Electrophysiological Effects of Lidocaine in Sick Sinus Syndrome

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SUMMARY

Electrophysiological studies were performed to see the effects of lidocaine on the conduction system, particularly sinus node and atrium in 40 patients of SSS, using HBE recordings, rapid atrial pacing and atrial extrastimulus technique. Sinus cycle length, PA (P'A), AH, HV intervals, calculated SACT, and refractory periods of atrium, AV node and His-Purkinje system did not change after lidocaine. Only maximum CSRT was significantly increased with lidocaine. These results were not affected by pretreatment of atropine.

In conclusion, the combining rapid atrial pacing with lidocaine may be useful to manifest the masked sinus node abnormalities. It was suggested that lidocaine directly depressed sinus node automaticity in SSS patients, without affecting perinodal tissue. Therefore, lidocaine should be used with caution in patients with known or suspected SSS.

Additional Indexing Words:

SRT   SACT   Refractory periods   Atropine   His bundle Electrogram

LIDOCAINE has been the most widely used for treatment of ventricular arrhythmias. The development of sinus arrest in some patients by lidocaine have been reported,¹⁾⁻⁸⁾ but there were few reports concerning lidocaine effects on human sinus node and atrium.^{1),10)} In the present study, the electrophysiological effects of lidocaine on the conduction system, particularly sinus node and atrium, were studied in patients with sick sinus syndrome (SSS) by His bundle electrogram (HBE) recordings, rapid atrial pacing and atrial extrastimulus technique.

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METHODS

Patients: 40 patients with sinus node dysfunction aged 24 to 80 years (mean age 60.5 years, SSS group) and control group of 28 patients (mean age 46.5 years) were studied. The patients of SSS group were defined by the presence of one or more of the following abnormalities:¹¹⁾ 1) persistent unexplained sinus bradycardia (10 patients), 2) documented episodes of SA block and/or sinus arrest (19 patients), 3) bradycardia with episodic supraventricular tachyarrhythmias (11 patients). There were 16 men and 24 women. None had cardiac medication for at least 48 hours before the studies.

Electrophysiological studies: HBE were recorded using previously described method.^{12),13)} A quadripolar catheter was positioned at the high right atrium in the vicinity of sinus node for atrial pacing (distal 2 poles) and for recording high right atrial electrogram (proximal 2 poles). Signals from atrium and His bundle were recorded on a Mingograph at paper speeds of 100 mm/sec. Simultaneous electrocardiographic leads II and V_1 were also recorded. In all patients, HBE of spontaneous rhythm were recorded and atrial pacing were performed at 10 beats/min increments in rate from 70/min to 180/min. The PA(P'A), AH, HV intervals were measured at basic tracing and atrial pacing. Sinus node recovery time (SRT) was defined as the interval from the last paced P wave to the first spontaneous P wave after sudden cessation of the pacing for 15 or 60 sec at various rates. The corrected SRT (CSRT) was defined as SRT minus the average sinus cycle length. Maximum SRT (max. SRT) and max. CSRT were defined as the longest SRT and CSRT, respectively. In 2 patients of SSS group, the recovery times were measured with the first spontaneous QRS deflection of ECG, because only junctional escape beats appeared after pacing. In 28 patients of SSS group and all patients of control group, refractory periods were measured using the atrial extrastimulus technique with the Fukuda-Denshi external pulse generator during sinus rhythm and atrial pacing with various cycle lengths (850, 700, 600, and/or 500 msec). Atrial premature beats were delivered with a variable coupling intervals after every 8 beats of the basic cycle at twice the diastolic threshold. Sinoatrial conduction time (SACT) was calculated by the following equation: $SACT = (\text{return cycle} - \text{spontaneous sinus cycle}) \div 2$, (Zone of reset).

