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Original article

Effects of suvorexant on sleep apnea in patients with heart failure: A protocol of crossover pilot trial

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ABSTRACT

Background: Suvorexant, an orexin receptor antagonist, is known as a safe and effective sleep medication. Many patients with heart failure (HF) have sleep-disordered breathing (SDB) and are short sleepers, and it is unknown whether suvorexant is effective in HF patients and can improve insomnia safely. The aim of this study is to examine the effect of suvorexant on SDB in patients with HF.
Methods: The Heart Failure with Insomnia and Suvorexant trial of Juntendo University Hospital and Juntendo Shizuoka Hospital (J-FLAVOR trial) is a multicenter trial with a randomized double crossover design. We will enroll a total of 30 HF patients treated in the Juntendo University Hospital and Juntendo Shizuoka Hospital. Eligible patients will undergo portable sleep monitoring twice with or without oral administration of suvorexant in a randomly assigned order. Before the study night, patients in the suvorexant first group will receive suvorexant for 4 consecutive days. There are at least 3 wash-out days between the study nights with and without suvorexant. Primary outcome measures of the non-inferiority trial of suvorexant include the apnea-hypopnea index and the severity of SDB, and the results will be compared between the study nights with and without suvorexant.
Conclusion: The present study can determine whether suvorexant can be used in HF patients without affecting their SDB. This is a pilot study to primarily assess whether suvorexant affects the severity of SDB in patients with HF. Therefore, further study is warranted to investigate whether suvorexant alters short- and long-term clinical outcomes by providing longer and better sleep in patients with HF.

Introduction

Sleep is an important resting period for the cardiovascular system, and impairments in sleep quality and quantity can thus lead to cardiovascular disease [1]. The quantitative impairments of sleep, such as short sleep duration, are reportedly associated with increased mortality [2]. In particular, short sleep raises blood pressure and heart rate (HR), promotes tachyarrhythmia through sympathetic nerve activation [3,4], and consequently increases risks of incident heart failure (HF) [5] and cardiovascular mortality [6,7]. The qualitative impairments of sleep are generally derived from insomnia including difficulties in initiating and maintaining sleep, both of which result in the impairment of daytime function [8], and from other sleep-related disorders, such as sleep-disordered breathing (SDB). Insomnia and SDB can deteriorate

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cardiovascular function [1,9] and are associated with increased incidence of cardiovascular disease including comorbidities, such as HF, acute coronary syndrome (ACS), or atrial fibrillation (AF) [10–13], and consequently with enhanced mortality [14,15]. Patients with HF reportedly have approximately 4–12 min longer sleep onset latency and 70 min shorter total sleep time than healthy controls [16]. Indeed, insomnia symptoms are common in patients with HF [17]. Although it remains unclear why patients with HF have insomnia, the high prevalence of SDB in patients with HF [9,18] may contribute to such sleep issues. In patients with HF, the presence of either insomnia or SDB is associated with poor clinical outcomes [9,18,19].

It has been reported some hypnotics could affect hemodynamics such as blood pressure (BP) or (HR) [20,21]. Thus, hypnotics may also affect cardiac output (CO) and/or stroke volume (SV). This is particularly important in patients with heart failure. However, specific studies regarding hypnotics for comorbid insomnia in patients with HF have not been performed to date, but they are strongly needed. Although benzodiazepine receptor agonists, a major class of hypnotics, have generally been used for insomnia even in patients with HF [22], their safety and efficacy have been rarely investigated in HF patients, and their effects on comorbid SDB remain controversial [23]. Furthermore, it has reported that clearance and absorption of some drugs are impaired in patients with congestive HF compared with healthy subjects because of multiple organ dysfunction such as liver, kidney, gastric, or gut [24,25]. In patients with HF, effects of hypnotics including side effects may also be different from those in healthy subjects. Recently, suvorexant, an orexin receptor antagonist, has come into use as a new class of hypnotics [26], and it reportedly can improve insomnia, mainly maintaining and improving quality of sleep but without increasing severity of SDB [27], and can be beneficial for lowering the incidence of delirium in elderly patients with critical illnesses, including cardiovascular disease [28]. However, whether suvorexant improves sleep quality but does not worsen SDB even in patients with HF remains unclear. In addition, whether suvorexant affects hemodynamics during sleep is of great interest.

