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Effect of nalfurafine hydrochloride in patients with chronic liver disease with refractory pruritus on sleep disorders: a study protocol for single-arm, prospective, interventional study

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ABSTRACT

Introduction Chronic liver disease (CLD)-related pruritus manifests as cholestasis symptoms, which can cause severe itches in the whole body and significantly decrease quality of daily activities and sleep. The actigram, which documents movement by means of an accelerometer, has been demonstrated to be useful for assessing sleep quality. Nalfurafine hydrochloride, which is a selective κ-opioid receptor agonist, exerts its antipruritic efficacies through a novel mechanism. We aimed to prospectively examine the effect of nalfurafine hydrochloride on sleep quality for patients with CLD with pruritus utilising actigram.

Methods and analysis This study will be a single-centre, prospective, interventional, single-arm study. Our study participants are subjects whose pruritus was confirmed to be uncontrollable by antihistamines or antiallergics within 6 months before informed consent (IC). Evaluation time points using actigram will be (1) before administration of testing drug; (2) after 1 week; (3) after 4 weeks (primary endpoint); and (4) every 4 weeks thereafter. The follow-up period will be 6 months. We will prospectively assess and compare changes in sleep quality in patients with CLD with pruritus undergoing nalfurafine hydrochloride therapy using actigram. Quantitative variables will be compared by paired t-test.

Ethics and dissemination This study has received approval from the Institutional Review Board at Hyogo College of Medicine (approval no 2325). The study protocol, IC form and other documents were reviewed and approved. Final data will be publicly disseminated regardless of the results. A report releasing study results will be submitted in an appropriate journal.

Trial registration number UMIN000028161; Pre-results.

INTRODUCTION

Chronic liver disease (CLD)-related pruritus manifests as cholestasis symptoms, which can cause severe itches in the whole body and significantly decrease quality of life (QOL), including daily activities and sleep.[1–7] The accumulation of bile acids in the sera and tissues as a consequence of chronic liver injury in patients with CLD is considered to be one of the major causes of pruritus.[7] Pruritus is associated with difficulty in falling asleep, middle awakening and loss of sufficient sleepiness. Although pruritus may not be directly linked to clinical outcomes in patients with CLD, a recent systematic review denoted that pruritus has an impact on health-related QOL in patients with cholestatic liver disease.[8] The international guidelines include criteria for the management of pruritus in patients with CLD.[9 10] Recommendations to all patients with CLD should include the application of cooling and moisturising ointments and shortening of the nails with the purpose of avoiding secondary skin damage.[9 10] For patients with CLD with pruritus, antihistamines, antiallergics, and hypnotics are in general prescribed; however, they may not be always effective in some patients.[11]

Pruritus involves the central nervous system.[6 12–16] Nalfurafine hydrochloride, which is a selective κ-opioid receptor agonist, exerts its antipruritic efficacies through a novel meenomoto@hyo-med.ac.jpchanism.[15–17] In non-clinical previous investigations, nalfurafine hydrochloride was demonstrated to have antipruritic effects in a model of itch that is refractory to antihistamines.[17] The usefulness

and safety of nalfurafine hydrochloride were previously reported in Japanese clinical trials in patients on haemodialysis with pruritus that was refractory to conventional treatments.[18 19] Additionally, a recent Japanese clinical trial reported that nalfurafine hydrochloride (2.5 µg daily or 5 µg daily) was effective for patients with refractory pruritus in CLDs.[20] The long-term safety and efficacy of this agent were also confirmed in a Japanese trial.[21]

On the other hand, the actigram is a device that documents movement by means of an accelerometer, and it is the size of a wristwatch and can be worn without interfering with activities of daily life.[22–26] The actigram is a non-invasive and cost-effective assessment tool used to estimate sleep quantity and sleep quality as compared with polysomnography, demonstrating accuracies of up to 90% in several reports for total sleep time and sleep efficiency.[27 28] However, there have been no data with regard to the effect of nalfurafine hydrochloride on sleep quality for patients with CLD with pruritus undergoing nalfurafine hydrochloride therapy. The aim of the current study is to prospectively examine the effect of nalfurafine hydrochloride on sleep quality for patients with CLD with pruritus utilising actigram.

