

Comparison of Class II and Class III Activity of dl-Sotalol in Healthy Volunteers

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SUMMARY

Racemic sotalol has demonstrated anti-arrhythmic properties which include Class II (β blockade) and Class III (potassium channel blockade) activity. The Class II activity is demonstrated primarily in l-sotalol, and Class III activity is almost equipotent in each isomer.

Class II and Class III activity of dl-sotalol was investigated following repeated oral administration (80 mg b.i.d.) for 7 days. Class II activity was evaluated according to the low frequency spectral power obtained by fast Fourier analysis of the R-R interval variation. Class III activity was evaluated according to the change in the QTc interval of the surface electrocardiogram.

The low frequency spectral power decreased after administration of the first dose on day 1 and this trend continued throughout the duration of the study. The QTc interval did not change with dl-sotalol administration.

These findings may suggest that Class II activity is more potent than Class III activity. (Jpn Heart J 1998; 39: 79-86)

Key word: Sotalol, Pharmacodynamics, β adrenergic blocker, Heart rate variability, Potassium channel blocker, Spectral analysis

RACEMIC sotalol has demonstrated anti-arrhythmic properties which include both Class II (β -blockade) and Class III (potassium channel blockade) activity. Class II activity, which is devoid of membrane-stabilizing activity and intrinsic sympathomimetic activity, is demonstrated primarily in l-sotalol. Class II activity of l-sotalol is 50 times more potent than that of d-sotalol. Class III activity is almost equal for each isomer.¹⁻⁵⁾

Recent studies have reported that cardiac autonomic function plays a key role in the long-term survival of patients with cardiac disorders. Excessive cardiac sympathetic activity is thought to be a major risk factor for sudden cardiac

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death.⁶⁻¹⁰⁾ Thus, anti-arrhythmic drugs with β adrenergic blocking action may be more useful clinically for such patients.¹¹⁻¹⁴⁾ Recently, some clinical trials have demonstrated an improvement of long-term survival rate when sotalol and amiodarone, which have potassium channel blocking action and anti-sympathetic activity, were administered.¹⁵⁻²¹⁾

In the present study, the effects of dl-sotalol on cardiac sympathetic activity and repolarization time were evaluated by spectral analysis of the R-R interval variation and QTc interval of the surface electrocardiogram, respectively.

MATERIALS AND METHODS

Subjects and protocol: Volunteers participating in this study were 6 healthy males ranging in age from 25 to 39 years and in weight from 52.4 to 69.8 kg. The study protocol was approved by the Institutional Ethics Committee. Informed consent was obtained from all subjects. Eighty mg of dl-sotalol were administered twice daily at 9:00 and 21:00 for 6 days and once at 9:00 on day 7. Ambulatory ECG records were obtained from 9:00 to 13:00 using a 2-channel bipolar recorder (DMC-3252, Nihonkoden, Tokyo, Japan) on the day prior to administration and on days 1, 4 and 7. During recording the subjects were maintained at a 45° upright position in bed. Ambulatory ECG records were digitized using a Holter ECG analyzing system (DMC4100, Nihonkoden). Power spectral analysis of R-R interval variation was performed every 2 min using fast Fourier analysis (QP-413D, Nihonkoden) with a personal computer (PC9801RX, NEC, Tokyo). The R-R interval trendgrams were resampled every 300 msec and data sets containing 512 points were processed. The low frequency (0.04–0.15 Hz) and high frequency (0.15–0.5 Hz) power spectra were estimated and then used as an index of sympathetic and parasympathetic activity, respectively.^{22,23)} The mean spectral power and mean R-R interval from 3 to 4 hours after administration were determined on days 0, 1, 4 and 7. Conventional surface electrocardiograph was performed 4 hours after administration on days 0, 1, 2, 3, 4 and 7. The QT and R-R intervals of three serial waves were measured according to the criterion of Lepeschkin and Surawicz (1952).²⁴⁾ The QT intervals were corrected using the square root of the R-R intervals. The mean value of three corrected QT intervals (QTc) was calculated for each ECG recording.

Statistical analysis: All data are represented as mean \pm SEM. Analysis of variance (ANOVA) was used to compare the R-R interval spectral powers and Student's *t*-test was used to analyze the QTc intervals. Statistical significance was established at the $p < 0.05$ level.

