Journal of Cardiology 66 (2015) 69–72

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Design of a prospective observational survey on landiolol in atrial fibrillation/atrial flutter patients with chronic heart failure – AF-CHF landiolol survey

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ARTICLE INFO

Article history:
Received 25 July 2014
Received in revised form 29 August 2014
Accepted 17 September 2014
Available online 6 November 2014

Keywords:
Atrial fibrillation
β-Blocker
Landiolol
Heart failure
Long-term outcome

ABSTRACT

Background: In Japan, intravenous digoxin was previously recommended as a standard drug for acute control of the heart rate in atrial fibrillation (AF)/atrial flutter (AFL) patients with chronic heart failure (CHF). Treatment alternatives for such cases were limited and new drugs for this purpose are needed. In November 2013, landiolol hydrochloride (Onoact® 50 for Injection, Ono Pharamaceutical, Osaka, Japan) was approved with the indication for "tachyarrhythmia (AF/AFL) in patients with cardiac dysfunction." However, clinical experience with this condition is still insufficient. Therefore, it is important to conduct a surveillance of landiolol under actual clinical settings. In addition, collecting data on the mid- and long-term outcomes in patients treated with landiolol which have not been collected in clinical trials are indispensable.

Methods: This prospective survey will involve patients treated with landiolol for the treatment of tachyarrhythmia (AF/AFL) in cardiac dysfunction at Japanese medical facilities from June 2014 to May 2017. The planned number of patients for analysis is approximately 500. The evaluations will be made not only to identify the adverse events and clinical effectiveness of the drug, but also to characterize the mid- and long-term outcomes of patients receiving and switching to oral-β-blockers after the discontinuation of landiolol.

Results: This study was started in June 2014 (registration period 2 years, survey period 3 years) and will end in May 2017.

Conclusions: This survey will clarify both the characteristics and mid- and long-term outcome of using landiolol to treat AF/AFL patients with cardiac dysfunction in clinical practice. Moreover, this survey will simultaneously provide important data that will reveal the possible gap between clinical trials and clinical practice in these patients.

Introduction

Atrial fibrillation (AF) is an arrhythmia that often develops in the presence of heart failure (HF) [1,2]. The presence of AF reduces cardiac output by about 15–25% and possibly results in a deterioration of the hemodynamics in HF patients [3]. Furthermore, the excessive ventricular rate, loss of atrial contraction, and irregular ventricular filling time that is associated with AF may all cause negative clinical outcomes in patients with HF [4–10].

Drug treatment of AF and atrial flutter (AFL) entails a rhythm control and a rate control. Rhythm control is typically achieved with the administration of Na channel blockers and K channel blockers, either alone or in combination based on the patient characteristics [2,11]. Rate control has been primarily regulated with the administration of β-blockers, Ca channel blockers, and digoxin, again either alone or in combination. Before selecting a drug for rate control it is necessary to consider the presence/absence of other complications, such as Wolff–Parkinson–White syndrome, left ventricular dysfunction, and obstructive pulmonary disease; Ca channel blockers and β-blockers have negative inotropic actions while digoxin does not. Therefore, digoxin has conventionally been recommended the most effective drug for rate control in AF/AFL patients with cardiac dysfunction. In addition, it is recommended to follow-up digoxin treatment with low doses of

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http://dx.doi.org/10.1016/j.jjcc.2014.09.008
0914-5087/

β-blockers to act as the second-line drug. However, there is currently no consensus for the proper methods for using oral β-blockers in AF/AFL patients with HF and treatment with these drugs has only been done empirically.

Landiolol is a short-acting β-blocker that is rapidly metabolized to inactive forms in the blood and liver, resulting in a half-life of approximately 4 min in the human blood. In addition, it selectively binds to β1 receptors, with a β1 receptor selectivity ratio (β1/β2) as high as 251. Furthermore, landiolol rapidly reduces heart late (HR) without lowering blood pressure [12]. Based on these properties, landiolol has been reported to be useful for treating several acute disorders. A clinical study (J-Land Study) was carried out in order to evaluate the efficacy and safety of landiolol in comparison to digoxin in AF/AFL patients with a New York Heart Association class III–IV, a left ventricular ejection fraction (LVEF) of 25–50%, and a HR 120 bpm or higher [13]. On the basis of the results, in 2013, landiolol was approved for "tachyarrhythmia (AF/AFL) in patients with cardiac dysfunction".