METHODS AND ANALYSIS

Patient eligibility criteria

Inclusion criteria

1. gender is not limited
2. patients aged 20 years or more
3. patients with CLDs (hepatic inflammation persisting for at least 6 months) who were not expected to show rapid changes in the general condition; there is a possibility that patients with decreased liver function show rapid changes in the general condition, thus they will not be included in our analyses
4. patients whose pruritus was confirmed to be uncontrollable by antihistamines or antiallergics within 6 months before informed consent.

Exclusion criteria

1. patients with history for hypersensitivity for the ingredients of testing drugs
2. female patients who are pregnant or suspected of being pregnant, or those desiring pregnancy during study period
3. lactating female patients
4. patients who were judged to be inappropriate as study subjects.

Study protocol

study design: single-arm and open-label trial.

Our study participants are subjects whose pruritus was confirmed to be uncontrollable by antihistamines or antiallergics within 6 months before informed consent. The current study will be a single-centre, prospective, interventional, single-arm study. We planned the current single-arm study due to the ethical consideration for patients with CLD with pruritus.

Dosage and method of administration

Nalfurafine hydrochloride (2.5 µg/cap) one cap per day will be prescribed orally after dinner or before going to bed.[20 21]

Actigram

Actigram is a motion-sensing accelerometer in the size of a wristwatch. It is a device for gathering objective sleep/wake data in the natural sleep environment over an extended time interval.[22 24 25 29] The study participants in our study will be advised to wear a wrist actigram on their non-dominant wrist over a period of 3 days according to the instruction of the manufacturer.[22 24 25 29] Evaluation time points using actigram will be (1) prior to administration of testing drug; (2) after 1 week; (3) after 4 weeks; and (4) every 4 weeks thereafter (figure 1). The follow-up period will be 6 months. Data for laboratory parameters, questionnaire and clinical symptoms will be also obtained at the same time points (figure 1). As a rule, study participants will be advised to visit our hospital in an outpatient basis.

Results in the actigram will be downloaded into a dedicated computer and the following five sleep-related variables will be assessed: (1) sleep onset latency; (2) wake after sleep onset (defined as the minutes awake during the sleep period after the beginning of sleep (the first two continuous minutes scored as sleep)); (3) activity index (average amount of activity

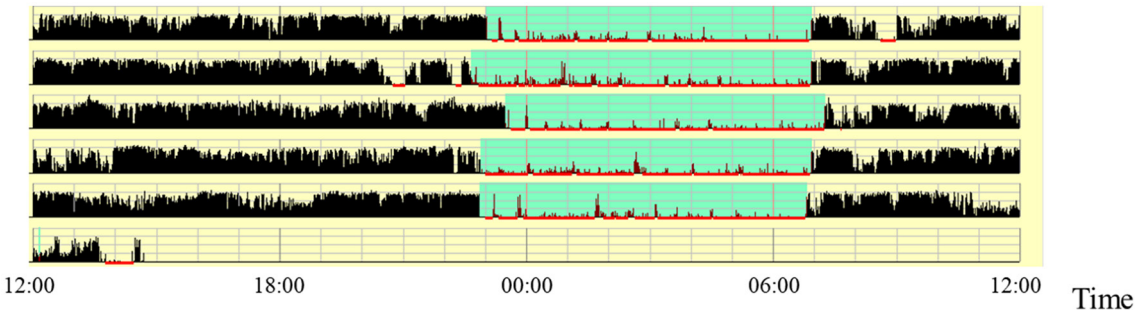

Figure 1 Study design. BDI-II, Beck Depression Inventory, Second Edition; PSQI, Pittsburgh Sleep Quality Index.

