Effects of SK&F 93479 on experimentally induced ventricular arrhythmias in dogs, rats and mice

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Abstract

The effects of SK&F 93479, a potent histamine H2-receptor antagonist, on ventricular arrhythmias induced by coronary artery ligation in dogs and rats, and by aconitine infusion in mice were investigated. It was found that SK&F 93479 in large doses, significantly prevented the occurrence of spontaneous ventricular fibrillation and the changes in ventricular fibrillation threshold following coronary artery ligation in dogs. In rats subjected to ligation of the main left coronary artery, it significantly reduced the incidence of ventricular fibrillation, and significantly prolonged the time of onset of ventricular tachycardia and ventricular fibrillation. On the contrary, SK&F 93479 did not significantly alter the incidence or the time of onset of cardiac dysrhythmias caused by aconitine infusion in mice. These findings suggest that SK&F 93479 lacks non-specific antiarrhythmic activity and that its protective effects against coronary artery ligation may be mediated by its histamine H2-receptor antagonizing action. They also support the hypothesis that histamine may contribute to the genesis of ventricular arrhythmias resulting from acute myocardial ischaemia.

Introduction

Ventricular arrhythmias continue to be important causes of death following myocardial infarction. The mechanisms for their production, however, have not been fully elucidated.

HARRIS [1] has postulated that some endogenous substances liberated from the ischaemic myocardium may take part in the genesis of ectopic impulses. It was also reported by HIRATA et al. [2] that ventricular arrhythmia induced by coronary occlusion in dogs disappeared after retrograde bleeding through collateral vessels; these workers suggested that accumulation of certain arrhythmogenic substances in the ischaemic tissues may contribute to the production of ventricular irregularities after coronary occlusion. Recent evidence has shown that the release of catecholamines [3], prostaglandins and thromboxanes [4] from the ischaemic myocardium may be involved in the causation of early ventricular arrhythmias arising from acute myocardial ischaemia.

Histamine is present in cardiac muscle [5] and its release can be increased by anoxia [6]. It is also known that histamine is highly arrhythmo-genic [7]. Thus, it is possible that histamine release may also play a role in the pathogenesis of ventricular dysrhythmias during acute myocardial ischaemia.

This study examines the effects of SK&F 93479, a potent H2-receptor histamine antagonist, on the changes in cardiac rhythms induced by acute coronary artery ligation in anaesthetized dogs and rats. The possible non-specific antiarrhythmic effect of this drug is also evaluated by observing its effects on aconitine-induced cardiac arrhythmias in mice.

Materials and methods

Ventricular arrhythmias and changes in ventricular fibrillation threshold induced by coronary artery ligation in dogs

Male mongrel dogs weighing 12–20 kg were used. They were anaesthetized with pentobarbitone sodium 30 mg/kg given intravenously. The animals were intubated through a tracheostomy and ventilated under positive pressure with room air by a respirator (Model V100KG, E. & M Instrument Co., Inc.). The left femoral vein was cannulated for intravenous injection and infusion of drugs. Peripheral limb electrocardiogram was monitored in lead II by the use of a high-gain preamplifier (E & M Instrument Co., Inc.), and was displayed on a physiograph (E & M Instrument Co., Inc.).

The dogs were then subjected to left thoracotomy at the fifth intercostal space. After the pericardium was opened the left anterior descending coronary artery (LAD) was dissected free for a few millimetres near the distal edge...
of the left auricular appendage. This freed section of LAD was ligated with a 00 braided silk suture when acute coronary artery ligation was performed at 10 min after drug administration.

Ventricular fibrillation (VF) was produced using the method of Fiedler et al. [8] with slight modifications. A plaque of platinum electrodes was sutured to the epicardial surface of the right ventricle near the conus arteriosus. The interelectrode distance was 1 cm and the surface area of each electrode was 4 mm². VF was induced by a train of electrical impulses which lasted for 5 sec and was delivered from a square-wave stimulator (Palmer, England), with a frequency of 50 Hz, 1 msec in duration and variable voltages. Starting from 1.0 V, the heart was stimulated once every minute with increasing voltage by increments of 0.25 V until VF occurred. The minimum voltage required to induce VF was defined as ventricular fibrillation threshold (VFT). VFT was determined immediately before and 10 min after drug administration, 15, 30, and 45 min following LAD ligation. Defibrillation was achieved within 5 sec of VF with 117 V a.c. current using an a.c. defibrillator (E & M Instrument Co., Inc.).

