The Effects of Lidocaine and Verapamil on Overdrive-Induced Suppression of Pacemakers in Dogs with Complete Atrioventricular Block

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SUMMARY

When the ventricle is electrically stimulated at a faster rate, the cessation of the drive is followed by a temporary suppression of automaticity (overdrive suppression). The effects of lidocaine and verapamil on overdrive suppression were studied in dogs. Lidocaine slowed the ventricular escape rate and prolonged the pause following overdrive; occasionally, it was about twice the next succeeding RR interval. On the contrary, verapamil influenced neither the ventricular escape rate nor the pause following overdrive. It is suggested that lidocaine not only suppresses the automaticity of ventricular escape pacemaker but also induces exit block and that the spontaneous depolarization of the ventricular pacemaker is not slow channel-dependent.

Additional Indexing Words:

Ventricular escape rhythm Overdrive suppression Exit block Slow channel dependent activity

THIS study was designed to assess the effects of lidocaine and verapamil on ventricular automaticity and the pause following ventricular overdrive in dogs with complete atrioventricular (A-V) block. Our reasons for performing this study were as follows. First, lidocaine is a widely used antiarrhythmic drug in the treatment and prevention of ventricular arrhythmias in acute myocardial infarction. Apart from its well known side effects on the central nervous system, serious conduction disturbances and cardiac arrest have been reported in the literature.¹⁾⁻⁷⁾ However, its effects on already compromised A-V conduction⁸⁾⁻¹⁰⁾ and impulse formation¹¹⁾⁻¹⁵⁾ are equivocal. Second, verapamil has received considerable attention as an antiarrhyth-

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mic agent for supraventricular arrhythmia. Furthermore, verapamil has been shown to prevent the development of ventricular fibrillation during coronary artery ligation in dogs.¹⁶⁾ Zipes and associates¹⁷⁾ demonstrated a slowing of the sinus node discharge rate and depression of A-V conduction when verapamil was administered to dogs. However, little information is available about the effects of verapamil on ventricular automaticity.¹⁸⁾

METHODS

Seventeen mongrel dogs, weighing 11–23 Kg, were anesthetized with sodium pentobarbital (30 mg/Kg, intravenously). A Harvard respirator using room air provided mechanical ventilation through a cuffed endotracheal tube. The temperature of the animals was monitored and maintained at 37°C using heat lamps. The aortic pressure and electrocardiographic leads II and aV_F were recorded on an eight channel, switched-beam oscilloscope. The chest was opened by a right thoracotomy in the fourth intercostal space and the heart was suspended in a pericardial cradle. A bipolar electrode was sutured to the epicardial surface of the right ventricular outflow tract for electrically driving the ventricles. Acute atrioventricular block was induced by injection of 40% formaldehyde into the region of the bundle of His.¹⁹⁾ The ventricle was driven at 60 beats/min between the experimental procedures. Before any procedure was carried out, the ventricular drive was discontinued and sufficient time was allowed for the ventricular escape rate to stabilize. The ventricle was driven for 1 min at 2 and 4 times the intrinsic rate. The escape rhythm recovery time (ERRT) was measured as the time elapsing from the last driving spike to the first spontaneous ventricular escape beat (Fig. 1).

Lidocaine:

In 8 dogs, lidocaine was administered into the jugular vein in a bolus of 2 mg/Kg, followed by a constant infusion of 4.3 mg/Kg/hour.

Verapamil:

In 9 dogs, verapamil was administered into the jugular vein in a bolus of 0.2 mg/Kg, followed by a constant infusion of 0.005 mg/Kg/min.

The results are expressed as a mean $\pm$ SE and were analyzed with Student's paired t-test. P values of 0.05 or less were considered significant.

RESULTS

1. Effects of lidocaine

The average ventricular escape rate was 52.3 ± 3.7 beats/min before and

Fig. 1. Suppression of ventricular automaticity by overdrive. II, aV_F = lead II and aV_F of the standard ECG. Bp = aortic blood pressure tracing; the vertical bar at the left of the blood pressure trace shows the calibration for the blood pressure in mmHg. ER = ventricular escape rate. The period of drive (1 min) is indicated by the arrows.

Table I. Effects of Lidocaine on Ventricular Automaticity and Overdrive Suppression

Expt.	Control			Lidocaine		
	ER (beats/min)	Drive 2×ER ERRT (sec)	Drive 4×ER ERRT (sec)	ER (beats/min)	Drive 2×ER ERRT (sec)	Drive 4×ER ERRT (sec)
1	56	1.50	2.96	47	2.08	9.96
2	65	1.44	2.18	44	2.99	3.45
3	57	1.89	2.47	48	7.59	9.63
4	58	2.49	3.40	35	4.21	8.75
5	53	1.86	4.82	45	3.07	8.91
6	53	1.93	4.84	36	3.38	11.22
7	27	2.99	4.07	19	7.24	15.26
8	49	1.45	1.56	36	2.84	4.40
Mean	52.3	1.94	3.29	38.8*	4.18†	8.95†
SE	3.7	0.18	0.40	3.2	0.69	1.23

Expt. = identifying number; ER = ventricular escape rate; ERRT = escape rhythm recovery time, measured as the elapsed time from the last driving spike to the first spontaneous ventricular escape beat. Mean ± SE = Mean values ± standard error. All hearts driven for 1 min at 2 and 4 times the ventricular escape rate.