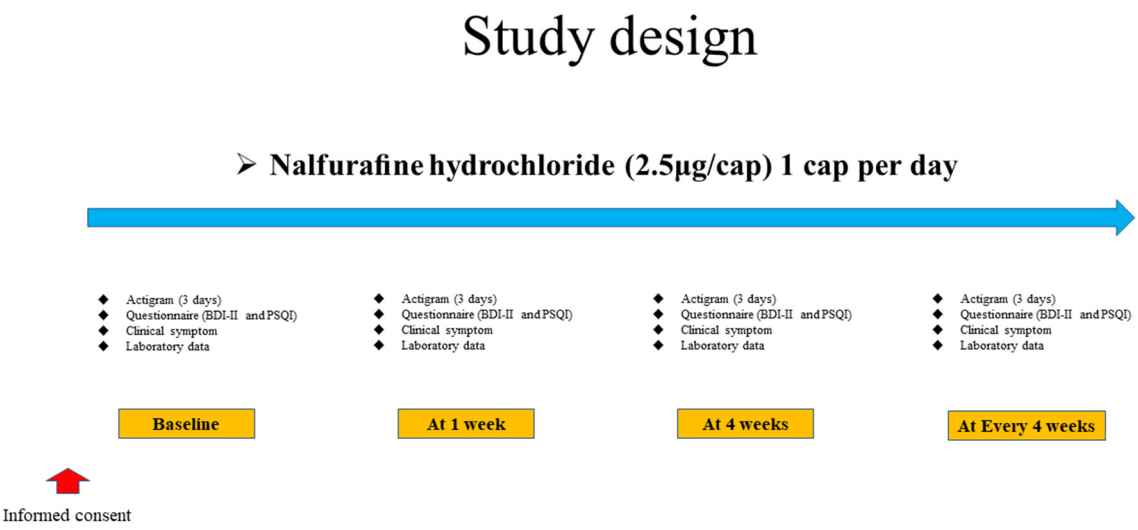

Figure 2 Typical example of actigram. Black thin line suggests activity level, red bold line suggests sleeping state and light green rectangle suggests time in bed.

in sleep); (4) wake episodes (total number of wake counts between trying to start to sleep and wake-up times); and (5) sleep episodes in daytime (total number of sleep counts in daytime). The elevated score in each variable suggests the worse quality of sleep. We primarily assessed sleep quality using activity index. Typical example in actigram is shown in figure 2.

Primary endpoints

Sleep-related variable using actigram (activity index) at 4 weeks.

Secondary endpoints

1. Questionnaire survey
   Changes in sleep rhythm and depressed state in daily life will be assessed using questionnaire surveys (the Beck Depression Inventory, Second Edition[30] and Pittsburgh Sleep Quality Index[31]).
2. Clinical symptoms
   Degree of pruritus (subjective assessment: no symptom, minor, mild, moderate and severe).
3. Blood biochemical examination
   Complete blood cell count, leucocyte fraction, prothrombin time, aspartate aminotransferase (AST), alanine aminotransferase, total bilirubin, total bile acid, alkaline phosphatase, gamma glutamyl transpeptidase, lactate dehydrogenase, total protein, serum albumin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose, HbA1c, homeostasis model assessment of insulin resistance, blood urea nitrogen, serum creatinine, chorine esterase, serum electrolytes, alpha-fetoprotein and liver fibrosis markers (AST to platelet ratio index, FIB-4 index, Wisteria floribunda agglutinin-positive Mac-2-binding protein[32 33]).[18–21]

Stopping criteria

For the following reasons, when it becomes difficult to continue to administer the testing drug to the subject, the responsible physician or the shared medical doctor will decide to discontinue administration of the testing drug.

1. when it is found that it does not meet the selection criteria or conflicts with exclusion criteria
2. in cases where non-compliance is remarkable concerning study protocols such as medication, survey or visit to the hospital
3. if an adverse event occurs and when the responsible or shared medical doctor will decide that administration of the testing drug should be discontinued
4. when there will be a request to withdraw from this study from the subject
5. when the subject will transfer to a hospital, or when the patient will cease to visit due to a move.