Therefore, in the current "AF Treatment Guidelines" (revised edition, 2013) landiolol is recommended as the rate control treatment drug for use in AF patients with HF (Class I, Level B) [14]. However, a sufficient evaluation of the safety and efficacy of landiolol during clinical use has not been performed. Moreover, no information about mid- and long-term outcome is available and information about switching to oral β-blockers from landiolol is also not sufficient.

Under such circumstances, it is mandatory to continue collecting data on landiolol treatment in AF/AFL patients with cardiac dysfunction especially in view of the anticipated increase of these patients in our aging society. To achieve these goals, we propose the design and details of the present study in this report.

Methods

Patients

The target patients for this study will be AF/AFL patients with cardiac dysfunction. Because this study is performed under clinical settings, no special exclusion criteria will be applied for the selection of patients. The number of patients feasible to enroll and that enables a comparison analysis with the results from the domestic clinical trials is established as 500 patients and it was obtained by using an interval estimation of population ratio. Further, the planned number of patients for this study was established as 800 patients by taking into consideration possible occurrences of patient dropout and exclusion from analysis. Patients' informed consent will not be obtained because this study is a survey conducted under the Re-examination system in compliance with Good Post-marketing Study Practice ordinance under the Japanese Pharmaceutical Affairs Act.

Research facilities

In view of the purpose of this study, this study will be performed in hospitals with sufficient experience in HF treatment; the target numbers of patients for this study is 800; namely, 5–10 patients per medical institution (hospital department) in a total of 80–160 medical institutions.

Design

This study will be carried out continuously with the use of an electronic data capture (EDC) system; the ADDIN System (ASKLEP Inc., Tokyo, Japan) will be employed as an EDC system, with the electronic signature serving as the physician's signature. Baseline data will be collected from the admission episodes between June 2014 and May 2016 (plan) while outcome data will be collected until 180 days after the start of treatment with landiolol.

Objectives

The objectives of the present study are to identify:

1) Patient characteristics that required landiolol to control the conditions with rapid AF/AFL with cardiac dysfunction.
2) Status (frequency, type, severity, etc.) of adverse drug reactions (adverse events) associated with the negative inotropic effects of landiolol.
3) Status of concomitant medication and interactions with drugs acting on the circulation, among others.
4) Landiolol dosage and its effects on heart rate and blood pressure (BP) during the treatment.
5) Dose, presence/absence of oral β-blocker after discontinuation of landiolol, and dose of oral β-blockers.
6) Death and readmission due to HF during the 180-day period after the start of treatment with landiolol.

Data collection/processing (attachments)

Data will be entered with the web-based EDC system. For each patient, the following baseline data will be collected: demographic characteristics, complications, HR, BP, cardiac function, and electrocardiographic (ECG) findings. The condition of all patients will be investigated from the start of treatment with landiolol to 7 days after discontinuation of its use and will cover the following information: status of treatment with landiolol, status of switching to oral β-blockers, HR, BP, cardiac function, ECG findings, and any status related to adverse events. In addition, information on the survival of individual patients will be collected for investigation of outcome until 180 days after the start of treatment with landiolol.

Confidentiality of patients

The confidentiality of individual patients will be protected in this study because it is not designed to collect information about direct identifiers (name, address, telephone number, etc.). Access to the EDC system from each hospital is carefully managed by the system administrator of the system vendor. The study is performed in compliance with Good Post-marketing Study Practice, an ordinance issued by the Ministry of Health Labor and Welfare establishing the standards for implementation of post-marketing surveillance of all new drugs approved in Japan.

Statistical analysis

Frequency distribution, summary statistics, etc. will be calculated concerning background variables, safety endpoints, and effectiveness endpoints. For the subgroup analysis of adverse drug reactions, the incidence and 95% confidence interval (Clopper–Pearson method) will be calculated for each category. Regarding death and readmission due to HF, independent determinants will be analyzed in an explorative manner by multivariate analysis. Furthermore, we will utilize the SAS program (latest version; Carey, NC, USA) for all statistical analysis related to this study.

Results planning

This study was started in June 2014 (registration period 2 years, survey period 3 years) and will end in May 2017.