The effect of sinus node depression on heart rate variability in humans using zatebradine, a selective bradycardic agent

Yaariv Khaykin, Paul Dorian, Anthony Tang, M. Green, Jan Mitchell, Zaev Wulffhart, and David Newman

Abstract: Zatebradine is a bradycardic agent with a selective effect on the pacemaker current in the sinus node. The effect of such drugs on heart rate variability is not known. Thirty-six patients without structural heart disease were randomly assigned to receive 10 mg of zatebradine i.v. (n = 24) or isotonic saline (n = 12). Heart rate variability (HRV) was recorded as power in the very low frequency (VLF; 0.003–0.040 Hz), low frequency (LF; 0.040–0.150 Hz), and high frequency (HF; 0.150–0.400 Hz) spectral bands as well as total power (TP; 0.003–0.400 Hz) during 5 min ECG acquisitions at baseline, 30, and 60 min following the start of the infusion. No change in heart rate variability was detected in the control group. Zatebradine significantly reduced heart rate variability at 60 min in all frequency bands: VLF (−12 ± 4%, p < 0.001), LF (−19 ± 4%, p < 0.001), and HF (−26 ± 5%, p < 0.001). The reduction in HRV following zatebradine is due to depression of sinus node response to all external stimuli and underscores the need for documentation of normal sinus node function in HRV research.

Key words: zatebradine, sinus node, heart rate variability, HRV, autonomic nervous system.

Résumé : La zatebradine est un bradycardiant ayant un effet sélectif sur le courant du centre rythmogène du nœud sinusal. L’effet de ce type de médicaments sur la variabilité de la fréquence cardiaque n’est pas connu. Trente-six patients sans maladie cardiaque structurale ont reçu aléatoirement 10 mg de zatebradine i.v. (n = 24) ou une solution saline isotonique (n = 12). On a étudié la variabilité de la fréquence cardiaque (VFC) à partir de mesures de la puissance dans des bandes spectrales de très basse fréquence (TBF; 0.003–0.040 Hz), de basse fréquence (BF; 0.040–0.150 Hz) et de haute fréquence (HF; 0.150–0.400 Hz), ainsi qu’à partir de la mesure de la puissance totale (PT; 0.003–0.400 Hz) durant des acquisitions ECG de 5 min aux valeurs de base ainsi que 30 et 60 min après le début de la perfusion. Aucun changement de variabilité de la fréquence cardiaque n’a été détecté chez le groupe témoin. La zatebradine a réduit significativement la variabilité de la fréquence cardiaque à 60 min dans toutes les bandes de fréquences : TBF (−12 ± 4%, p < 0.001), BF (−19 ± 4%, p < 0.001) et HF (−26 ± 5%, p < 0.001). La réduction de la VFC après la perfusion de zatebradine est due à une diminution de la réponse du nœud sinusal à tous les stimuli externes et souligne le besoin de connaître la fonction normale du nœud sinusal dans la recherche sur la VFC.

Mots clés : zatebradine, nœud sinusal, variabilité de la fréquence cardiaque, VFC, système nerveux autonome.

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**Introduction**

Heart period or rate variability (HRV) has been advocated as a noninvasive probe of the autonomic nervous system modulating the heart rate as represented by its cumulative effect on sinus node automaticity, the control parameter for heart rate (Sayers 1973; Luczak and Lauring 1973). HRV may also be a clinically useful marker to assess the risk of serious arrhythmias or cardiovascular events in patients with cardiac disease (Malik et al. 1996). Despite the utility of heart rate variability, the relationship between the related parameter of heart rate and its variability is not well understood.

Zatebradine is a member of a class of investigational agents known as “specific bradycardic agents,” which slow heart rate but have no hemodynamic, β-blocking, or calcium channel blocking effects (Bril et al. 1995). Voltage clamp studies have shown that zatebradine selectively blocks sinus node hyperpolarization-activated pacemaker current (I\(_{f}\)), slowing the heart rate (DiFrancesco 1986; DiFrancesco and Zaza 1992; van Bogaert and Goethals 1992). As such, zatebradine provides a pharmacological probe to slow the heart rate independently of any direct effect on the autonomic nervous system.