A total of 12 dogs was used. They were randomly divided into 2 groups. Group I received an intravenous bolus injection 0.5 ml/kg of 0.9% NaCl w/v (saline) followed by 0.5 ml/kg/h infusion of saline as vehicle control. Group II received an intravenous bolus injection of SK&F 93479 (Smith Kline & French) 1 mg/kg followed by 1 mg/kg/h infusion of the drug. Intravenous bolus injection was given 10 min before LAD ligation. Intravenous infusion was provided by an infusion pump (Harvard) at a rate of 0.5 ml/kg/h. The pump was started immediately after the bolus injection was given, and was continued until completion of the experiment. SK&F 93479 was freshly prepared immediately before use by dissolving in saline.

Ventricular arrhythmias induced by coronary artery ligation in rats

The technique of Clark et al. [9] was used to induce ventricular dysrhythmias in rats.

Male Sprague-Dawley rats, weighing 400–500 g, were anaesthetized with pentobarbitone sodium, 60 mg/kg intraperitoneally. The trachea and a jugular vein were cannulated to allow artificial ventilation and intravenous administration of drugs, respectively. The electrocardiogram (ECG) was monitored via standard limb lead II by using a Universal coupler (Narco Bio-systems), and was displayed on a physiograph (Narco Bio-systems).

The mice were randomly divided into groups and were pretreated with intravenous injection of SK&F 93479 5, 10, and 20 mg/kg followed by 5, 10, and 20 mg/kg/h infusions of the drug, respectively. Intravenous bolus injection was given 15 min before coronary artery ligation (5 min before thoracotomy). Intravenous infusion was provided by an infusion pump (Harvard) at a rate of 2 ml/kg/h. The pump was started immediately after the bolus injection was given, and was continued until the experiment was completed.

Ventricular arrhythmias induced by aconitine infusion in mice

The method of Nwangwu et al. [10] was adopted for inducing cardiac dysrhythmias in mice.

Male ICR mice, weighing 20–25 g, were used. They were anaesthetized with pentobarbitone sodium, 50 mg/kg intravenously. Each anaesthetized animal was placed on its back on a surgical board and its tail vein cannulated with a 27 gauge needle for intravenous injection or infusion of drugs. The electrocardiogram (ECG) was monitored via standard limb lead II by using a Universal coupler (Narco Bio-systems), and was displayed on a physiograph (Narco Bio-systems).

Cardiac arrhythmias were induced by intravenous infusion of 5 µg/ml aconitine (Sigma) at a flow rate of 0.28 ml/min. Aconitine was dissolved in saline immediately before use. Intravenous infusion was provided by an infusion pump (Harvard). The time of onset of initial cardiac arrhythmia at which the first discernible sign of persistent (>5 sec) deviation from normal sinus rhythm appeared, and the time of onset of sustained ventricular tachycardia (>5 sec) were recorded.

The mice were randomly divided into groups and were pretreated with intravenous injection of SK&F 93479 10, 20, 40, and 80 mg/kg 3 min before aconitine infusion. Similar volumes (0.1 ml/10 g) of saline were given by the same route and at the appropriate time to animals acting as controls.

Statistical analysis

The ventricular fibrillation threshold measured in dogs and the times of onset of cardiac arrhythmias observed in rats and mice were expressed as mean ± SEM and were analysed by Student's t-test. The incidence of occurrence of ventricular dysrhythmias following coronary artery ligation was analysed by the χ² test.

Results

Spontaneous ventricular fibrillation (VF) and changes in ventricular fibrillation threshold (VFT) induced by coronary artery ligation in dogs

In saline control, all six dogs (100%) developed spontaneous VF within 6 min (average 4.13 min) following LAD ligation. The incidence of spontaneous VF was significantly lower in