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Alpha$_1$-adrenergic Blockade Raises Epinephrine–Arrhythmia Threshold in Halothane-anesthetized Dogs in a Dose-dependent Fashion

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The authors determined whether increasing alpha$_1$-adrenergic blockade resulted in progressively less arrhythmic activity in the canine halothane–epinephrine arrhythmia model. Dogs (n = 7) were anesthetized with halothane (1.5%) in oxygen. Stepwise increases in steady-state plasma levels of either of two alpha$_1$-adrenoceptor antagonists (droperidol, doxazosin) were produced by applying Wagnerian principles to the known pharmacokinetic parameters of these drugs. At each steady state plasma level of these antagonists, the extent of the alpha$_1$-adrenergic blockade produced was assessed by defining a phenylephrine (PE) dose pressor response curve. The degree of alpha$_1$-blockade produced was quantitated as the dose of PE that caused a 25-mmHg increase in mean arterial pressure (ED_{25}) as derived by polynomial regression analysis. By analysis of variance (ANOVA) the ED_{25} increased significantly for each targeted steady state plasma level of either droperidol ($P < 0.001$) or doxazosin ($P < 0.001$). For an assessment of the antiarrhythmic activity of these alpha$_1$-antagonists, the arrhythmogenic dose of epinephrine (ADE) was determined at each of the states of alpha$_1$-adrenergic blockade previously defined. By ANOVA there was a significant increase in the ADE over the range of alpha blockade produced for either droperidol ($P < 0.001$) or doxazosin ($P < 0.001$). A close correlation (r^2) existed between the ED_{25} and the ADE for the target steady state levels that were achieved for either droperidol (0.99) or doxazosin (0.74). These data support the contention that the antiarrhythmic activity of these antagonists is on the basis of their alpha$_1$ adrenergic blockade, and the authors suggest that this antiarrhythmic action is mediated by blockade of the myocardial alpha$_1$ adrenoceptors. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmia. Pharmacology: doxazosin; droperidol. Receptors: alpha adrenergic. Sympathetic nervous system: catecholamines, epinephrine.)

HALOTHANE sensitizes the heart to the arrhythmogenic potential of catecholamines.[1] The mechanism of arrhythmia production is unknown, but alpha$_1$-adrenergic blockade has been shown in both clinical[2] and experimental[3] studies to be effective antiarrhythmic therapy in this setting. Prazosin, a selective alpha$_1$-adrenergic antagonist, caused an increase in the dose of epinephrine required to induce arrhythmias in halothane-anesthetized dogs to a greater extent than did selective beta$_1$ blockade with metaprolol.[4] These experiments were conducted using a single prazosin dose, calculated to achieve supramaximal alpha$_1$ adrenergic blockade; thus, we could not exclude the possibility that a nonspecific dose-independent action mediated prazosin's antiarrhythmic effect. The current study was designed to determine whether a dose–response relationship between alpha$_1$-adrenergic blockade and antiarrhythmic effect exists in the canine halothane–epinephrine arrhythmia model.

Phentolamine and phenoxybenzamine were not considered appropriate adrenoceptor blockers for this study because they lack either selectivity or specificity for the alpha$_1$-adrenergic receptor.[5] Prazosin was also rejected because it is not readily available for parenteral administration. Droperidol, a selective alpha$_1$ antagonist, has been used experimentally for alpha$_1$-adrenergic blockade[6] and clinically for its antiemetic,[7] sedative,[8] neuroleptic,[9] and antihypertensive effects.[10] These actions of droperidol may be attributed to other pharmacologic properties, including its interaction with dopamine receptors. Droperidol has been shown to possess antiarrhythmic properties, although the mechanism of this protective action was not defined.[2] Doxazosin (UK 33,274) is an alpha$_1$-adrenoceptor antagonist being evaluated as an antihypertensive agent in clinical trials.[11] Doxazosin is functionally and structurally analogous to prazosin and does not exhibit central nervous system side effects.[12]

Based on the pharmacologic profiles of droperidol and doxazosin, we selected these novel alpha$_1$-antagonists to determine whether putative antiarrhythmic activity is a dose-dependent property of their alpha$_1$-adrenergic blockade.

