Arrhythmogenic potential of dopexamine hydrochloride during halothane anaesthesia in dogs

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Dopexamine hydrochloride (Dopacard®) is the novel synthetic catecholamine designed for use in the acute management of a low cardiac output status. In addition to dopaminergic receptor stimulation, dopexamine hydrochloride is a potent β_2 adrenoceptor agonist with negligible direct β_1 and no alpha adrenergic effect. The objective of this study was to compare the arrhythmogenic effects of dopexamine hydrochloride and dopamine in dogs anaesthetized with halothane (1.2 MAC). The starting dose for dopexamine hydrochloride was $3.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and for dopamine was $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Concentrations of the drugs were increased until four or more premature ventricular contractions within 15 seconds were produced. All dogs developed ventricular tachycardia when dopamine was administered in concentrations ranging between 18 – $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Unlike dopamine, dopexamine hydrochloride even at concentrations as high as $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ did not induce any atrial or ventricular ectopic beats. Lack of β_1 and alpha adrenergic agonist effects is a likely explanation for low arrhythmogenicity of dopexamine hydrochloride. Both drugs increase cardiac output; dopexamine hydrochloride primarily by a dose-related increase in heart rate and increased afterload. At the maximal concentration dopexamine hydrochloride increased heart rate from 114 to 150 $\text{beat} \cdot \text{min}^{-1}$, mean arterial pressure decreased from 81 mmHg to 45 mmHg and SVR decreased from 2418 to 962

$\text{dyne} \cdot \text{sec}^{-1} \cdot \text{cm}^{-5}$. Myocardial contractility increased only moderately, as evaluated by dP/dt , which increased from 1290 to 1696 $\text{mmHg} \cdot \text{sec}^{-1}$. Dopamine had a more marked inotropic effect: the dP/dt increased, at the maximal concentration, from 1480 to 2570 $\text{mmHg} \cdot \text{sec}^{-1}$. Dopamine also produced vasoconstriction: SVR increased from 2325 to 2683 $\text{dyne} \cdot \text{sec}^{-1} \cdot \text{cm}^{-5}$ and mean arterial pressure from 86 mmHg to 110 mmHg. In conclusion, dopexamine hydrochloride is less arrhythmogenic than dopamine, has less of an inotropic effect, and a greater effect on afterload.

L'hydrochlorure de dopexamine (Dopacard®) est une nouvelle catécholamine synthétique destinée au traitement des états de bas débit cardiaque. En plus de stimuler les récepteurs dopaminergiques, l'hydrochlorure de dopexamine est un agoniste adrénocepteur β_2 puissant avec effets directs β_1 négligeables mais sans effets alpha-adrénergiques. Cette étude vise à comparer les effets arythmogènes de l'hydrochlorure de dopexamine avec la dopamine sur des chiens anesthésiés à l'halothane (1,2 MAC). La dose initiale d'hydrochlorure de dopexamine est de $3,5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ et de dopamine de $3,5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. La concentration des drogues a été augmentée jusqu'à l'apparition de quatre contractions prématurées ou plus en deçà de 15 secondes. Tous les chiens ont développé de la tachycardie ventriculaire pendant l'administration de dopamine à des doses se situant entre 18 et $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Contrairement à la dopamine, l'hydrochlorure de dopexamine n'a pas provoqué de battements ectopiques auriculaires ou ventriculaires même à des concentrations aussi élevées que $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. L'absence d'effets β_1 et agonistes alpha-adrénergiques constitue une explication plausible pour la faible arythmogénécité de l'hydrochlorure de dopexamine. Les deux drogues augmentent le débit cardiaque; l'hydrochlorure de dopexamine principalement par augmentation en rapport avec la dose de la fréquence cardiaque et une baisse de la post-charge. A la concentration maximale d'hydrochlorure de dopexamine, la fréquence cardiaque augmente de 114 à 150 $\text{b} \cdot \text{min}^{-1}$, la pression artérielle moyenne baisse de 81 à 45 mmHg et la résistance vasculaire systémique (RVS) baisse de 2418 à 962 $\text{dyne} \cdot \text{sec}^{-1} \cdot \text{cm}^{-5}$. La contractilité myocardique

Key words

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mesurée par le dP/dt n'augmente que modérément de 1290 à 1696 mmHg $\cdot$ sec⁻¹. Par contre, la dopamine a un effet inotrope plus marqué: le dP/dt augmente de 1480 à 2570 mmHg $\cdot$ sec⁻¹ à la concentration maximale. La dopamine produit aussi de la vasoconstriction: la RVS augmente de 2325 à 2683 dyne $\cdot$ sec $\cdot$ cm⁻⁵ et la pression artérielle moyenne de 68 mmHg à 110 mmHg. En conclusion, l'hydrochlorure de dopexamine est moins arythmogène que la dopamine, a moins d'effets inotropes mais agit plus sur la post-charge.