RESULTS

Analysis of R-R interval: Figure 1 shows the change in R-R interval after administration of dl-sotalol. The initial R-R interval was 963.3 ± 118.3 msec. This increased to 1088.1 ± 100.7 msec following the first dl-sotalol administration ($p < 0.01$). The increase in the R-R interval remained following subsequent dl-

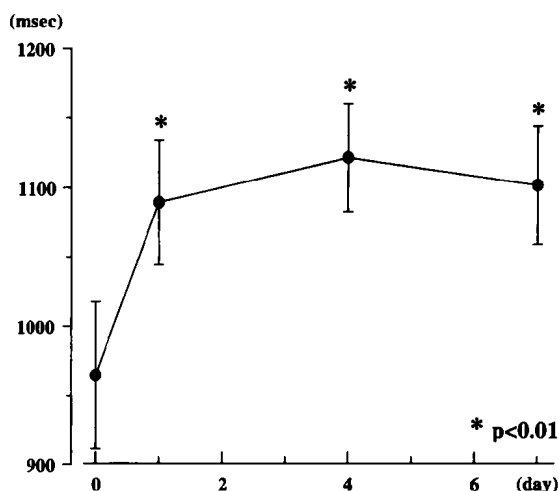


Figure 1. Change in R-R interval following dl-sotalol administration. R-R interval was prolonged on day 1 and remained so during the period of administration.

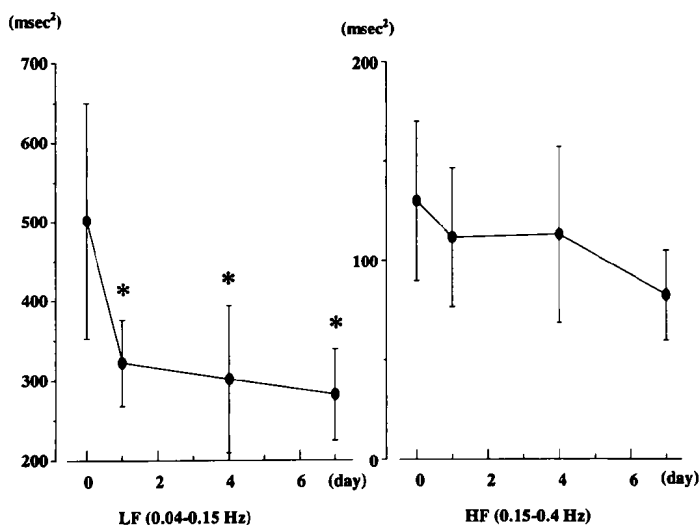


Figure 2. Change in spectral power of R-R interval. Low frequency spectral power decreased after the first dose on day 1 ($p < 0.01$). No further change was observed with repeated administrations. Daily high frequency spectral power was low compared to low frequency spectral power. The slight decrease in high frequency power during the observation period was not statistically significant.

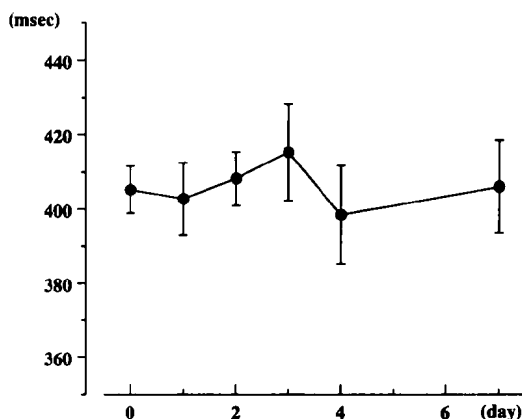


Figure 3. Change in QTc intervals after dl-sotalol administration. There was no change in QTc interval.

sotalol administration (1120.5 ± 86.7 msec on day 4 and 1100.7 ± 95.4 msec on day 7).

Spectral analysis of the R-R interval variation is shown in Figure 2. The low frequency spectral power (501.3 ± 331.9 msec² on day 0) decreased to 322.4 ± 120.3 msec² after the first dose on day 1 ($p < 0.01$). However, subsequent administration did not result in any further changes (301 ± 204.8 msec² on day 4 and 281.8 ± 127.4 msec² on day 7). This trend is similar to that seen for the R-R interval. The high frequency spectral power, which is an index of cardiac parasympathetic activity, was lower than the low frequency spectral power when compared on a daily basis. High frequency spectral power did not show significant change during the observation period (129.8 ± 90.1 msec² on day 0, 111.3 ± 71.7 msec² on day 1, 112.8 ± 99.4 msec² on day 4 and 82.2 ± 50.4 msec² on day 7).

Changes in QTc interval: Figure 3 shows the changes in QTc interval following dl-sotalol administration. The increased QTc interval is associated with an increase in the repolarization and refractory periods that accompany dl-sotalol administration.

