Antiarrhythmic Effects of Dichloroisoprenaline, H 56/28, ICI 50172, LB 46, MJ 1999 and Propranolol on Aconitine-Induced Atrial and Ouabain-Induced Ventricular Arrhythmias

Previously the authors compared the potencies of β-adrenergic blocking agents, DCI, methoxamine, propranolol, LB 46, H 56/28, MJ 1999 and ICI 50172 to block the positive chronotropic[1] and the positive inotropic response[2] and the vasodilation[3] induced by catecholamine in dogs. In this study the authors compared the antiarrhythmic effects of these compounds on aconitine-induced atrial and also ouabain-induced ventricular arrhythmias.

For induction of atrial arrhythmia, the authors devised a cup method[4] instead of the cotton pledget (WINBURY[5]) to restrict aconitine solution on the atrial surface to an area of 10 mm². The cup method was found to be very useful to obtain a sustained atrial arrhythmia of a relatively uniform severity for several hours without any significant disorder in the cardiac function. For inducing ouabain arrhythmia, the authors gave initially 40 μg/kg of ouabain, 20 μg/kg after 30 min and an additional dose of 10 μg/kg every 15 min. Usually a total amount from 60 to 80 μg/kg was enough to induce a ventricular arrhythmia, which supramaximal stimulation of the vagus nerve could not affect at all (ROBERTS et al.[6]). In aconitine-induced atrial arrhythmia, test compounds were administered by i.v. infusion at a constant rate by titration procedure to block arrhythmia within a period of 10 to 30 min. In ouabain-induced ventricular arrhythmia, 10 mg/kg of test compound was infused during a period of 20 min, and the total amount necessary determined to restore sinus rhythm in which vagal stimulation effectively induced sinus bradycardia.

Results in aconitine-induced atrial and ouabain-induced ventricular arrhythmias are summarized in the Table, and typical results with LB 46 are shown in Figures 1 and 2. Propranolol is found to be significantly more potent to block aconitine-induced atrial arrhythmia than any other compound, including representative antiarrhythmic agents such as ajmaline or quinidine. The potency is as follows; propranolol > MJ 1999, ajmaline > LB 46 > quinidine, which roughly correspond to 10:1: $^1/_2$:$^1/_5$. The systolic blood pressure at the endpoint, however, was significantly depressed with MJ 1999 and quinidine. Antiarrhythmic effects of H 56/28, ICI 50172 and DCI could not be determined in a majority of cases due to cardiovascular depression. Antiarrhythmic potencies of propranolol, LB 46 and H 56/28 in ouabain-induced ventricular arrhythmia were almost the same, while heart rate and systolic blood pressure were significantly depressed with H 56/28. MJ 1999 and ICI 50172 were not effective in ventricular arrhythmia.

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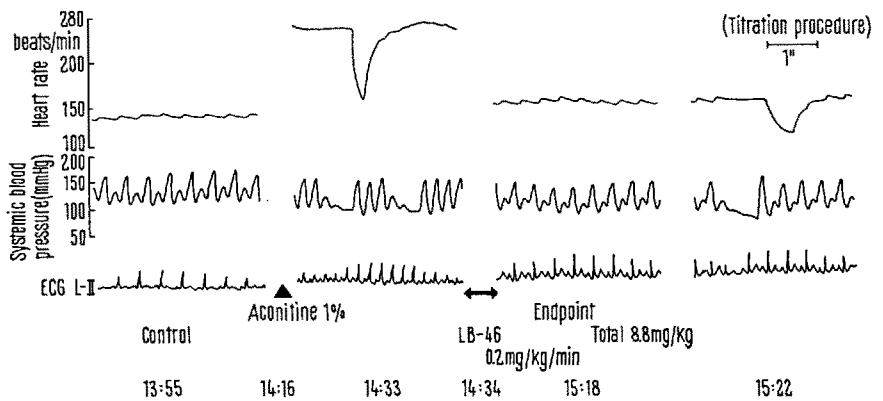

Fig. 1. Antiarrhythmic effect of LB 46 on aconitine-induced atrial arrhythmia. HR stands for heart rate measured by cardiotachograph and SBP for systemic blood pressure by pressure transducer. Filled triangle represents the time when the cup adherred on atrial surface was filled with 1% aconitine solution.

Summarized data of antiarrhythmic effects on aconitine-induced atrial and ouabain-induced ventricular arrhythmias

Drugs	Aconitine-induced atrial arrhythmia			Ouabain-induced ventricular arrhythmia	
	No. of effective cases / No. of experiments	Effective dose (μg/kg)	Duration (min)	No. of effective cases / No. of experiments	Effective dose
Propranolol	6/6	0.24 ± 0.05	40 ± 9	5/5	3.4 ± 0.8
LB 46	5/5	5.9 ± 1.2	6 ± 3	4/5	3.4 ± 1.0
MJ 1999	6/6	4.3 ± 1.0	37 (n = 3) 120 (n = 2)	0/2	–
H 56/28	2/5	2.8 (n = 2)	10	5/5	4.3 ± 1.0
ICI 50172	1/5	2.6 (n = 1)	1	0/2	–
Ajmaline	8/8	3.2 ± 0.3	17 ± 3	5/7	4.5 ± 1.4
Quinidine	5/6	15.3 ± 1.7 (n = 5)	9 ± 2	5/5	13.4 ± 2.0