The following definition were used in regard to refractory periods: S_1 , A_1 , H_1 , and V_1 represented the stimulus artifact, atrial, His bundle and ventricular electrograms of spontaneous sinus or driven beats, respectively. S_2 , A_2 , H_2 , and V_2 represented the stimulus artifact, atrial, His bundle, and ventricular electrograms in response to the extrastimulus, respectively. Effective refractory period (ERP) of the atrium (ERPA) was the longest S_1 - S_2 interval, at which S_2 did not propagate into the atrium. Functional refractory period (FRP) of the atrium (FRPA) was the shortest attainable propagated A_1 - A_2 interval. ERP of the AV node (ERP_{AVN}) was the longest A_1 - A_2 interval, at which A_2 failed to depolarize the His bundle. FRP of the AV node (FRP_{AVN}) was the shortest H_1 - H_2 interval in response to any A_1 - A_2 . Relative refractory period of the His-Purkinje system (RRPHPS) was the longest H_1 - H_2 interval at which H_2 conducted to the ventricle with a longer HV interval and/or with an aberrant QRS complex.

Lidocaine was administrated intravenously in a dose of 1 mg/Kg after control

recordings. The measurements were initiated 2 min after administration. Further, in 10 patients of SSS group, atropine was pre-medicated intravenously in a dose of 0.025 mg/Kg, 20 min before lidocaine. Max. CSRT were measured before and after lidocaine.

Statistical analysis of data was performed using Student's t test for paired values, and the results were expressed as mean $\pm$ standard errors of the mean.

RESULTS

The mean sinus cycle length, the mean PA(P'A), AH, and HV intervals during sinus rhythm and atrial pacing showed no significant difference between before and after lidocaine in both control and SSS groups (Table I). The HV interval remained fixed at all paced rates in each patient with normal HV interval. The HV interval increased in 2/3 patients with initially prolonged HV interval (>55 msec) in SSS group. However, there were no significant difference between before and after lidocaine in HV interval of SSS group as a whole.

In control group, SRT and CSRT (at a rate of 130/min for 60 sec), max. SRT and max. CSRT did not change significantly with lidocaine. However, in SSS group, SRT, CSRT, max. SRT, and max. CSRT increased from $2,156 \pm 282$, 994 ± 269 , $2,935 \pm 317$, $1,769 \pm 302$ msec before to $2,882 \pm 370$, $1,627 \pm 342$, $3,472 \pm 398$, $2,317 \pm 384$ msec after lidocaine, respectively ($p < 0.005$, $p < 0.005$, $p < 0.01$, and $p < 0.01$, Table I). The max. CSRT was

Table I. Electrophysiological Data before and after Lidocaine in Both Control and SSS groups

	Control group			Sick sinus syndrome group		
	Before	After	P value	Before	After	P value
Sinus cycle length (S.C.L)	871 ± 34	854 ± 33	NS	1184 ± 54	1158 ± 54	NS
PA interval (S.C.L)	31.2 ± 1.6	31.6 ± 1.7	NS	34.3 ± 1.6	36.3 ± 1.5	NS
P'A interval (130/min A.P)	49.9 ± 3.3	53.1 ± 3.6	NS	55.7 ± 2.6	56.3 ± 3.1	NS
AH interval (S.C.L)	93.4 ± 2.9	92.9 ± 3.0	NS	100.1 ± 4.2	99.7 ± 4.6	NS
AH interval (130/min A.P)	140.0 ± 8.0	145.1 ± 8.3	NS	170.4 ± 10.1	167.0 ± 10.6	NS
HV interval (S.C.L)	40.3 ± 1.2	41.1 ± 1.3	NS	42.2 ± 1.2	43.2 ± 1.2	NS
HV interval (130/min A.P)	40.9 ± 1.6	41.7 ± 1.7	NS	42.0 ± 1.5	42.1 ± 1.6	NS
SRT (130/min 60 sec)	$1,030 \pm 42$	$1,065 \pm 47$	NS	$2,156 \pm 282$	$2,882 \pm 370$	< 0.005
CSRT (130/min 60 sec)	185 ± 25	229 ± 32	NS	994 ± 269	$1,627 \pm 342$	< 0.005
Maximum SRT	$1,212 \pm 48$	$1,191 \pm 48$	NS	$2,935 \pm 317$	$3,472 \pm 398$	< 0.01
Maximum CSRT	326 ± 19	326 ± 24	NS	$1,769 \pm 302$	$2,317 \pm 384$	< 0.01

Abbreviations: A.P=atrial pacing; SRT=sinus node recovery time; CSRT=corrected sinus node recovery time.