Methods

Anesthesia was induced and maintained in seven unpremedicated dogs with halothane 1.5% in oxygen. End-tidal halothane and carbon dioxide were monitored continuously (Beckman). The dogs were intubated without

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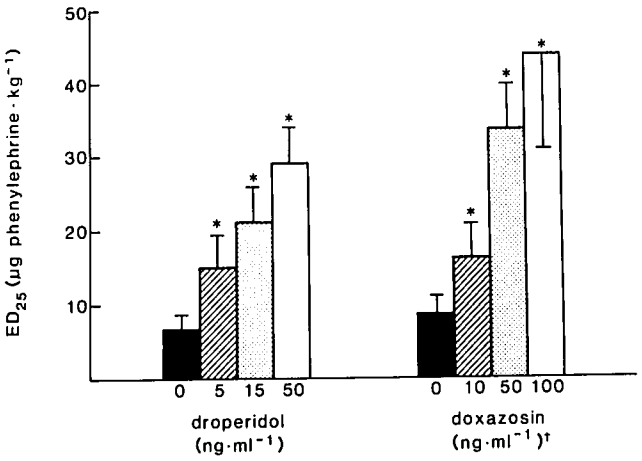

FIG. 1. Alpha-adrenergic blockade at different plasma levels of antagonist in halothane-anesthetized dogs (n = 7). The degree of alpha-adrenergic responsiveness (ED_{25}) is quantified by the dose of phenylephrine required to increase the mean arterial pressure by 25 mmHg as described in "Methods." *Significantly different ($P < 0.001$) from the preceding value by paired t test with Bonferroni correction. †For droperidol the plasma levels were confirmed by assay, while the levels for doxazosin are the predicted values.

muscle relaxants and ventilated to achieve normocarbia. Arterial pressure was continuously monitored through a percutaneously placed femoral arterial catheter. Five per cent dextrose is 0.2% NaCl was infused through a foreleg vein at 4 $ml \cdot kg^{-1} \cdot h^{-1}$. Sodium bicarbonate, 89 mEq/l, was added to prevent the metabolic acidosis noted with repeated epinephrine infusions.[13] Arterial blood gas analyses were performed to confirm normal acid–base status, and additional correction with sodium bicarbonate was not required. Nasal temperature was monitored and maintained at 38.5° C with warming blankets and heating lamps. End-tidal carbon dioxide, end-tidal halothane, arterial pressure, and lead II of the ECG were continuously recorded on a strip chart recorder (Beckman).

Blood pressure response curves to the selective $alpha_1$-adrenergic agonist, phenylephrine, were defined according to a modification of the method of Hamilton and Reid.[14] Phenylephrine, 100 $\mu g \cdot ml^{-1}$, was infused (Harvard Syringe Pump®) over 1 min, and the highest mean arterial pressure (MAP) achieved was noted. By 10 min, the MAP had returned to the basal state. Logarithmically spaced doses, ranging from 1.25 $\mu g \cdot kg^{-1}$ to 50 $\mu g \cdot kg^{-1}$, were infused at 10-min intervals. Phenylephrine log dose pressor-response curves were derived by polynomial regression,[15] and the dose of phenylephrine corresponding to a 25-mmHg increase in MAP (ED_{25}) was calculated. The ED_{25} was then used as a measure of $alpha_1$-adrenergic responsiveness.

Using known pharmacokinetic data,‡ droperidol infusion regimens were calculated to produce steady state plasma concentrations of 5, 15, and 50 $ng \cdot ml^{-1}$. Plasma was sampled for droperidol analysis by an HPLC technique using a C 18 reverse phase column as the stationary phase and 60% acetonitrile, 40% 0.01 M KH_2PO_4, pH 3.9 at 50° C as the mobile phase.[16] The ED_{25} then was redetermined at each droperidol steady state. In separate experiments, doxazosin regimens were calculated from known pharmacokinetic parameters§ and this drug infused to produce target steady state plasma doxazosin concentrations of 10, 50 and 100 $ng \cdot ml^{-1}$. The increase in ED_{25} with progressively higher droperidol or predicted doxazosin plasma levels was used as a measure of the degree of $alpha_1$-adrenergic blockade obtained. At each of these states of either droperidol or doxazosin induced alpha-adrenergic blockade, the arrhythmogenic dose of epinephrine (ADE) was determined. The ADE was defined as that dose of epinephrine required to produce four or more ventricular ectopic beats within 15 s.[17] Epinephrine doses were logarithmically increased after a 10-min recovery period until an arrhythmia threshold was achieved and the ADE thereby established. For the doxazosin studies, the ED_{25} and the ADE were determined during the course of a single experiment, while for the droperidol experiments the data pairs (ED_{25}, ADE) were obtained on separate days (minimum 7 days apart) in the same animals under similar conditions. The changes in both the ED_{25} and ADE at each of the droperidol levels were compared by analysis of variance for repeated measurements followed by pairwise comparisons of successive values using the paired t test with Bonferroni correction for multiple comparisons.[18] The ED_{25} and ADE data for doxazosin were analyzed in a similar fashion.