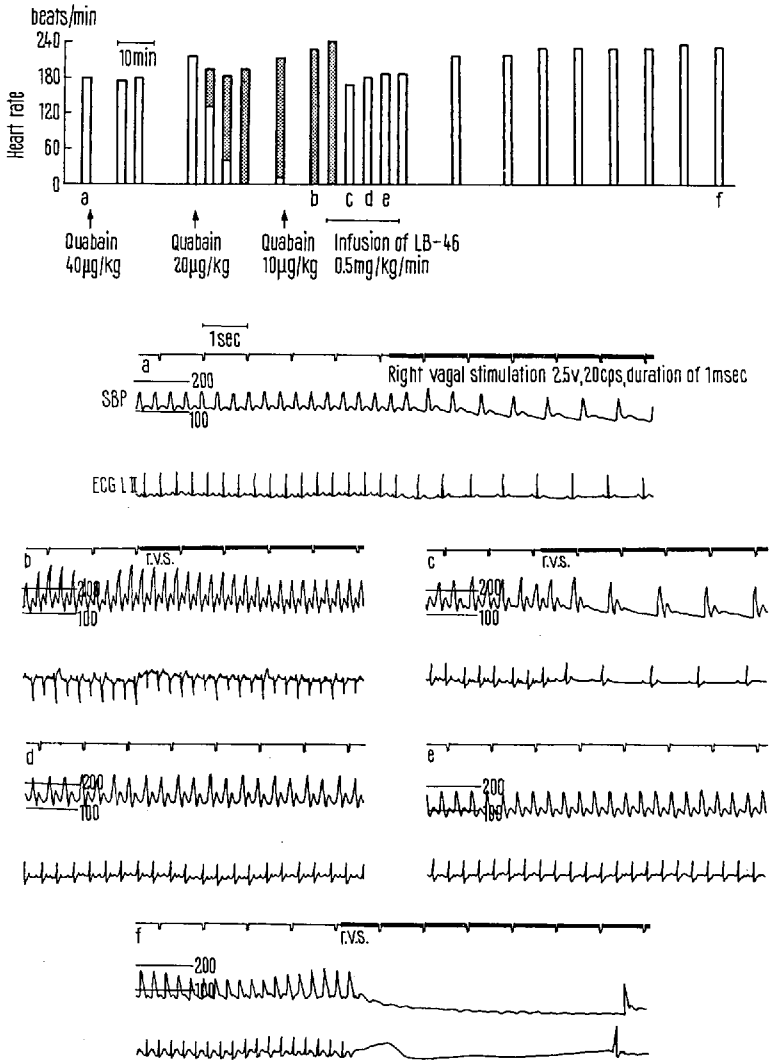

Fig. 2. Antiarrhythmic effect of LB 46 on ouabain-induced ventricular arrhythmia. HR stands for heart rate, a, b, c, d, and e for time when corresponding ECG was recorded.

Both acceleration of sinus rhythm and hypotensive response to i.v. administration of 0.3 µg/kg of isoprenaline are completely blocked by 0.1 mg/kg of LB 46, while the antiarrhythmic dose is 3–6 mg/kg both in aconitine-induced atrial and ouabain-induced ventricular arrhythmias. That means that about 50 to 100 times larger dose is necessary for development of antiarrhythmic activity, even by use of the most potent β-adrenergic blocking agent, LB 46. On the other hand, an antiarrhythmic dose of propranolol in aconitine-induced atrial arrhythmia, 0.24 mg/kg, is much closer to its β-adrenergic blocking one, because a little over 0.2 mg/kg i.v. of propranolol is necessary to block completely cardiovascular effects of 0.3 µg/kg isoprenaline i.v. H 56/28 and ICI 50172 are practically devoid of antiarrhythmic activity in aconitine arrhythmia, while these compounds have an almost similar β-adrenergic blocking effect to that of propranolol. MJ 1999 shows relatively high antiarrhythmic action only in aconitine-induced atrial arrhythmia, but none in ouabain-induced ventricular arrhythmia[7,8], though it is inconsistent with the report by RAPER and WALE[9]. Thus, β-adrenergic blocking activity does not go parallel with antiarrhythmic potency. Furthermore, these results show definite superiority of LB 46 in its specificity as β-adrenergic blocking agent, because heart rate and systemic blood pressure, when regular rhythm is restored, are not significantly different from the initial levels before arrhythmia is induced[10].

Zusammenfassung. Der Effekt von sechs β-adrenergischen Blockierungsmitteln auf Akonitin-Arrhythmia bzw. Ouabain-Arrhythmia wurde mittels i.v. Verabreichung vergleichend untersucht. Reihenfolge der Wirksamkeit auf Akonitin-Arrhythmia: Propranolol > MJ 1999 > LB 46 > H 56/28, ICI 50172 und DCI, und dieselbe auf Ouabain-Arrhythmia: Propranolol, LB 46 und H 56/28 gleichwertig, MJ 1999 und ICI 50172 wirkungslos.

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