Thermostable intravenous epoprostenol for the treatment of pulmonary arterial hypertension – a transition safety study

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What is already known about this subject

Intravenous epoprostenol is an important treatment option in the management of severe pulmonary hypertension and is thus far the only disease-targeted therapy to confer an overall survival benefit to patients. For many years the only available formulation of the drug was thermolabile and had to be kept refrigerated continuously. This had an adverse impact of patient quality of life and uptake for epoprostenol therapy.

What this study adds

This study provides reassurance that the new and more thermostable formulation of epoprostenol is a safe alternative to the previously available preparation, as evidenced by a lack of deterioration in the clinical parameters examined. It has also highlighted that thermostable epoprostenol is more acceptable to our patient group for reasons of convenience. In clinical practice, this provides more confidence to the clinical team in recommending epoprostenol therapy to patients with severe pulmonary vascular disease.

Abstract

Intravenous epoprostenol remains an important treatment for pulmonary arterial hypertension (PAH) but can only be given intravenously. Until recently the only formulation available to our patients (Flolan 10.5) was thermolabile and required daily preparation. In 2016, we transitioned all patients in our service to a new, thermostable formulation (Flolan 12).

All patients in our unit using epoprostenol as of November 2016 were recruited to this prospective study which examined for safety issues and effects on QoL, 6MWD and serum NT-proBNP. We also collected qualitative data regarding activities of daily living.

The transition process did not result in any clinical deterioration. There were no safety issues identified and all but one of the participants preferred the new formulation.

We therefore conclude that transitioning patients from intravenous Flolan 10.5 to Flolan 12 is safe, does not lead to any clinical deterioration and is acceptable to patients for reasons of convenience.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive and incurable condition defined by elevated blood pressure in the pulmonary arterial vasculature. This leads to adaptive and maladaptive processes in the right ventricle, eventually leading to right ventricular failure and death (1). It is recognised that patients with PAH exhibit a deficiency in prostacyclin, an endogenous vasodilator, and the vasoconstriction resulting from this imbalance is one of the mechanisms which drives progressive PAH (2). The prostacyclin pathway is therefore an important therapeutic target in PAH (3).

Epoprostenol is a synthetic prostacyclin analogue which has been used in the treatment of PAH for a number of years (4). It is the only disease targeted therapy to have demonstrated an overall survival benefit for PAH patients (5). Epoprostenol can only be administered intravenously, and must be given via continuous infusion due its short half-life (approximately 3-6 minutes) (6). The drug is generally administered through a tunnelled central venous catheter using an infusion pump. It is the responsibility of the patient to administer the drug and deal with any immediate technical issues, for example interruption of flow or pump malfunctions.

The previously available formulation of epoprostenol (Flolan 10.5) was thermolabile, requiring daily preparation and storage on ice to delay degradation (7). A new thermostable formulation (Flolan 12) has now become available which negates the requirement for continuous refrigeration. Patients are therefore able to make up several batches of medication in advance of administration.

As of November 2016, our national pulmonary hypertension centre had 22 patients receiving continuous epoprostenol for a variety of types of pulmonary hypertension.

Objectives

The objective of our study was to transition patients onto Flolan 12 and examine for any safety issues associated with this transition, as well as looking at impact on quality of life (QoL), 6-minute walk distance (6MWD) and N-terminal pro B-type natriuretic peptide (NT-proBNP).

Methods

Patient selection

All patients in Scotland receiving a stable dose of intravenous epoprostenol prescribed by the Scottish Pulmonary Vascular Unit (SPVU) for at least 3 months as of November 2016 were included in the study (n=22). The only exclusion criteria were a) ongoing dose titration in the 3 months prior to the study and b) the use of epoprostenol for an unapproved indication.

Study design

This was a single-arm, open label study with a primary endpoint of patient safety. Secondary endpoints were effects on QoL, 6MWD, serum NT-proBNP and patient perceptions of convenience. As this was effectively a service development due to the withdrawal of the older epoprostenol preparation, formal ethical approval was deemed unnecessary (following discussion with the local Ethics officer).

Study procedures

Over the next 12 months the participants were transitioned onto Flolan 12 during a nurse-led outpatient clinic visit at the Golden Jubilee National Hospital (GJNH). At the first study visit, QoL using the Emphasis-10 questionnaire was completed by each patient. A 6-minute walk test (6MWT) was performed to normal clinical standard and serum NT-proBNP was analysed. Patients were then counselled on the changes to their drug regimen and given training on the use of the new formulation before being discharged home.

QoL, 6MWD and NT-proBNP were all repeated at each participant's next routine clinical review (typically 3 months following transition). At both initial and follow-up reviews, participants also completed a brief questionnaire concerning the effects of epoprostenol treatment on their daily life and were asked to comment on which of the two preparations they preferred. The questionnaire asked participants to allocate a score of 1-5 to a variety of aspects of daily life, with a higher score indicating greater restriction imposed by epoprostenol treatment.