Dopexamine hydrochloride (Dopacard) is a short-acting analogue of dopamine, with a pharmacological profile that offers some advantages over dopamine and dobutamine in the treatment of severe congestive heart failure. It is a dopaminergic receptor agonist and a β_2 -adrenoreceptor agonist devoid of α and direct β_1 receptor activity.¹ This profile offers some advantages over other inotropes in terms of a greater reduction in afterload and less positive inotropic effect.² Strong positive inotropy is usually mediated by β_1 -adrenoreceptor agonism and may be undesirable because of its effect on myocardial energy requirements and arrhythmogenicity.^{1,2}

In both conscious and anaesthetized dogs, dopexamine hydrochloride (in doses ranging from 12.3 to 40 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) causes a dose-related decrease in blood pressure and peripheral vascular resistance together with a moderate increase in heart rate and myocardial contractility. In clinical studies of patients with severe congestive heart failure,¹⁻³ dopexamine hydrochloride improved ventricular performance but this effect diminished with long-term infusion.⁴⁻⁷

The parenteral administration of catecholamines (epinephrine, dopamine, or dobutamine) during halothane anaesthesia can initiate malignant ventricular tachycardia.⁸ Although the exact mechanism by which halothane sensitizes the myocardium to catecholamines is poorly understood, it has been assumed that stimulation of beta-adrenergic (β_1 and β_2) and/or alpha adrenergic receptors is mainly responsible for these arrhythmias.⁸⁻¹¹

The purpose of this study was to determine whether infusion of dopexamine hydrochloride, given in increasing concentration, would induce ventricular arrhythmias during halothane anaesthesia in dogs. Haemodynamic and arrhythmogenic effects of dopexamine hydrochloride were compared with those produced by an infusion of dopamine. Halothane was used because the amount of adrenergic agent that will elicit such arrhythmias is less during halothane anaesthesia than with other presently used inhalational anaesthetics. Dogs were used because most of the previous experiments on catecholamine-induced arrhythmias during halothane anaesthesia were done using the dog model.

Methods

Following approval of the protocol by the Institutional Animal Investigation Committee, eight mongrel dogs of either sex, weighing 18–20 kg, were anaesthetized with thiopentone 10 $\text{mg}^{-1} \cdot \text{kg}^{-1}$ *iv*. Tracheal intubation was performed and then mechanical ventilation instituted to maintain pH 7.35 ± 0.5 , and PaCO_2 35–40 mmHg. Anaesthesia was maintained with halothane in oxygen at an end tidal concentration of 1% (1.2 MAC), which was continuously monitored using an airway gas analyzer (Datex 254, Datex/Puritan Bennet Co., Wilmington, MA).

Oesophageal temperature was servo-controlled between 37–39°C with a heating lamp. Normovolaemia was maintained by infusing lactated Ringer's solution via an intravenous cannula at a rate of 4 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. A 14-gauge polyurethane cannula was inserted into the femoral artery to measure aortic pressure and for obtaining intermittent arterial blood gas and electrolyte measurements. A 7.5 F thermodilution pulmonary artery catheter was placed in the pulmonary artery via the femoral vein.

Aortic, pulmonary artery, and central venous pressures were continuously monitored and intermittent pulmonary artery capillary wedge pressures (PACWP) were determined. Intermittent thermodilution cardiac output (CO) measurements were obtained, and recorded as the mean of three measurements.

A micromanometer-tipped catheter (Millar Instrument Model PC 350) was used to measure dP/dt and left ventricular (LV) pressure. The catheter was inserted into the left ventricle via the left atrium using a left thoracotomy incision. Cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) were calculated using the standard formulas.

Following 60 min of haemodynamic stability during halothane anaesthesia, either dopamine or dopexamine hydrochloride was infused in a randomized order with an infusion pump. The starting dose for dopexamine hydrochloride was 3.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and for dopamine was 5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Drugs were given in standardized logarithmically spaced increasing doses for dopamine (5.0, 6.1, 7.4, 9.0 etc. $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and for dopexamine hydrochloride (3.5, 4.3, 5.2, 6.4 etc. $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The arrhythmogenic dose was defined as the dose ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) which produced four or more premature ventricular contractions within 15 sec. In the absence of arrhythmias during three minutes of drug infusion, the infusion was terminated for ten minutes, and then the next higher dose was repeated until the arrhythmogenic dose was reached.

