Hemodynamic and Inotropic Effects of Antiarrhythmic Drugs Used to Treat Paroxysmal Supraventricular Arrhythmias

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Abstract. Episodes of sustained paroxysmal supraventricular tachycardias can be terminated by antiarrhythmic drugs given intravenously. The cardiodepressive effects of these drugs are an important limitation of this therapeutic procedure. The dose-dependent circulatory and myocardial effects of the nucleoside adenosine (0.5, 2.0, 5.0 mg/kg/minute) and the class I antiarrhythmic drug ajmaline (1.0, 2.0, 4.0 mg/kg) were investigated in 73 open-chest rats. Hemodynamic measurements in the intact circulation and isovolumic registrations (peak isovolumic left ventricular systolic pressure and peak isovolumic dP/dt_{max}) were compared with saline controls. Adenosine has a short-lasting, negative, chronotropic effect that causes a dose-dependent reduction of cardiac output (-34%, -54%, -65% vs control). The peak isovolumic left ventricular systolic pressure (LVSP) is not changed significantly by adenosine (-6%, -4%, +5% vs control). The negative chronotropic effect of ajmaline with consecutive reduction of cardiac output is less pronounced (cardiac output: -18%, -20%, -38% vs control). The highest dose of ajmaline causes a significant reduction of peak isovolumic LVSP (-2%, -1%, -7% vs control). Adenosine has an impressive negative chronotropic effect with a consequent marked decrease of cardiac output. The reduction of cardiac output by adenosine is more pronounced compared with ajmaline. Nevertheless, adenosine has—in contrast to ajmaline—no cardiodepressive effects in vivo.

Introduction

Episodes of sustained paroxysmal AV junctional reentrant tachycardia which do not terminate by vagal maneuvers [1] can be treated by antiarrhythmic drugs. Therefore, intravenous infusions of class-I antiarrhythmic drugs such as propafenone [2], flecainide [3], and ajmaline [4,5], class-IV antiarrhythmic drugs such as verapamil [4,6], and the nucleoside adenosine [7–12] are given. Cardiodepressive effects of antiarrhythmic drugs may be an important limitation of this therapeutic procedure since these drugs can aggravate heart failure. In previous in vivo animal studies we could also demonstrate that class-I antiarrhythmic drugs have a cardiodepressive effect and that this effect is especially more pronounced in animals with reduced left ventricular function [13,14].

An i.v. bolus of 6–12 mg adenosine [8] or doses of about 50 mg ajmaline in a short i.v. infusion [7] can be given for emergency treatment of paroxysmal supraventricular tachycardia. It was the aim of this study to compare the acute dose-dependent hemodynamic and inotropic effects of short intravenous infusions of the nucleoside adenosine with that of the class I antiarrhythmic drug ajmaline (AJM). We used an open-chest animal model [13–15], which permits, besides measurements of circulatory effects in the intact circulation, the determination of direct myocardial effects independently of peripheral vascular effects by isovolumic measurements in vivo.

Materials and Methods

The study was performed on 4-month-old male Wistar rats (n = 73, 350–400 g) which were anesthetized with urethane 50% (2.4 ml/kg bodyweight) intraperitoneally. An ECG (lead II) was recorded to estimate the heart rate. A venous line was established through the right jugular vein for drug infusion. After tracheotomy, a plastic tube was inserted into the trachea for artificial ventilation. The heart and the great vessels of the thoracotomized animals (median sternotomy) were exposed and the pericardium was opened. To measure aortic blood pressures (AoP\textsubscript{a}, AoP\textsubscript{d}) a flexible plastic tube was advanced via the left carotid artery to the aortic arch and was connected to a fluid-filled (heparinized saline) pressure transducer. The left ventricular pressure (LVP) was recorded via a short fluid-filled 18-gauge metal cannula, which was positioned through the apex in the left ventricle and connected with a 3-way stopcock to a pressure transducer. The transducer signal was additionally preamplified for the left ventricular enddiastolic pressure (LVEDP) recording and differentiated to calculate the first derivative of the left ventricular pressure (dP/dt). For measuring the stroke volume (SV, except the coronary flow) an electromagnetic flow probe (internal diameter 2 mm) was fitted around the ascending aorta.
An ECG lead, the flow signal, aortic pressure, LVSP, amplified diastolic left ventricular pressure, and dP/dt were recorded on a multichannel ink jet recorder. The mean aortic pressure (AoP_\text{m} = \frac{2 \times \text{AoP}_a + \text{AoP}_d}{3}) stroke volume (planimetry of the phasic flow signal), and the cardiac output (CO) were recorded on a multichannel ink jet recorder. The mean aortic pressure (AoP_\text{m} = \frac{2 \times \text{AoP}_a + \text{AoP}_d}{3}), stroke volume (planimetry of the phasic flow signal), and the cardiac output (CO) were recorded on a multichannel ink jet recorder.