The objectives of the present study are to examine the effects of suvorexant on SDB severity, sleep quality, and hemodynamics during sleep in patients with HF.

Methods

Study design

The Heart Failure with Insomnia and Suvorexant trial of Juntendo University Hospital and Juntendo Shizuoka Hospital (J-FLAVOR trial), is a multicenter, randomized double crossover study. According to the guidelines of full-night polysomnography to examine baseline status of SDB, a total of 30 enrolled subjects will be randomly assigned as either the suvorexant first group or the control first group (without suvorexant first). Subjects will undergo the sleep study with a portable sleep monitor based on the peripheral arterial tone (Watch-PAT 200, Itamar Medical Ltd., Caesarea, Israel) [29] and a digital photoplethysmography (Portapres; Finapres Medical Systems, Amsterdam, The Netherlands) [30] twice, with and without suvorexant in a randomly assigned order, to examine severity of SDB, sleep status, and hemodynamics during sleep. Following randomization, subjects assigned to the suvorexant first group will take 15 or 20 mg of suvorexant for 3 consecutive nights before the sleep study, and steady-state plasma concentrations are typically achieved after 3 days of dosing with minimal accumulation. Patients younger than 65 years of age will be administered a single 20-mg oral dose of suvorexant, and patients older than 65 years of age will be administered a single 15-mg oral dose of suvorexant, which is a standard dose in Japan. Subsequently, after 3 wash-out days, the second sleep study without suvorexant will be administered. Subjects assigned to the control first group will undergo the sleep study without suvorexant immediately after randomization, and they will take suvorexant 3 days before the second study with suvorexant (Fig. 1).

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards, and the study will be performed in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent will be obtained

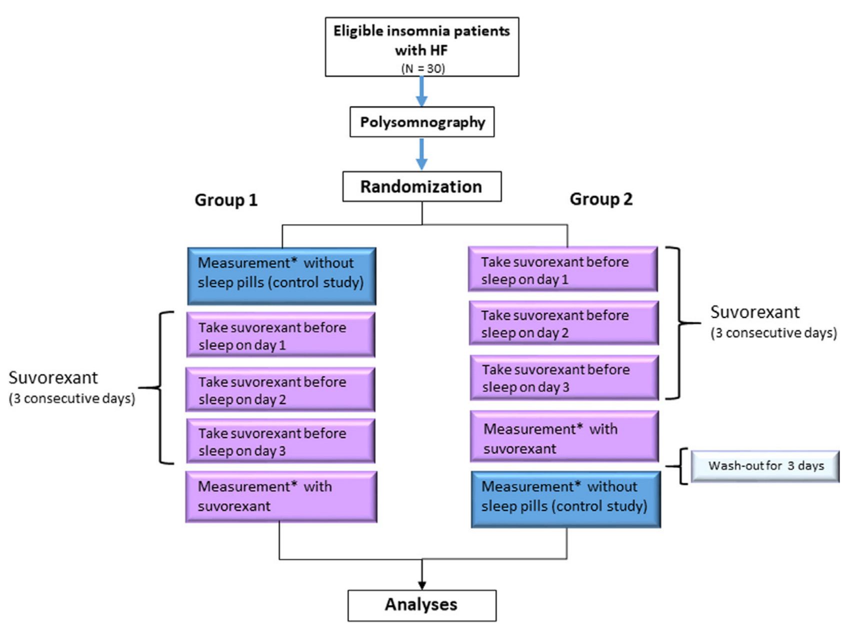

Fig. 1. Enrollment and randomization of study participants. The study flow chart shows a randomized double crossover study design. Subjects assigned to the control first group will undergo the study without suvorexant immediately after randomization, and they will take suvorexant for 3 days before the second study with suvorexant. Subjects assigned to the second group will take suvorexant for 3 days before the first study with suvorexant and will undergo the second study without suvorexant after 3 wash-out days. *Abbreviation*: HF, heart failure.

from all participants. This study has been registered with the UMIN Clinical Trials Registry (identifier: UMIN000031942).

