$ of 25-45 mm Hg and a PaO_2 of >90 mm Hg. Both femoral arteries were percutaneously cannulated for the measurement of arterial blood pressure and for blood gas sampling. The arterial catheters were flushed with heparinized saline (1 U/ml) to prevent coagulation at the catheter tips. The saphenous vein was used for administration of fluids and supplemental doses of sodium pentobarbital for maintenance of anesthesia. Heart rate and arterial blood pressure were continuously monitored with a polygraph recorder (79D, Grass Instruments, Quincy, MA, USA).

Each dog received each of the studied treatments in randomized crossover fashion with a 1-week washout period between the different treatments: a) intravenous adrenaline; b) endotracheal adrenaline without pretreatment; c) endotracheal adrenaline following metoprolol pretreatment; and d) endotracheal adrenaline following propranolol pretreatment.

To achieve steady state conditions, the anesthesia induction, endotracheal intubation and catheter insertions were followed by a 20 min stabilization period after which baseline blood samples were drawn. Pretreatment with propranolol (0.1 mg/kg as propranolol HCl; Zeneca Ltd., Cheshire, England) or metoprolol (0.1 mg/kg as metoprolol tartrate; Ciba-Geigy, Switzerland) was administered intravenously 3 minutes before time 0. The doses of metoprolol and propranolol were based on the results of preliminary experiments and

were intended to produce 10% decrease in heart rate. At time 0, adrenaline hydrochloride (Teva Pharmaceuticals Industries, Petach Tikva, Israel) solution (1:1000, w/v) was administered endotracheally or intravenously at a dose of 0.02 mg/kg. Following endotracheal adrenaline administration, the endotracheal tube was immediately occluded with a gloved finger for 5 sec to prevent expulsion of the instilled material, and five forced manual ventilations were delivered with an Ambu bag. Blood samples were drawn at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, and 60 min after adrenaline administration and the concentration of blood gases was determined.

Experimental results were analyzed using BMDP Statistical Software (SPSS, Chicago, IL, USA) by means of analysis of variance with repeated measures. $p < 0.05$ was considered significant.

RESULTS

The blood pressure changes after endotracheal adrenaline administration with or without pretreatment with propranolol or metoprolol are illustrated in Figures 1 and 2. ET administration of adrenaline produced an early and pronounced decrease in systolic, diastolic and mean arterial blood pressure in all dogs as compared to the baseline values (data shown for diastolic and mean blood pressure only). The maximal decreases of blood pressure occurred 30 seconds after injection with recuperation to baseline values a few minutes after adrenaline administration. The observed initial decrease in blood pressure following ET administration of adrenaline was abrogated by pretreatment with either propranolol or metoprolol. Pretreatment with propranolol or metoprolol produced 10% and 20% decrease in heart rate, respectively, compared to the baseline heart rate (data not shown).

DISCUSSION

Adrenaline is a potent vasoconstrictor that increases aortic diastolic pressure by increasing systemic vascular resistance, and improves coronary perfusion pressure and myocardial blood flow /7/. The adrenaline-induced increase in aortic diastolic pressure during cardiopulmonary resuscitation is important for maintaining coronary

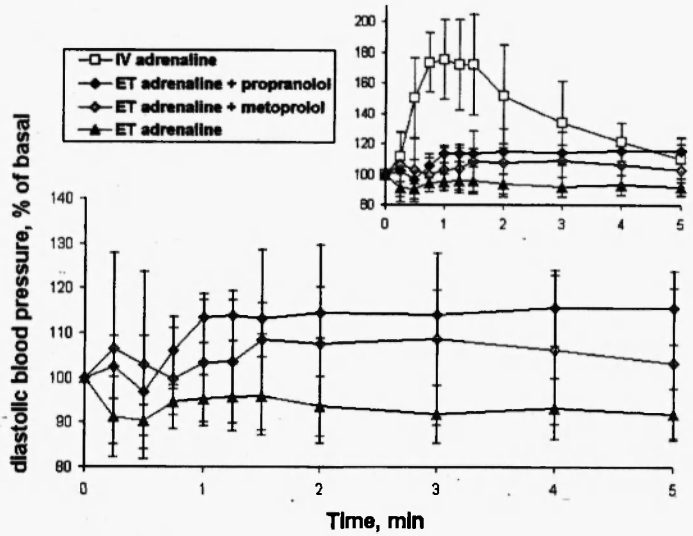

Fig. 1: Diastolic blood pressure (as % of baseline values) in the experimental dogs (mean ± SEM, n = 5) following endotracheal administration of adrenaline with or without pretreatment with propranolol or metoprolol, or intravenous administration of adrenaline (see insert).