The QTc intervals on days 0, 1, 2, 3, 4 and 7 were 405.25 ± 14.24 msec, 402.80 ± 21.72 msec, 408.21 ± 16.09 msec, 415.33 ± 29.05 msec, 398.48 ± 29.54 msec and 406.08 ± 27.77 msec, respectively. There was no significant change.

DISCUSSION

Class II and Class III activity was examined and compared following repeated administration of dl-sotalol. The activity was evaluated in terms of the low

frequency component of the R-R interval variation and prolongation of the QTc interval, respectively. The low frequency component was reduced, whereas the QTc interval did not change following drug administration.

A previous study showed that the pharmacokinetics of each dl-sotalol isomer are quite similar.²⁵⁾ The time to maximum concentration is approximately 3 to 4 hours after administration.^{5,26,27)} The pharmacodynamics of each isomer are reported to be closely correlated with the dose or plasma concentration and the minimum QTc prolongation was observed at a dose of 80 mg.^{5,27,28)} In the present study, the effects of d- or l-sotalol were evaluated 3 to 4 hours after drug administration, as the maximum effect was expected at that time and the dose of 80 mg was administered twice a day.

Wang *et al.* (1989) reported that the concentration associated with significant Class III activity was greater than that for Class II activity.²⁹⁾ In contrast, Funk-Brentano, *et al.* (1991) reported that the plasma concentration of sotalol associated with minimal Class II action was very similar to that associated with minimal Class III action.³⁰⁾ Although the Class II activity was evaluated according to a decrease in the peak exercise heart rate in both reports, Yasuda *et al.* (1993) reported that d-sotalol decreases the peak exercise heart rate through a mechanism other than the β adrenergic receptor.³¹⁾ Since d-sotalol has little Class II activity, the reduction in heart rate might be caused by a prolongation of the sinus node action potential due to Class III activity. These findings suggest that a decrease in peak exercise heart rate might not be a suitable indicator of the class II activity of dl-sotalol. Therefore, spectral analysis of the R-R interval variation was used in the present study. Previous studies have reported that the low frequency component (0.04–0.15 Hz) of the R-R interval variation may increase as a result of external manipulation such as moving to an upright position, lower body negative pressure, and exercise which stimulates the sympathetic nerve system,^{22,32)} and is reduced by β -adrenergic receptor blockade.³³⁾ Bekheit *et al.* (1990) observed that metoprolol suppressed the low frequency component augmented by upright position.³⁴⁾ In the present study, the low frequency component of the R-R interval variation, which provides an index of cardiac sympathetic activity, was significantly reduced after the initial dl-sotalol administrations, and this trend continued throughout the observation period. Similarly, the R-R interval became prolonged from day 1 to day 7.

The low frequency spectral component of the R-R interval is reportedly modulated by both sympathetic and parasympathetic activity, whereas the high frequency component is modulated primarily by parasympathetic activity.³⁵⁾ Although the low frequency component is related to both sympathetic and parasympathetic activity, the change in the low frequency component was thought to result from a suppression of cardiac sympathetic activity due to the lack of change

in the high frequency component of the R-R interval variation, which is an index of cardiac parasympathetic activity.

These findings suggest that dl-sotalol reduces the power of the low frequency component of the R-R interval variation by suppressing cardiac sympathetic activity without changing the parasympathetic activity.

In previous studies, dl-sotalol prolonged the QTc intervals in a dose-dependent manner and a linear correlation was observed between interval prolongation and the plasma concentration of dl-sotalol. The QTc interval was increased by 3.81% and 13.23% after oral administration of dl-sotalol at doses of 80 mg and 160 mg, respectively.²⁷⁾ This is a well-known effect induced by the Class III action of dl-sotalol.²⁸⁾ The QTc interval, which was used as an index of Class III activity, did not change in the present study. With the low dose of dl-sotalol used in this study, R-R interval prolongation may be caused primarily by Class II activity.

These findings suggest that Class II activity, which is present mainly with the l-isomer, is more potent than Class III activity in both d- and l-sotalol.

It has been previously reported that sensitivity to β -adrenergic blockers varies among different racial groups. In the present study, the Class II activity may have been enhanced due to the subject pool which consisted exclusively of an Asian population, since Asians may be more sensitive than Caucasians.³⁶⁾ Furthermore, the spectral analysis of the R-R interval variation used in this study is sensitive to the change of autonomic modulation. These may be the reasons that β -adrenoceptor blocking action was the one predominantly detected.

In conclusion, the Class II activity of dl-sotalol might be more potent than its Class III activity, as indicated by the QTc interval. Furthermore, the spectral power analysis of the R-R interval variation provides a useful tool for evaluating β -adrenoceptor blocking action.

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