Statistical analysis

As this was an exploratory study, the chosen study population of 22 patients was based on feasibility rather than a formal calculation of sample size. Data were largely presented in a descriptive fashion. To test for statistical significance, we also performed a paired t-test for 6MWD and a Mann Whitney test for NT-proBNP.

Results

All 22 patients included in the study completed the follow-up period. The majority (12 patients) had a diagnosis of IPAH, with smaller numbers of PVOD, heritable PAH, CTD-PAH, inoperable CTEPH and portopulmonary hypertension. 68% of patients were using epoprostenol as part of triple combination therapy.

The primary endpoint of patient safety was achieved, with no safety issues identified during or following the transition. No deaths occurred during the study period. There were no adverse events which necessitated any change of formulation or dosage.

Post-transition measurements showed no significant changes in 6MWD or NT-proBNP (see *Figure 1a and 1b*). This was corroborated by the results of the paired t-test for 6MWD ($p = 0.9$) and Mann Whitney test for NT-proBNP ($p = 0.8$). Mean 6MWD measurements pre-and post-transition were 318.5m and 319.3m respectively. Median NT-proBNP was 246.8 pg/ml pre-transition and 205.0 pg/ml post-transition. We observed no significant difference in pre- and post-transition QoL, as evidenced by Emphasis-10 and transition questionnaire scores *(Figure 1c)*.

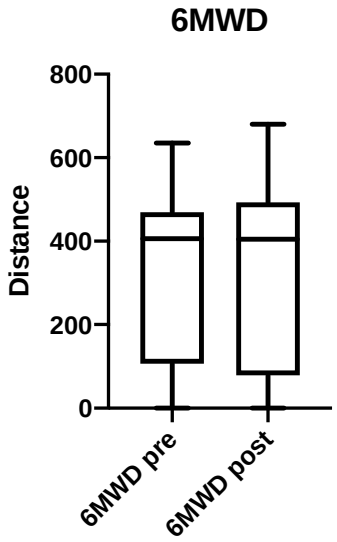

Figure 1a

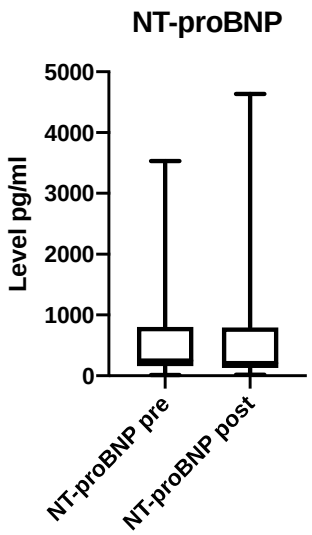

Figure 1b

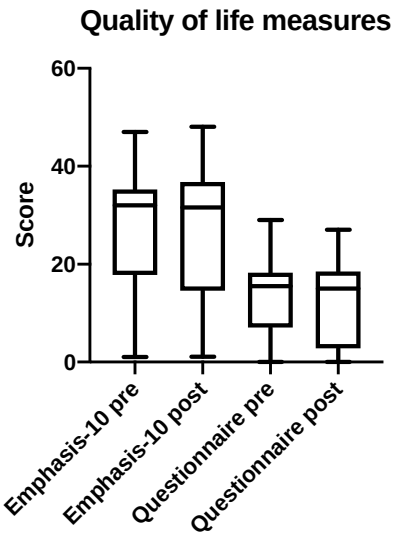

Figure 1c

Questionnaire responses showed that 21 of the surveyed participants preferred the thermostable formulation, with the one remaining participant expressing no preference. Following transition, a number of patients chose to reduce the frequency with which they reconstituted the drug, adding to its convenience.

Discussion

This single-arm prospective study was performed in order to compare the safety and efficacy of Flolan 12 compared to Flolan 10.5, as well as assessing patient preference. The switch was mandated to patients since the Flolan 10.5 was being withdrawn from manufacture. The study design was exploratory in nature and as such detailed statistical analysis was not performed. As far as possible, study measurements were obtained from routinely collected clinical data.

There were no safety issues identified during the transition process and analysis of 6MWD, NT-proBNP and QoL measures showed no detrimental clinical effects from the transition to the newer formulation. Flolan 12 has been well received by our patients due to its convenience. Overall, the use of thermostable intravenous epoprostenol has been demonstrated as a safe and more convenient alternative to the older formulation.

Conflicts of Interest Statement

Funding was received from GSK to cover research-related costs arising from this transition study.

Dr Colin Church has previously received honoraria and travel grants from GSK.

Data availability statement

Research data are not shared.

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