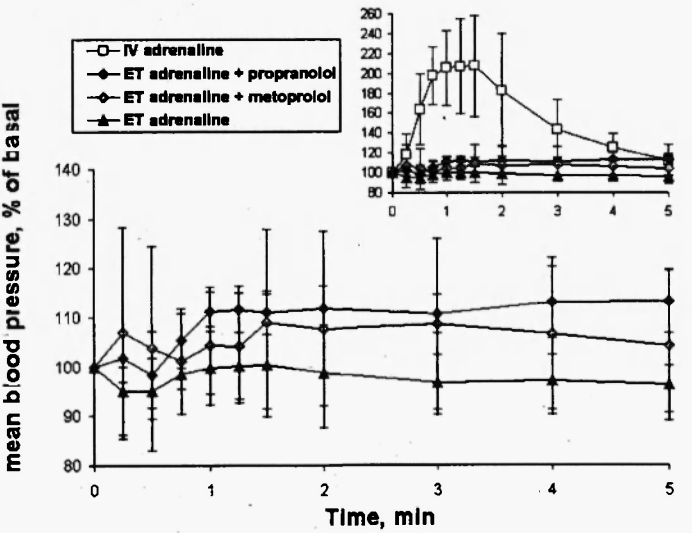

Fig. 2: Mean blood pressure (as % of baseline values) in the experimental dogs (mean ± SEM, n = 5) following endotracheal administration of adrenaline with or without pretreatment with propranolol or metoprolol, or intravenous administration of adrenaline (see insert).

perfusion pressure and myocardial blood flow and is the key to successful outcome in cardiac arrest. In contrast to these α-adrenoreceptor-mediated beneficial effects during resuscitation, the stimulation of the β_2-adrenoreceptors, which normally occurs at lower doses of adrenaline, may be counterproductive by causing peripheral vasodilatation, lowering aortic pressure and reducing coronary perfusion pressure /8/.

Results of clinical studies revealed that endotracheal adrenaline administration exerts deleterious effect on blood pressure during resuscitation /9/. Our previous investigations assessed the nature of this effect and have demonstrated that endotracheal administration of adrenaline (0.02 mg/kg) is associated initially with predominantly β_2-mediated effects (peripheral vasodilatation) that are unopposed by α-mediated effects (vasoconstriction) resulting in hypotension /4,6/. In another study, using a similar experimental model, we demonstrated that ET administration of adrenaline at a dose of 0.05 mg/kg caused a similar initial decrease in blood pressure that was abolished by pretreatment with a non-specific β-blocker (propranolol) and, therefore, was attributed to the preferential initial stimulation of the β-adrenoreceptors /5/.

In order to further investigate the nature of this effect and to determine whether it is mediated by activation of β_1- or β_2-adrenoreceptors, we applied pretreatment with a selective β_1-blocker (metoprolol) or non-selective β-blocker (propranolol). Unexpectedly, metoprolol, a β_1-selective adrenoreceptor antagonist with a weak membrane stabilizing activity and no intrinsic sympathomimethic activity /6/, attenuated the hypotensive effect following ET adrenaline administration that was previously attributed to β_2-adrenoreceptors. The outcome of the current investigation demonstrates that pretreatment with metoprolol was effective to almost the same extent as pretreatment with propranolol in attenuating the initial decrease of the diastolic blood pressure following ET administration of adrenaline.

This outcome may be attributed to the fact that the selectivity of metoprolol and other β_1-specific antagonists to the β_1-receptors is not absolute, and at higher drug concentrations they are also able to exert β_2-antagonist activity /10,11/. The concentration at which this selectivity is lost depends on the specific drug and may be different between species. In this study, relatively high doses of metoprolol (0.1 mg/kg) were applied, as compared to the doses recommended for i.v.

administration in humans (5 mg dose at a rate of 1 to 2 mg per minute, that corresponds approximately to 0.07 mg/kg /12/).

It should be noted that this decrease in diastolic blood pressure was observed following endotracheal administration of adrenaline only, and not following bolus i.v. administration of adrenaline. This outcome is attributed to the differences in relative activation of α-adrenoreceptors and β_2-adrenoreceptors by different concentrations of adrenaline. Relatively slow input of the drug to the central circulation was obtained following ET administration that apparently resulted in preferential activation of β_2-adrenoreceptors and vasodilatation, whereas higher concentrations were obtained following bolus i.v. administration of adrenaline leading to a prominent increase in diastolic blood pressure.

Clinical evaluation of the pharmacological effects of endotracheal administration of adrenaline in humans could not be readily performed due to technical and ethical obstacles. This study applied a non-CPR model /13,14/ in healthy animals to determine the effects of metoprolol and propranolol on the initial decrease in blood pressure following endotracheally administered adrenaline. In such experimental settings the physiological homeostasis may be different from that observed in humans /4/, leading to differences in the pharmacokinetics and pharmacodynamics of adrenaline /15-17/. In addition, direct application of the doses applied in this study to humans is not necessarily appropriate despite similarity in the pharmacological processes related to adrenaline action in humans and other mammals. Therefore, additional studies are necessary for better understanding of the effects of endotracheal adrenaline administration in such hemodynamic scenarios as cardiac arrest, ventricular fibrillation, or cardiac arrest in hypovolemic shock.

CONCLUSIONS

The selective β_1-blocker metoprolol was effective almost to the same extent as the non-selective β-blocker propranolol in attenuating the initial decrease in blood pressure following endotracheally administered adrenaline, a phenomenon that was previously attributed to inhibition of β_2-adrenoreceptors. Further study is warranted to refine the pharmacological means to abort the initial blood pressure lowering effect of endotracheally administered adrenaline.

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