Mean $\pm$ S.E. (msec).

abnormally prolonged (>525 msec) in 30/40 (75%) patients of SSS group before lidocaine. In 5 of 10 patients who had normal max. CSRT before lidocaine, the max. CSRT increased toward abnormal value (>525 msec) after lidocaine. As a whole, the max. CSRT of SSS group was abnormally prolonged in 35/40 (87.5%) patients after lidocaine. Further, in 10 patients of SSS group, the max. CSRT was prolonged to more than 1,000 msec after lidocaine. Case S.Y. was a 71-year-old female with a history of syncope. The max. CSRT was 1,560 msec before, but markedly increased to over 6470 msec after lidocaine (Fig. 1). The effects of lidocaine on the max. CSRT were investigated in 10 patients of SSS group when the parasympathetic con-

Fig. 1. Case S.Y. Typical example of remarkably increased maximum corrected sinus node recovery time (max. CSRT) after lidocaine. Upper panel represented before lidocaine with atrial pacing at a rate of 90/min. Lower panel represented after lidocaine with atrial pacing at a rate of 130/min. From top to bottom were ECG leads II, V1, and His bundle electrogram (HBE).

Table II. Effects of Lidocaine on Maximum CSRT in SSS Patients Pretreated with Atropine (msec)

Case No.	Before	After
1	1,440	2,740
2	1,720	8,040
3	260	260
4	5,520	5,780
5	360	305
6	795	780
7	830	780
8	540	530
9	2,140	4,890
10	2,580	3,730
Mean $\pm$ S.E.	1,619 $\pm$ 498	2,784 $\pm$ 866

Table III. Electrophysiological Data before and after Lidocaine in both groups

	Control group			Sick sinus syndrome group		
	Before	After	p value	Before	After	p value
Calculated SACT	98±6	100±3	NS	131±13	139±13	NS
ERAA (S.C.L)	261±6	258±6	NS	373±13	366±14	NS
ERPA (Paired A.P)	238±7	231±4	NS	294±7	294±7	NS
FRPA (S.C.L)	299±6	292±6	NS	413±12	414±12	NS
FRPA (Paired A.P)	282±4	273±3	NS	331±6	333±5	NS
ERPAVN (S.C.L)	316±12	330±13	NS	441±77	466±33	NS
ERPAVN (Paired A.P)	329±10	327±9	NS	386±14	386±13	NS
FRPAVN (S.C.L)	431±13	444±12	NS	501±70	500±61	NS
FRPAVN (Paired A.P)	436±10	443±11	NS	454±11	472±12	NS
RRPHPS (S.C.L)	521±18	482±18	NS	559±30	532±25	NS
RRPHPS (Paired A.P)	418±18	408±15	NS	472±9	467±19	NS

Abbreviations: SACT=sinoatrial conduction time; SCL=sinus cycle length; A.P=atrial pacing; ERPA=atrial effective refractory period; FRPA=atrial functional refractory period; ERPAVN=AV node effective refractory period; FRPAVN=AV node functional refractory period; RRP_{HPS}=relative refractory period of the His-Purkinje system.
Mean±S.E. (msec).

trol of the heart had already been antagonized by atropine. The max. CSRT did not change in 6 patients but increased in 4 patients (Table II).

The calculated SACT was 98±6 msec before and 100±3 msec after lidocaine in control group (NS) and 131±13 msec before and 139±13 msec after lidocaine in SSS group (NS) (Table III). Before lidocaine, in 7 of 28 patients of SSS group, the SACT could not be calculated due to showing a non-reset (2 patients) or a chaotic pattern (5 patients) of the return cycles. After lidocaine, the SACT could not be calculated in another 5 patients due to a chaotic pattern (3 patients) or ectopic atrial responses to atrial extrastimuli (2 patients). The calculated SACT was not decreased in any patient but increased by 25 msec in only 4 patients of SSS group after lidocaine. However, in control group, there was no patient in whom the calculated SACT was prolonged.