After establishment of the arrhythmogenic dose and a 30 min recovery period, the arrhythmogenic dose of

the second drug was determined, by the same method. The sequence of the administered drugs was altered in each experiment.

Statistical methods

All data are presented as mean $\pm$ SD of the mean. Significant changes among multiple observations for each variable were detected by two-way analyses of variance, and individual differences between observations were then determined using a paired *t* test.

Results

All dogs, during 1.2 MAC halothane anaesthesia, developed ventricular tachycardia when dopamine was administered at concentrations ranging between 18–20 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Unlike dopamine, dopexamine hydrochloride even at concentrations as high as 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ failed to induce any cardiac arrhythmias. The haemodynamic effects of the maximum dose of dopexamine hydrochloride and dopamine are presented in the Table. Dopexamine hydrochloride produced a dose-related decrease in blood pressure and total peripheral resistance, with increases in cardiac output, contractility (dP/dt) and heart rate. In contrast, dopamine increased both blood pressure and heart rate and produced a dose-related increase in contractility (dP/dt).

Discussion

There is a concern that inotropic stimulation as a means of treating heart failure may cause deterioration of an already damaged myocardium.^{1,2} An alternative approach to the management of congestive heart failure has been successfully established with the use of vasodilatation that improves cardiac output by reducing afterload.¹ One mechanism for afterload reduction is stimulation of β_2 adrenoreceptors.^{3,5} The β_2 adrenoreceptors are located in arterial vascular smooth muscle and mediate vasodilatation. Recently, it has been recognized that the β_2 adrenoreceptors also coexist in the heart with β_1 adrenoreceptors where they have both inotropic and chronotropic actions in response to catecholamine stimulation.^{12,13} The β_2 adrenoreceptors may assume increased importance in the late stage of congestive heart failure because of a decrease in density and responsiveness of cardiac β_1 adrenoreceptors. This down regulation does not occur with β_2 adrenoreceptors.^{12,13}

Dopexamine hydrochloride produces afterload reduction as a result of β_2 adrenoreceptor stimulation, but in contrast to other inotropes, has minimal effect at β_1 and α adrenoreceptors.

Clinical trials in patients with acute exacerbation of chronic severe heart failure and in acute cardiac failure following myocardial infarction indicate that dopexamine

TABLE The haemodynamic effects of the maximally used dose of dopexamine hydrochloride and dopamine (Mean $\pm$ SD).

	Dopamine*	Dopexamine hydrochloride†
Heart rate (beats $\cdot$ min ⁻¹)		
Baseline	118.1 $\pm$ 3	114.6 $\pm$ 4
Max infusion	131.8 $\pm$ 5	150.1 $\pm$ 6‡
Systolic pressure (mmHg)		
Baseline	109.5 $\pm$ 4	105.6 $\pm$ 3
Max infusion	170.8 $\pm$ 6‡	70.3 $\pm$ 3‡§
Diastolic pressure (mmHg)		
Baseline	72.6 $\pm$ 3	69.1 $\pm$ 4*
Max infusion	90.5 $\pm$ 4	32.6 $\pm$ 1‡§
Mean arterial pressure (mmHg)		
Baseline	86.1 $\pm$ 4	81.0 $\pm$ 5
Max infusion	110.8 $\pm$ 3	45.1 $\pm$ 4‡§
dP/dt mmHg $\cdot$ sec ⁻¹		
Baseline	1480 $\pm$ 30	1290 $\pm$ 28
Max infusion	2570 $\pm$ 42‡	1690 $\pm$ 36
Cardiac Index (L $\cdot$ min ⁻¹ $\cdot$ m ⁻²)		
Baseline	2.75 $\pm$ 0.4	2.4 $\pm$ 0.3
Max infusion	3.7 $\pm$ 0.5	5.2 $\pm$ 0.4‡
Stroke volume index (ml $\cdot$ m ⁻²)		
Baseline	30 $\pm$ 1	24.5 $\pm$ 2
Max infusion	38.3 $\pm$ 2	31.8 $\pm$ 1
Systemic vascular resistance dyne $\cdot$ sec $\cdot$ cm ⁻⁵		
Baseline	2325 $\pm$ 32	2418 $\pm$ 28
Max infusion	2683.3 $\pm$ 36	962.5 $\pm$ 35‡§

*Maximal infusion, dopamine 18–20 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

†Maximal infusion, dopexamine 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

‡*P* < 0.05 when comparing baseline with maximal infusion value, same group.