Besides these measurements in the intact circulation, isovolumic measurements were made to estimate myocardial function independently of circulatory changes. By cross-clamping the ascending aorta for 5-8 beats the maximum of the isovolumic left ventricular pressure was obtained. From the beat generating the highest isovolumic (isovol.) LVSP the peak dP/dt_\text{max} (isovol. dP/dt_\text{max}) was determined. At the end of the experiments the pressure-volume relationship of the left ventricle was measured (for details of the procedure see [15]) and the left ventricular end-diastolic volume was derived as the volume corresponding to the respective end-diastolic pressure.

After a 12-minute stabilization period, control data in the intact circulation and isovolumic registrations were obtained. Three minutes after these measurements the drug infusion with a precision pump was started. Adenosine has only a very short half-life it was given as an i.v. infusion during the whole experiment. Auxotonic and isovolumic measurements were done 7 minutes after the beginning of infusion, when a steady state under adenosine-infusion was obtained. Adenosine was given in doses of 0.5, 2.0, and 5.0 mg/kg/minute. Ajmaline (AJM) was infused in a final volume of 1 ml over a period of 7 minutes. The animals received 1.0, 2.0, or 4.0 mg/kg AJM dissolved in NaCl. The drug control group received 1 ml 0.9% NaCl solution. Hemodynamic data in the intact circulation of these groups were recorded every minute during the infusion period and 5 and 15 minutes after termination of infusion. Isovolumic registrations were recorded at the end of the infusion.

All data are expressed as mean ± SEM. Hemodynamic data were normalized to the individual preinfusion control data (= 100%). The data from the drug infusion groups were compared with the saline control group by analysis of variance followed by Dunnett’s test [16]. A p < 0.05 was accepted as level of significance.

Results

The results of the auxotonic and isovolumic preinfusion measurements were comparable in all groups (data not shown).

Measurements in the Intact Circulation

Adenosine causes a significant heart rate reduction (Fig. 1). At a concentration of 2.0 mg/kg/minute adenosine causes a third-degree atrioventricular block. This explains the missing effect on heart rate after a further increase of the adenosine dosage. Although there is an increase of stroke volume by adenosine its negative chronotropic effect causes a dose-dependent reduction of cardiac output (Table 1). Adenosine also causes a fall of the mean aortic blood pressure (Fig. 1). This fall is more pronounced for the diastolic aortic pressure (Table 1) due to prolongation of the diastole. These effects of adenosine are very short lasting and only some minutes after termination of adenosine-infusion the preinfusion values were reached again.

The effect of AJM on heart rate is less pronounced compared with adenosine (Fig. 2). Consequently the decrease of cardiac output by AJM is not so impressive (Table 1). The fall of blood pressure by AJM (Fig. 3, Table 1) is also less pronounced compared with adenosine. Its hemodynamic effects also persist until 15 minutes after termination of infusion.

The diastolic pressure-volume relationship of the left ventricle was not altered by adenosine or AJM postinfusion (data not shown).

Isovolumic Registrations

The effects of adenosine and AJM on the isovolumic measurements are shown in Figure 4. Though the peak of the isovolumic left ventricular systolic pressure is not changed significantly by adenosine, the corresponding isovolumic dP/dt_\text{max} is lowered by 0.5 and 2.0 mg/kg/minute adenosine. The two lower doses of AJM have no significant effect on either indices of myocardial contractility, but 4.0 mg/kg AJM significantly reduces the isovolumic LVSP and the isovolumic dP/dt_\text{max}.

Discussion

Adenosine

Adenosine slows conduction through the atrioventricular node and may cause atrioventricular block. This was first described by Drury and Szent-Györgyi [17]. The negative chronotropic effect of adenosine was demonstrated in several experiments [18,19]. Our experiments show a strong negative chronotropic effect of adenosine. In contrast to our experiments, other studies described a fall in heart rate followed by an increase [20] or even a positive chronotropic effect of adenosine in vivo [21]. Ohnishi et al. [22] measured bradycardia after infusion of adenosine in normotensive Wistar-Kyoto rats but they found no effect of i.v. adenosine on heart rate of spontaneously hypertensive rats. After i.a. infusion of adenosine (i.e., a lower concentration of adenosine at the sinoatrial node) Ohnishi et al. [22] described an increase in heart rate. The effect on heart rate was reduced after ganglionic blockade. These results indicate that the direct negative chronotropic effect of adenosine can be masked in vivo by reflex tachycardia because of the vasodilating [22] and coronary dilating [23–25] effects which may cause an increased sympathetic tone. In our experiments the reflex pathways may be altered by anesthesia. As