Results

The degree of alpha-adrenergic blockade obtained, as reflected by the ED_{25} value, increased progressively over the range of droperidol steady state levels achieved (fig. 1). Analysis of variance for repeated measures yielded an F statistic of 86, which exceeds the critical $F_{3,18}$ 0.001 value. At each successive concentration of droperidol, the ED_{25} values were significantly increased ($P < 0.001$). The ADE values at each of the droperidol-induced states of $alpha_1$-adrenergic blockade were significantly greater ($P < 0.001$) than the previous value (fig. 2). The relationship between the ED_{25} and the ADE values is shown in figure 3*A* and reveals a significantly positive correlation with an r^2 value of 0.99.

The results of the experiments conducted with doxazosin were similar. By analysis of variance the ED_{25} values significantly increased with the increase in predicted doxazosin plasma level with an F statistic of 154, which ex-

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§ Personal communication; NJ Cussans, Pfizer Central Research, Sandwich, Kent, England.

ceeds the critical $F_{3,18}$ 0.001 value (fig. 1). By the paired t test with Bonferroni correction there was a significantly ($P < 0.001$) greater degree of alpha$_1$-adrenergic blockade produced at each level (fig. 1). The antiarrhythmic effect of doxazosin on the halothane–epinephrine interaction increased progressively and significantly with each increase in the predicted doxazosin plasma level obtained ($P < 0.001$) (fig. 2). The individual ADE and ED_{25} values at the different doxazosin levels are significantly positively correlated ($P < 0.001$) with an r^2 value of 0.74 (fig. 3*B*).

Discussion

The precise mechanism whereby halothane sensitizes the heart to the arrhythmogenic interaction with epinephrine remains unknown. Recently we suggested that both alpha$_1$ and beta$_1$ adrenoceptors are required for the full expression of the effect of halothane to sensitize the heart to exogenously administered catecholamines.[4] However, the arrhythmia threshold for epinephrine was increased to a greater extent by alpha$_1$-adrenergic blockade than by relatively selective beta$_1$-adrenergic blockade.[4] The dose of adrenoceptor antagonist that we used in the earlier study was chosen to provide supramaximal adrenergic blockade, and at these doses nonspecific antiarrhythmic effects may become operative. Now our data indicate that in the halothane-anesthetized dog model the antiarrhythmic effect of droperidol and doxazosin on epinephrine-induced ventricular arrhythmias increases proportionately, in a dose-dependent manner, with alpha$_1$-adrenergic blockade.

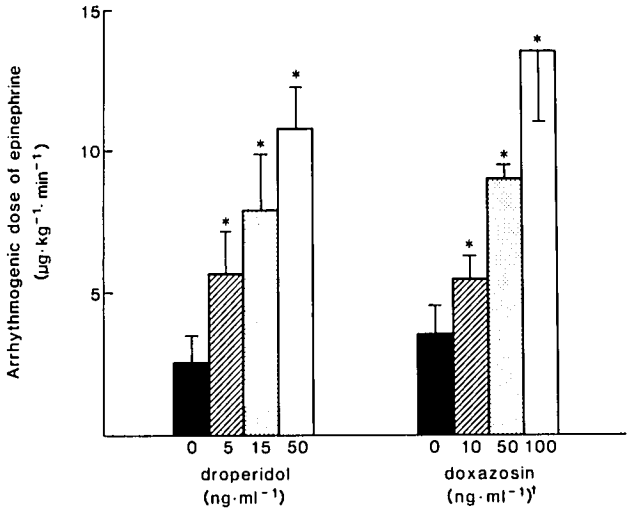

FIG. 2. Arrhythmogenic dose of epinephrine at different plasma levels of droperidol and doxazosin in halothane-anesthetized dogs (n = 7). The arrhythmogenic potential at different steady states of alpha-adrenergic antagonist is determined by the dose of epinephrine needed to achieve an arrhythmia threshold as described in "Methods." *Significantly different ($P < 0.001$) from the preceding value by paired t test with Bonferroni correction. †For droperidol the plasma levels were confirmed by assay while the levels for doxazosin are the predicted values.