§*P* < 0.05 when comparing maximal infusion values dopamine vs. dopexamine group.

hydrochloride produces beneficial systemic vasodilatation coupled with an improvement in myocardial function.^{5,6,14} Dosages used in these studies ranged from 1 to 8 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Santman⁷ successfully used dopexamine hydrochloride to treat low cardiac output after cardiac surgery. In this study dopexamine hydrochloride was used over 24 hr in doses from 1 to 4 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Parrat *et al.*¹⁵ reported that dopexamine hydrochloride was associated with a lower incidence of ventricular arrhythmias following coronary artery ligation in animal models of myocardial ischaemia. This lower arrhythmogenic potential of dopexamine hydrochloride was explained by its relative lack of activity at β_1 adrenoreceptors which have been implicated in dysrhythmias induced by other ca-

techolamines. Studies of isolated cardiac conduction tissue also suggest that under ischaemic conditions dopexamine hydrochloride has a class I-like antiarrhythmic effect.¹⁵

Our haemodynamic data revealed that both drugs, dopamine and dopexamine hydrochloride, augmented cardiac performance (Table) as displayed by increased cardiac output and LV dP/dt. The mechanism by which this was achieved was different. In the case of dopexamine hydrochloride, the increase in cardiac output resulted mainly from the decrease in systemic blood pressure (decreased afterload) and from the resultant increased heart rate. There was also a moderate increase in myocardial contractility as assessed by the moderate increase in LV dP/dt. In contrast, dopamine produced an increase in cardiac output and stroke volume index apparently through a combination of increased heart rate and contractility (dP/dt). It appears that dopamine increased cardiac performance predominantly through a positive inotropic effect. Similar haemodynamic data from anaesthetized dogs were reported by other investigations.^{1,3,15}

Despite extensive investigation, the exact mechanism by which catecholamines induce arrhythmias during halothane anaesthesia has not been established. Katz *et al.*^{8,11} reported that stimulation of myocardial beta adrenoreceptors β_1 and β_2 was mainly responsible for these arrhythmias. Hayashi *et al.*⁹ have shown in dogs that the cardiac β_1 adrenoreceptors play an important role in the genesis of myocardial sensitization by halothane, whereas the role of the β_2 receptor is insignificant. Maze *et al.*¹⁰ used selective adrenergic receptor blockade in dogs anaesthetized with halothane and exposed to epinephrine to determine whether ventricular arrhythmias were associated with α or β receptor activity. These results supported a predominant role for alpha-adrenergic agonists in epinephrine-halothane arrhythmias. This is in contrast to the widespread clinical observation of a higher incidence of these arrhythmias after the administration of a beta agonist.¹⁴ Furthermore Zuckerman *et al.*¹⁶ demonstrated little arrhythmogenic activity in myocardial cells exposed to an alpha-adrenergic agonist with or without halothane. Beta adrenergic agonist exposure resulted in more arrhythmogenic activity.

Our data confirmed that cardiac β_2 adrenoreceptors do not play an important role in the genesis of myocardial sensitization to halothane. Therefore, treatment with β_1 blockers is preferable to β_2 or non-selective β blockers for the treatment of catecholamine-halothane ventricular arrhythmias.¹⁷

Elevation in arterial blood pressure and heart rate has also been regarded as an important factor in the development of these arrhythmias by some investigators.^{18,19}

They suggested that treatment of elevated blood pressure and heart rate should be a primary goal in the prevention of epinephrine-halothane arrhythmias. Reynolds *et al.*¹⁸ reported that artificial elevation of the blood pressure during an infusion of a subthreshold dose of epinephrine could induce ventricle bigeminy which could be aborted by a sudden reduction of blood pressure. However, Maze *et al.*¹⁰ observed that while sodium nitroprusside prevented an increase in the blood pressure by epinephrine during halothane anaesthesia, it did not exert any antiarrhythmic activity. This indicates that hypertension induced by dopamine in our study is not solely responsible for ventricular arrhythmias.

Reynold *et al.*¹⁸ also reported acceleration of the heart rate with sinus tachycardia prior to the onset of arrhythmias. Atrial pacing at a similarly increased rate during a subthreshold infusion of epinephrine also induced ventricular arrhythmias. In our study we also observed acceleration of heart rate, especially following the administration of dopexamine hydrochloride, but this tachycardia did not initiate any ventricular arrhythmias. Furthermore, Hayashi *et al.*²⁰ demonstrated in the intact dog preparation that the increase in heart rate alone was not an important factor in the aetiology of epinephrine-halothane-induced arrhythmias.

In conclusion, dopexamine hydrochloride unlike dopamine and other catecholamines produces no atrial or ventricular arrhythmias in dogs anaesthetized with halothane. The lower arrhythmogenic potential of dopexamine may result from its relative lack of activity at β_1 receptors which have been implicated in arrhythmias induced by other catecholamines.

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