Subjects

We will recruit hospitalized patients with acute decompensated HF (ADHF) according to modified Framingham criteria in the Juntendo University Hospital (Tokyo, Japan) and Juntendo Shizuoka Hospital (Shizuoka, Japan) [31]. Insomnia disorder will be diagnosed according to the International Classification of Sleep Disorders 3rd edition (ICSD-3) definition [8], and a report of sleep initiation or maintenance problems and daytime consequences will be produced for every subject, even after improvement in acute signs and symptoms of ADHF during initial hospitalization. Clinical data of candidates will be collected to find out eligibility and will be summarized as baseline characteristics of subjects (Table 1). Eligible patients comprise men and women aged over 20 years. Patients will be excluded from this study if they meet the following criteria: those who cannot take medicine orally; those treated with any drugs that interact with suvorexant; those who are taking any hypnotics regularly; those treated with α-adrenergic blocking agents or nitrates; or those with cardiac pacemaker-dependent rhythm throughout the polysomnography night, oxygen supplementation, the use of positive airway pressure, shock, cerebrovascular disease with neurological deficits, narcolepsy, parasomnias, sleep-related hypoventilation disorders, apparent obstructive lung disease, end-stage renal disease requiring dialysis, or severe hepatic disorders.

Polysomnography

All patients will undergo overnight polysomnography with a digital polygraph system (Alice PDX; Philips Respironics, Murrysville, PA, USA) before enrollment in order to assess eligibility. Definitions and scoring methods are based on the American Academy of Sleep Medicine manual Ver. 2.4. The thoracoabdominal motion will be monitored via respiratory inductance plethysmography. Airflow will be measured using an oronasal thermal airflow sensor and nasal pressure cannula. Oxyhemoglobin saturation will be monitored with oximetry.

Watch-PAT 200

We will use a Watch-PAT 200 device to evaluate the effect of suvorexant on breathing during sleep. Watch-PAT 200 is a portable sleep monitoring device, equipped with a peripheral artery tone (PAT) probe combined with a pulse oximetry sensor, snoring sensor, built-in actigraphy, and body position sensor. Respiratory events are identified by digital signals of vasoconstriction mediated by α-adrenergic receptors that are sensitive to surges in sympathetic nerve activity, which usually occurs following each respiratory event. Respiratory events will be scored when one of the following three criteria is met: a reduction in PAT amplitude with an acceleration of the pulse rate or an increase in wrist activity; a reduction in PAT amplitude with ≥3% oxyhemoglobin desaturation; and ≥4% oxyhemoglobin desaturation. The apnea-hypopnea index (AHI) will be defined as the number of episodes of apnea plus hypopnea per hour of sleep. Compared with the AHI derived from polysomnography [32], the AHI calculated using Watch-PAT 200 shows a relatively high degree of correlation even in patients with HF [33]. In the present study, the automated scoring algorithm is provided by a specific software (ZZZ PAT version 4.4.64.p, Itamar Medical Ltd.), and the resulting data are automatically analyzed to identify respiratory events and sleep states. The automated analysis identifies wake-sleep states using actigraphy and sleep stages, including rapid eye movement (REM) sleep and non-REM sleep (further classified as light reflecting N1 plus N2 in polysomnography and deep reflecting N3 in polysomnography), by PAT and actigraphy signals. Watch-PAT 200 has been extensively validated in the polysomnographic recording [29,34].

Table 1
Data collection.