ERPA (SCL, paired CL) and FRPA (SCL, paired CL) were not significantly changed with lidocaine in both groups. ERPAVN (SCL, paired CL), FRPAVN (SCL, paired CL), and RRP_{HPS} (SCL, paired CL) were not significantly changed with lidocaine in both groups (Table III).

DISCUSSION

Recently, several cases of severe sinus bradycardia and/or sinus arrest with lidocaine have been reported.¹⁾⁻⁸⁾ In these cases, such arrhythmias

were associated with or without preexistent sinus node dysfunction. However, the electrophysiological basis for these cases has not been fully elucidated. To clarify the mechanisms, electrophysiological studies of lidocaine effects on intracardiac conduction system were performed particularly in SSS patients. In the present study, lidocaine had no effect on sinus cycle length, PA(P'A), AH, and HV intervals, refractory periods of atrium, AV node, and His-Purkinje system and SACT in both groups. These observations were in agreement with previous^{9),10),15)-19)} reports except sinus cycle length, RRP_{HPS} and SACT.

Dhingra et al¹⁰⁾ and Ryden et al¹⁴⁾ demonstrated that lidocaine significantly decreased sinus cycle length in patients both with and without sinus node dysfunction. They speculated the cause of decreased sinus cycle length might reflect the vagolysis and/or β -sympathetic stimulation (central). On the other hand, Roos et al⁹⁾ demonstrated lidocaine had no significant effect on sinus cycle length in human with and without sinus node dysfunction, or Lieberman et al²⁰⁾ and Mandel et al²¹⁾ demonstrated negative chronotropic effects in animals with large doses (5 to 10 mg/Kg). In the present study, the effects of lidocaine on sinus cycle length were varied inconsistently and not significant in both groups. These changes were thought to be due to subtle spontaneous variations in autonomic nervous control rather than the direct drug effect.

It was reported that lidocaine shortened RRP_{HPS} in normal patients,¹⁹⁾ and did not shorten but increased in patients with conduction disturbance in distal His bundle.⁹⁾ In the present study, RRP_{HPS} were not significantly changed in both groups.

Dhingra et al¹⁰⁾ demonstrated lidocaine increased SACT and decreased SRT in patients with sinoatrial dysfunction but unchanged SACT and SRT in patients without. Decreased SRT could reflect increased sinus node automaticity and/or increased perinodal refractoriness, allowing entrance block to occur. While, Roos et al⁹⁾ demonstrated lidocaine did not change SRT in patients with and without sinus node dysfunction but they did not measure SACT. In experimental studies, there was no significant effect of lidocaine on SACT.²²⁾ In this study, calculated SACT did not change after lidocaine in both groups in contrast to the Dhingra's observation.¹⁰⁾ The SRT, CSRT at a paced rate of 130/min, max. SRT and max. CSRT increased significantly in SSS group and unchanged in control group after lidocaine. Even when vagal action was already abolished by atropine, max. CSRT was prolonged in 4/10 patients of SSS group. The major factors affecting SRT are sinus node automaticity, presence of entrance and/or exit block, and autonomic nervous control. It seemed difficult to consider the entrance and/or exit

block from the results of unchanged SACT, ERPA, and FRPA. Furthermore, autonomic nervous control seemed not to play an important role from the results that atropine failed to protect the effects of lidocaine. Therefore, it was suggested that the most possible explanation of the increased SRT was due to depressed sinus node automaticity. The cause of this depression seen only in SSS group even with therapeutic dose was unknown but appeared that these patients might be more sensitive to lidocaine.

In SSS group, there were patients in whom max. CSRT remarkably increased or in some cases max. CSRT increased from normal before to abnormal value after lidocaine. Therefore, overdrive suppression test during stressing of the sinus node by lidocaine was useful to manifest the masked sinus node abnormalities. In addition, lidocaine should be used with caution in the treatment of ventricular arrhythmias of patients with known or suspected sinus node disease.

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