Heart rate is modulated by autonomic tone. With increase in sympathetic tone at the sinus node level, it is expected to accelerate, while it will slow down with an increase in parasympathetic tone. Heart rate variability is defined by autonomic modulation of the sinus node within a physiological range, where sinus node receptors are sensitive to higher neurological inputs. The parasympathetic nervous system has been shown to modulate heart rate in the high frequency (HF: 0.150–0.400 Hz) range of HRV (Akselrod et al. 1981, 1985; Pomeranz et al. 1985; Pagani et al. 1986), although HRV may be dissociated from the autonomic nervous system modulation if vagal tone saturates the sinus node (Goldberger et al. 1994). The effect of direct sinus node inhibition on heart rate variability is not known. In an effort to understand if blockade of the I\(_{f}\) current per se alters the sinus node response to autonomic modulation, we set out to examine the effects of intravenous zatebradine or placebo on HRV parameters in a randomized double-blind controlled trial.

**Methods**

Thirty-five patients (22 males, 13 females), ages 45 ± 2.4 years, were randomly assigned to receive 10 mg of zatebradine i.v. (n = 23, 14 males and 9 females) or isotonic saline (n = 12, 8 males and 4 females) using a double-blind, placebo-controlled design. No subject had a history of diabetes mellitus, hypertension, syncope, palpitations, or significant structural heart disease. All subjects had undergone successful catheter ablation of a re-entrant pathway within 1–4 months of this study. Written informed consent was obtained prior to the study. Zatebradine was administered as a 5-mg bolus over 5 min, followed by a 40-min infusion of another 5 mg, a dosage demonstrated to effectively lower heart rate in previous studies (Duong et al. 1991). Study drug infusion was performed following completion of routine postablation EP studies, at least 15 min following insertion of catheters into the heart in a low-stimulation environment. The electrophysiologic effects of zatebradine at these doses have been previously reported (Dorian et al. 1996). Electrocardiographic data were acquired during 5-min recordings at baseline, 40, and 70 min following the start of the infusion using a Predictor II series HRV analysis system (ART-Corazonix, Oklahoma City, Okla.) with orthogonal (X, Y, Z) lead placement. A sampling frequency of 400 Hz was used, and recordings were stored for subsequent analysis (Bailey et al. 1990). RR interval tachograms were generated for each electrocardiographic recording using the ART-Corazonix Predictor II template-matching algorithm. All recordings were then manually over-read, and remaining ectopic beats were eliminated along with the subsequent beat (Lippman et al. 1994). Each recording contained approximately 300 RR intervals. All recordings used in the analysis had less than 5% of the beats erased with most recordings having only 1–5 beats eliminated. Missing data were filled in using linear interpolation and a resampling routine. The direct current component was subtracted, and the data were normalized by division by the mean interval. Fast Fourier Transform analysis with a Hanning windowing procedure was used for spectral analysis of the data. No detrending procedure was performed due to the short duration of the recordings (Malik 1996). Heart rate variability was recorded as power in the very low frequency (VLF, 0.003–0.040 Hz), low frequency (LF, 0.040–0.150 Hz), and high frequency (HF, 0.150–0.400 Hz) spectral bands as well as total power (TP, 0.003–0.400 Hz).

Logarithmic transformation of the spectral components was used prior to comparative analysis to normalize the distribution of results. Normalized measures were then divided by the baseline value for each patient. One-way analysis of variance (ANOVA) with repeated measures design was used to analyse changes in HRV Testing was two-tailed with a p-value of less than 0.05 considered significant. The study protocol was approved by the ethics review boards at each of the institutions.

**Results**

Of 35 patients who completed the trial, 23 received zatebradine, and 12 received placebo (3 subjects who received zatebradine, as well as 2 subjects receiving placebo, developed atrial fibrillation during atrial stimulation in the electrophysiological component of the study and were excluded from analysis). There were no significant blood pressure changes in either the experimental group or the controls.

**Effects on heart rate and total power (Table 1, Fig. 1)**

As expected, zatebradine reduced heart rate by 18 ± 2% from 70.5 ± 2.7 to 57.0 ± 2.0 beats/min. There was no significant change in heart rate among the controls. Similarly, total spectral power remained stable over time in controls and decreased by 14 ± 32% in the zatebradine group.

**Effects on HRV measures (Table 2, Fig. 2)**

Zatebradine reduced heart rate variability in all frequency ranges to a similar extent, very low frequency domain by 12 ± 4% (Fig. 2), low frequency domain by 19 ± 4%
Fig. 1. The effect of zatebradine (■) compared with placebo (broken lines) on heart rate (A) and total power (B). In both cases, there is no statistically significant difference compared with baseline at either time with placebo; however, a statistically significant difference was seen for zatebradine, compared with baseline ($p < 0.001$).

(Fig. 2B), and high frequency domain by 26 ± 5% (Fig. 2C). There was no significant change with time in any of the spectral components of heart rate variability in the controls.

Effects on HRV measures normalized by total power

When normalized by total power, no change could be found in any of the spectral components of HRV in either the experimental group or the controls.