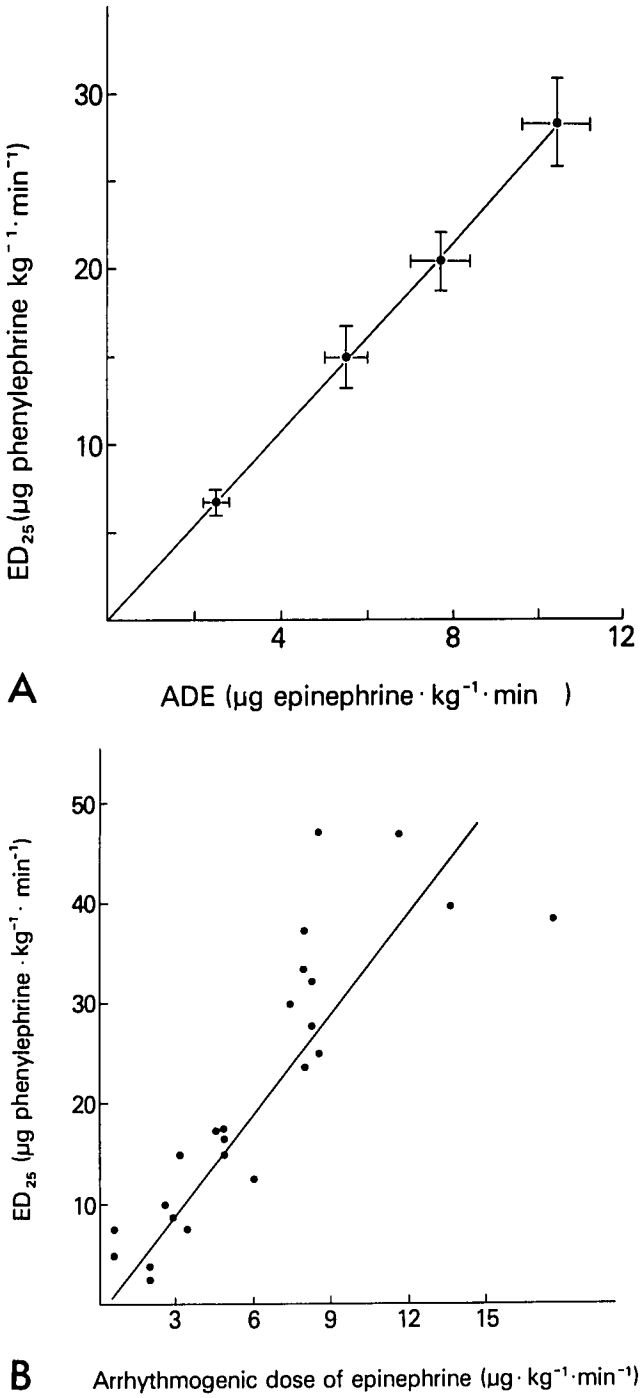

FIG. 3. Relationship between alpha-adrenergic blockade (ED_{25}) and arrhythmia threshold (ADE) for droperidol (*A*) and doxazosin (*B*) in halothane- (1.5%) anesthetized dogs (n = 7). For droperidol (*A*) data are represented as means ± SEM at each plasma level as the ED_{25}, and ADE values were obtained in separate experiments. The ED_{25} and ADE data were obtained during the same anesthetic for the doxazosin experiments (*B*).

Zink *et al.*[19] suggested that the heart may not be the principal site for the arrhythmogenic interaction between epinephrine and halothane. They argued that a critical blood pressure was needed before arrhythmias occurred and that an increase in afterload *via* the resistance vessels of the peripheral vasculature caused arrhythmogenic "stretching" of the Purkinje fibers.[20] By extending their line of reasoning, any maneuver that attenuates the epinephrine increase in afterload may lessen the likelihood of arrhythmia production. However, there are now several lines of evidence that the peripheral vasculature is not solely responsible for the halothane–epinephrine arrhythmia interaction. First, this interaction can be demonstrated both in an isolated perfused Langendorff heart preparation[21] and in myocardial cell culture.[22] Second, while sodium nitroprusside will prevent the increase in afterload effect of epinephrine, this antihypertensive action did not exert any antiarrhythmic activity in the halothane-anesthetized dog model.[4] Atlee's group demonstrated that, while pretreatment with either thiopental[23] or ketamine[24] could decrease the threshold for halothane–epinephrine arrhythmias, the onset of arrhythmias was not in any way correlated to the achieved blood pressure. Similar observations were made in this study. Therefore, we consider the suggestion that the antiarrhythmic effect of the alpha$_1$-adrenergic blockers is on the basis of their hemodynamic effects on the peripheral vasculature unlikely.

Another possible site at which antiarrhythmic drugs may exert their effect is the central nervous system.[25] While droperidol clearly possesses potent central nervous system effects, doxazosin does not cross the blood–brain barrier to any great extent and does not exhibit any central effects.[12]

We submit that the antiarrhythmic action of these two alpha$_1$-adrenoceptor antagonists is on the basis of their blockade of myocardial alpha$_1$-adrenergic receptors. The existence of alpha$_1$-adrenergic receptors on mammalian heart has only recently been demonstrated,[26] although the physiologic effects consequent on stimulation of these receptors remain controversial.[27] However, the role of the myocardial alpha adrenoceptor in the mediation of ventricular arrhythmias, especially in the setting of ischemia, is now well documented.[28–32] We speculate that the arrhythmogenic interaction of epinephrine in the presence of halothane anesthesia is mediated by the myocardial alpha$_1$-adrenergic receptor–effector mechanism. The precise molecular basis whereby this is achieved is currently being investigated.

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