	Baseline	Control	Suvorexant
Vital signs (blood pressure, heart rate, SO_2)	X	X	X
Body weight	X	X	X
LVEF by echocardiogram	X		
Presence or absence of AF	X	X	X
Blood test (hemoglobin, AST, ALT, creatinine, BNP, etc.)	X		
Polysomnographic data	X		
Data from Watch-PAT 200		X	X
Data from Portapres		X	X

Abbreviations: AF, atrial fibrillation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; SO_2, oxyhemoglobin saturation.

Digital photoplethysmography

Noninvasive beat-by-beat measures of arterial BP, HR, SV, CO, and total peripheral resistance (TPR) will be conducted using Portapres [35]. Portapres will be applied via cuffs wrapped around the third and fourth fingers of the left hand. The 2 finger cuffs are alternately inflated and deflated every 30 min during the night. Portapres has a height correction unit to adjust for differences between finger level and heart level to obtain comparable measurements of BP and SV irrespective of finger level. Continuous indices of SV, CO, and TPR are computed using the Modelflow method [36].

Outcome measures and safety assessment

The primary outcome measure in this study is a difference in the AHI evaluated by Watch-PAT 200 between the nights with and without suvorexant in order to assess the effects of suvorexant on the AHI. We will assume that the standard dose of suvorexant will not significantly increase the AHI in HF patients with insomnia disorder. We will define the significant level as an increase in the AHI at ≥5 events/hour [27]. In addition to the indices related to respiratory events, total sleep time, sleep efficiency, and sleep stages from Watch-PAT, hemodynamic parameters from Portapres (mean BP, HR, SV, CO, and TPR) will also be assessed and compared (Table 2). Adverse events will be assessed at each sleep study night. Serious adverse events are defined as those that result in death, are life-threatening, require prolongation of existing hospitalization, or lead to disability or incapacitation.

Sample size

The present study aims to test non-inferiority of suvorexant in terms of the AHI, which does not significantly increase at ≥5 events/hour compared with that during the night w

Table 2
Primary and secondary endpoint.

Primary endpoint	Apnea Hypoxia Index by Watch-PAT 200
Secondary endpoint	Total sleep time, Sleep stages, Respiratory events, Sleep efficiency by Watch-PAT 200
	Blood pressure, Heart rate, Stroke volume, Cardiac output, Total peripheral resistance by Portapres

ithout suvorexant. The within-patients variable is assumed as 8.94, and one-sided significant level and a power of test are set to 5% and 80%, respectively. To detect the non-inferiority effect of suvorexant with a margin of the AHI of 5 events/hour, the total sample size of 22 will be required. Assuming attrition of 8 patients, 30 patients will be required in this study.

Statistical analyses

To assess non-inferiority of suvorexant, a linear mixed effect model for a cross-over trial involving treatment, period, sequence, and random patient effect within sequence will be used, and the least square means of difference ([with suvorexant] – [non-administration]) and its two-sided 90% confidence interval (CI) will be obtained. If the upper bound of the CI does not exceed 5, non-inferiority of suvorexant compared with non-administration can be concluded.

In this study, all randomized patients (i.e. a full analysis set) will be included in an intention-to-treated (ITT) analysis. Because a non-inferiority design is used in this study, per-protocol (PP) analysis will also be performed in patients who will comply with the study protocol to confirm that PP and ITT analyses produce similar results. The safety population will include all patients who have received at least one dose of suvorexant. The frequency of adverse events will be described. All analyses will be performed by SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA).

Discussion

This study will reveal whether administration of suvorexant worsens SDB and alters hemodynamics in patients with insomnia and HF. Our results also can confirm the safety of suvorexant and determine whether suvorexant improves sleep.