Case registration period

From approval date to March 2020 (there may be a change depending on registration status).

Data collection

A research assistant will collect data elements from patient medical records, including the following:

Baseline data

1. gender, date of birth and age
2. height and body weight
3. vital signs
4. degree of drinking and smoking
5. cause for underlying liver diseases
6. previous treatments
7. comorbid conditions and concomitant medication
8. baseline laboratory tests
9. presence or absence of liver cirrhosis

10. presence or absence of ascites on radiological findings.

Statistical methods

Descriptive statistics

Data were transferred to JMP V.13 software (SAS Institute, Cary, North Carolina, USA) and all data were checked to ensure their consistency. Data in each time point (baseline, 1 week, 4 weeks and every 4 weeks thereafter) will be compared. As for primary endpoint, intention-to-treat analysis will be performed. Quantitative variables will be compared by paired t-test. Categorical variables will be compared using Pearson χ^2 test or Fisher's exact tests as appropriate.

Sample size

To the best of our knowledge, no data exist with regard to the objective assessment of nalfurafine hydrochloride in sleep activities for patients with CLD. This study will not stipulate a sample size a priori. The sample size was not therefore determined by power calculations. However, the current study will continue to recruit until a maximum cut-off of 50 participants considering case registration period in the current study.

DISCUSSION

As mentioned earlier, CLD can cause severe itches in the whole body and significantly deteriorate QOL including daily activities and sleep.[1–5] Pruritus can lead to difficulties in falling asleep, middle awakening and loss of sufficient sleepiness. Thus, objective assessment of the effect of nalfurafine hydrochloride on sleep activities may be clinically essential. Actigram is one of the well-established modalities in which the degree of sleep disorders can be evaluated objectively.[22–26 29] We thus believe that the setting of our primary outcome measure is valid. On the other hand, our secondary outcome measures are also clinically important, although these are only exploratory analyses.

No data exist with regard to the usefulness of nalfurafine hydrochloride in sleep activities for patients with CLD. To the best of our knowledge, this is the first prospective interventional study assessing objectively the effect of nalfurafine hydrochloride on sleep activities of patients with CLD. One study drawback is that the current study will be based on a Japanese population, and additional investigations on different ethnic populations are required to further verify the efficacy of nalfurafine hydrochloride and extrapolate to races other than Japanese. Another drawback is that this study will be a single-arm trial. We planned the current single-arm study due to the ethical consideration for patients with CLD with pruritus. However, if the effectiveness of nalfurafine hydrochloride in sleep activities is confirmed in this trial, useful information will be provided for clinicians.

Ethics and dissemination

Research ethics approval

This study has received approval from the Institutional Review Board at Hyogo College of Medicine (approval no 2325). The study protocol, informed consent form and other submitted documents were reviewed and approved. The trial registration number is UMIN000028161 (https://upload.umin.ac.jp/), preresults. No patient is registered at the submission of our manuscript.

Confidentiality

On recruitment, the research assistant will provide a unique scrambled identification number to each subject. Only the identification number will be used to identify subjects. Data sheets and any printout of electronic files will be saved in a locked filing cabinet in a secure office in the Department of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan, with limited access.

Dissemination policy

Final data will be publicly disseminated regardless of the study results. A report releasing study results will be submitted for publication in an appropriate journal after completion of data collection.

Our study protocol

Our current study protocol will be based on SPIRIT 2013 statement (http://www.equator-network.org/).

Contributors KY, HN and HE will analyse data and write the paper. SN is supervising this study. The remaining authors will recruit candidates and collect relevant data.

Competing interests None declared.

Ethics approval Institutional Review Board at Hyogo College of Medicine.

Provenance and peer review Not commissioned; externally peer reviewed.

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