Discussion

This study demonstrates that selective blockade of the $I_f$ current is associated with a significant decrease in all heart rate variability parameters with no change in relative proportions of spectral components to total power. No change in heart rate variability was found in the control group, indicating that frequency domain measures of heart rate variability are stable over time in an invasive clinical electrophysiological study setting. Although it is generally assumed that assessment of heart rate variability requires a normal effector organ, this is rarely formally tested. Zatebradine, by providing a novel direct depression of sinus node function, allows a unique assessment of the importance of intact sinus node function in heart rate variability studies.

It is important to note a distinction between autonomic tone and autonomic modulation. The relationship between these is not unlike that of a primary variable and its derivative, respectively. For instance, influx of acetylcholine into the sinus node would delay the If current and result in slowing of heart rate; the effect on heart rate variability, however, will be modulated by the way pulses of acetylcholine are delivered. So, saturation of acetylcholine receptors may be expected to slow heart rate while also decreasing heart rate variability in the high frequency domain (Goldberger et al. 1994). Pulsed release of acetylcholine, however, would increase heart rate variability in the region below a certain degree of saturation of acetylcholine receptors, where most of the studies of HRV to date have operated. Both sympathetic and parasympathetic pathways of heart rate regulation must converge on a final effector organ to regulate both heart rate and its variability. From the results of this trial it appears that $I_f$ channel is such an end organ in the sinus node control mechanism. Blockade of this channel resulted in acetylcholine-like effect on heart rate, while at the same time dissociating the sinus node from its controls. While heart rate may be a measure of autonomic tone, heart rate variability is a measure of its modulation.

Explanations for the observed effect of zatebradine include a dampening of autonomic nervous system modulation at a higher centre in addition to the undoubted blocking of the sinus node response to all external stimuli. It may be possible that zatebradine had a central effect, however, no evidence to that effect is available. Although zatebradine is a derivative of verapamil (Bril et al. 1995), it can be differentiated from both calcium channel blockers and β-blockers by relative effects on heart rate, cardiac contractility, and aortic
Table 2. Effects on heart rate variability measures.

<table>
<thead>
<tr>
<th></th>
<th>Ln(VLF) (beats/min^2 per cycle)</th>
<th>Ln(LF) (beats/min^2 per cycle)</th>
<th>Ln(HF) (beats/min^2 per cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Zatebradine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.9±0.5</td>
<td>7.0±0.2</td>
<td>7.1±0.3</td>
</tr>
<tr>
<td>40 min</td>
<td>7.7±0.3</td>
<td>6.3±0.2*</td>
<td>7.2±0.4</td>
</tr>
<tr>
<td>70 min</td>
<td>7.7±0.4</td>
<td>6.0±0.2</td>
<td>7.0±0.3</td>
</tr>
</tbody>
</table>

Note: All data mean ±SEM; Ln(VLF), Ln(LF), and Ln(HF) refer to the natural log of power spectra from very low (0.003-0.040 Hz), low (0.040-0.150 Hz), and high (0.150-0.400 Hz), respectively.

*p < 0.001.

*p < 0.005.

relaxation (Kobinger and Lillie 1984; Lillie and Kobinger 1986). Furthermore, zatebradine selectivity of block of I_f current, the final common pathway to control of heart rate at sinus node level, has been shown in sheep and rabbit sinoatrial cells (Goethals et al. 1993).

These observations demonstrate that factors other than autonomic modulation of sinus node function can alter HRV. In particular, sinus node disease may be expected to have effects similar to zatebradine on HRV. This implies that heart rate variability studies require a normal sinus node if used to infer information on autonomic modulation and possibly also to optimally provide clinically useful prognostic information. Normalization of the spectral components by the total power at baseline and after an intervention may be a useful tool to access the degree of sinus node responsiveness to external stimuli. If the change in spectral components is proportional across the spectra, factors other than frequency modulation within the component ranges are taking a toll on HRV.

There are a few limitations to our observations, especially with respect to the RR interval editing procedure employed. A maximum of 5% of the intervals were excluded; however, analysis was blinded and the validity of manual editing of the RR interval files has been demonstrated in prior human studies (Lippman et al. 1994). Patient sedation may have had some effect on HR and HRV, but this was controlled for by randomization with an identical sedative regimen used between experimental subjects and controls.

Conclusions

Zatebradine decreases heart rate variability across all the frequency spectra. The channel that controls I_f current may be the end organ in autonomic control of the sinus node. Alterations in sinus node function, such as may occur with disease, can alter heart rate variability measurement, thus making it impossible to assess the actuation autonomic modulation of the heart in a noninvasive manner using HRV.

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