Reportedly, risk factors of insomnia include aging; psychiatric disorders; and chronic diseases, such as HF [37,38]. HF patients are likely to be elderly and frequently have depression [39]; therefore, patients with HF could have multiple risk factors for insomnia. Some of the previous studies have demonstrated that insomnia is associated with deterioration of cardiovascular disease (CVD) [40], CVD mortality [41], and incident HF [10]. Thus, insomnia in HF patients might be an important interventional target, although whether improvement of insomnia reverses such poor clinical outcomes remains uncertain.

Insomnia symptoms in patients with HF may be partially explained by the high prevalence of SDB in the patient population. It has been found that SDB deteriorates cardiac function and is consequently associated with poor clinical outcomes in patients with HF through exaggerated negative inspiratory intrathoracic pressure, which increases left ventricular transmural pressure and afterload and decreases CO, and through sympathetic nerve overactivity, which increases cardiac load by elevation of blood pressure, HR, and susceptibility to arrhythmia [9,18,42]. In patients with HF, insomnia symptoms associated with SDB may also contribute to the deterioration of cardiac function and poor clinical outcomes. Therefore, improvement of insomnia in association with the alleviation of SDB by specific treatment of SDB, such as continuous positive airway pressure, could protect HF patients against deterioration of cardiac function and worsening of clinical outcomes. In addition, specific treatment of insomnia by hypnotics may also contribute to the improvement of cardiac function and clinical outcomes. However, an issue arises when we consider using hypnotics, especially benzodiazepines, because they reduce tonus of the upper airway muscle, possibly cause upper airway collapse, and suppress central respiratory drive, thus precipitating SDB [43]. Furthermore, the effects of hypnotics on hemodynamics during sleep are rarely investigated. Therefore, the efficacy and safety of hypnotics in HF patients with SDB are of great interest. Suvorexant, an orexin receptor antagonist, has been developed as a new class of hypnotics and has been currently in clinical use for insomnia. Orexin is a neuropeptide and contributes to the stability of wakefulness. Thus, suvorexant induces sleep by inhibiting stimulation of the nerve nucleus, which is controlled by orexin neuron and whose action is to maintain wakefulness. Suvorexant antagonizes orexin, whose action is limited in the sleep/wake transition, and does not suppress the whole activity broadly as do GABA receptor agonists, such as benzodiazepines. Thus, suvorexant initiates sleep from wakefulness physiologically and possibly maintains sleep and its quality [44]. Suvorexant has less adverse neuropsychiatry effects, such as delirium incidence, than GABA receptor agonists [28]. In addition, a usual dose of suvorexant does not affect SDB severity in patients without HF [27]. Thus, suvorexant will be one of the major hypnotics, which do not affect the upper airway and central respiratory drive, and can be used safely even in patients with HF.

To the best of our knowledge, no studies have investigated whether hypnotics affect SDB severity or hemodynamics, particularly in HF patients. Suvorexant has already been demonstrated not to worsen SDB in patients without HF and has been shown to improve sleep [27]. Thus, in the present study, we will first investigate the effect of a usual dose of suvorexant on SDB and hemodynamics in patients with HF.

Our study might indicate not only the safety of suvorexant but also efficacy on SDB severity and/or hemodynamics. As mentioned above, patients with HF generally have worse sleep quality and less sleep quantity than the general population [16,18]. Thus, qualitative and quantitative improvement of sleep may contribute to the amelioration of cardiac function and prognosis of HF patients. If so, insomnia in patients with HF could be used as a therapeutic target for the treatment of HF.

The present study has several limitations. First, the duration of administration of suvorexant is a minimum duration to achieve stability in its blood concentration; therefore, the effect of long-term administration cannot be identified. Second, suvorexant is the only study drug used in this study, and the comparison of suvorexant with other hypnotics cannot be performed. Third, the present study is only a pilot study to generate the further hypothesis that suvorexant improves cardiac function and prognosis of HF patients through improvement of sleep.

Conclusion

The present study can show whether administration of suvorexant improves sleep safely in patients with HF and insomnia symptoms.

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Conflict of interest

Dr Kasai is affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi. Dr Daida received manuscript fees, research funds, and scholarship

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