* $p < 0.001$ † $p < 0.01$

38.8 ± 3.2 beats/min after lidocaine administration (Table I, $p < 0.001$). The mean aortic pressure was not affected by lidocaine (53.5 ± 5.7 mmHg versus 50.6 ± 6.5 mmHg). The ERRT following ventricular drive at twice the ventricular escape rate was 1.94 ± 0.18 sec before and 4.18 ± 0.69 sec after lidocaine administration (Table I, $p < 0.01$). At 4 times the ventricular escape rate, the ERRT was 3.29 ± 0.40 sec before and 8.95 ± 1.23 sec after

Fig. 2. The ratio between escape rhythm recovery time and the next RR interval during recovery from pacing-induced overdrive suppression. Upper panel; control study, the ratio clustered around 1.1:1. With lidocaine (lower panel), two populations are seen, one with a mean ratio about 1.2:1 and one with a ratio greater than 2.0:1. no. obs.=number of observations.

Table II. Effects of Verapamil on Ventricular Automaticity and Overdrive Suppression

Expt.	Control			Verapamil		
	ER (beats/min)	Drive 2×ER ERRT (sec)	Drive 4×ER ERRT (sec)	ER (beats/min)	Drive 2×ER ERRT (sec)	Drive 4×ER ERRT (sec)
1	34	3.01	4.13	35	2.68	2.45
2	65	1.07	1.09	64	1.17	1.24
3	44	1.90	2.84	39	1.66	2.09
4	58	2.35	5.34	56	1.61	1.58
5	50	1.40	1.76	58	1.29	1.29
6	52	1.74	1.57	44	2.24	2.59
7	54	1.61	1.53	57	1.50	1.47
8	52	2.92	7.98	48	1.75	3.25
9	58	1.95	2.48	50	4.37	5.68
Mean	51.9	1.99	3.19	50.1	2.03	2.40
SE	2.8	0.21	0.71	3.0	0.31	0.44

Abbreviations are as in Table I.

lidocaine administration (Table I, $p < 0.01$). Before lidocaine administration, the ratio between ERRT and the next RR interval clustered around 1.1:1 (average 1.11:1, SD 0.0008) (Fig. 2). After lidocaine administration, the ratio between ERRT and the next RR interval clustered around 1.2:1 in 9 experiments, however, it was greater than 2.0:1 in 3 experi-

ments (exp 1, 6, 7) (Fig. 2). This gave the impression that one QRS in these 3 cases was missing and that ERRT therefore was approximately doubled.

2. Effects of verapamil

The average ventricular escape rate was 51.9 ± 2.8 beats/min before and 50.1 ± 3.0 beats/min after verapamil administration (Table II, NS). The ERRT following ventricular drive at twice the ventricular escape rate was 1.99 ± 0.21 sec before and 2.03 ± 0.31 sec after verapamil administration (Table II, NS), and at 4 times the ventricular escape rate the ERRT was 3.19 ± 0.71 sec before and 2.40 ± 0.44 sec after verapamil administration (Table II, NS). The mean aortic pressure decreased from 55.3 ± 2.3 mmHg to 47.7 ± 2.2 mmHg after verapamil administration ($p < 0.02$).

DISCUSSION

1. Lidocaine

It is generally believed that the use of lidocaine is contraindicated in patients with complete A-V block. This opinion is based on studies showing that (1) lidocaine suppressed diastolic depolarization in Purkinje fibers,²⁰⁻²² (2) lidocaine slowed the ventricular rate in dogs with surgically induced A-V block,¹³ and (3) 3 patients with A-V block developed prolonged asystole when the pacemaker was switched off after lidocaine administration.¹² However, Roos and Dunning¹⁴ reported that an intravenous bolus injection of 100 mg of lidocaine caused no slowing of the rate of the escape rhythm in the 5 patients with a complete A-V block. Furthermore, Aravindaksham et al¹⁵ reported that lidocaine caused either no or slight and transient slowing of the ventricular escape rate in 13 of 18 patients with a complete A-V block distal to the His bundle potential. They postulated that the ventricular escape pacemaker was due to slow channel-dependent activity and that the ventricular escape rate slowed abruptly in a manner suggesting 2:1 or 3:1 exit block in the remaining 5 patients. In our study, lidocaine slowed the ventricular escape rate and prolonged ERRT. In 3 experiments, the ERRT was about twice the next RR interval suggesting an exit block as the mechanism for this prolongation of ERRT.^{23), 24)}

2. Verapamil

Cellular electrophysiological studies have shown that verapamil has no effect on normal Purkinje fiber pacemakers.^{24), 25)} However, Hogan and Spitzer²⁶ demonstrated that overdrive suppression in electrically driven Purkinje fibers is diminished by verapamil. In isolated blood-perfused canine papillary muscles, verapamil changed the ventricular rate in a biphasic manner, but the changes remained as small as about 10% of the basal rate

in doses which markedly suppressed the force of contraction.²⁷⁾ *In vivo*, our study showed that the ventricular escape rate and ERRT are not altered by verapamil. Therefore, the ventricular escape pacemaker is not due to slow channel-dependent activity such as the spontaneous activity found in mitral valve leaflets,²⁸⁾ the transient low amplitude depolarization caused by digitalis²⁹⁾ and the spontaneous activity in ventricular muscle induced by depolarizing current.^{30),31)}

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