厚生労働科学研究費補助金（難治性疾患政策研究事業）
分担研究報告書

Successful epoprostenol withdrawal and termination with an aid of the exercise stress test in pulmonary arterial hypertension

研究分担者　伊波巧
杏林大学 医学部循環器内科 学内講師

研究要旨

エポプロステノール（EPO）の持続静注療法は，肺動脈性肺高血圧症（PAH）の運動能力と生存率を向上させるが，副作用を伴う。本研究では、運動負荷試験を用いて EPO を安全に減量・中止できた経験を紹介することを目的とした。

この後ろ向き研究では、EPO からの離脱に成功した PAH 患者を対象とした。EPO 投与前、休薬時、休薬後の血流動態データが得られた。平均肺動脈圧（mPAP）が 25mmHg 未満に低下した状態が 1 年以上続いた後、右心カテーテル下での運動負荷試験を実施した。運動性肺高血圧症が記録されなかった場合（mPAP-CO slope ＜ 3）に EPO は中止した。

EPO の投与を受けた 99 名の患者のうち、10 名が安全に中止することに成功した。mPAP は投与前の 61（54-71）mmHg から休薬前には 19（17-21）mmHg に減少し、EPO 中止の 1 年後には 19（14-23）mmHg と横ばいだった。中央値で 32 ヵ月の追跡調査の結果、すべての患者が生存した。正常な血行動態機能を回復した PAH 患者は、運動負荷試験を行うことで EPO から安全に離脱できる可能性がある。

A. 研究目的

安静時の血行動態の正常化を達成し、運動負荷試験を用いて EPO 投与の中止に成功した患者の経験を報告する。

B. 研究方法

本研究は後ろ向き研究で、EPO からの離脱に成功した PAH 患者を対象とした。EPO 投与前、休薬時、休薬後の血流動態データが得られた。平均肺動脈圧（mPAP）が 25mmHg 未満に低下した状態が 1 年以上続いた後、右心カテーテル下での運動負荷試験を実施した。運動性肺高血圧症が記録されなかった場合（mPAP-CO slope ＜ 3）に EPO は中止した。

C. 研究結果

mPAP は投与前の 61（54-71）mmHg から休薬前には 19（17-21）mmHg に減少し、EPO 中止の 1 年後には 19（14-23）mmHg と横ばいだった。中央値で 32 ヵ月の追跡調査の結果、すべての患者が生存した。

D. 考察

一般的に、安静時 PAP の上昇が検出されるのは、肺循環の 50%以上が閉塞されてからである（有効肺血流、≦50%）。したがって、安静時の血行動態が正常であっても、重大な血管閉塞の存在を否定することはできない。運動中の mPAP-CO slope が 3.0 以上の場合、安静時の mPAP が 25mmHg 未満であっても、肺血管障害や残存する肺リモデリングを示している可能性がある。運動負荷試験は、EPO の安全な離脱が可能かを裏付けてくれる可能性がある。

E. 結論

正常な血行動態機能を回復した PAH 患者は、運動負荷試験を行うことで EPO から安全に離脱できる可能性がある。

F. 研究発表

1. 論文

Takeuchi K, Goda A, Ito J, et al. Successful epoprostenol withdrawal and termination with an aid of the exercise stress test in pulmonary arterial hypertension. Int J Cardiol. 2022;346:80-85. doi:10.1016/j.ijcard.2021.11.041.

International Journal of Cardiology 346 (2022) 80–85

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Successful epoprostenol withdrawal and termination with an aid of the exercise stress test in pulmonary arterial hypertension

Kaori Takeuchi, Ayumi Goda *, Junnosuke Ito, Hanako Kikuchi, Takumi Inami, Takashi Kohno, Kyoko Soejima, Toru Satoh

Department of Cardiovascular Medicine, Kyorin University Hospital, Tokyo, Japan

ARTICLE INFO

Keywords:
Pulmonary hypertension
Epoprostenol
Withdrawal
Exercise

ABSTRACT

Continuous infusion of intravenous epoprostenol (EPO) improves exercise capacity and survival in pulmonary arterial hypertension (PAH); however, it is associated with side effects. This study aimed to describe our experience on safe EPO withdrawal with the aid of an exercise stress test.

This retrospective review included patients with PAH who were successfully withdrawn from EPO. Haemodynamic data were obtained before EPO administration, at withdrawal, and after discontinuation. After the mean pulmonary arterial pressure (mPAP) decreased to <25 mmHg for at least 1 year, an exercise test under right heart catheterisation was performed. If exercise pulmonary hypertension was not record (mPAP - cardiac output slope < 3), EPO was withdrawn.

Of the 99 patients who received EPO, ten were identified as having undergone withdrawal or termination. mPAP decreased from 61 (54–71) mmHg before treatment to 19 (17–21) mmHg before withdrawal and remained unchanged, at 19 (14–23) mmHg, 1 year after EPO discontinuation. After a median follow-up of 32 months, all the patients survived.

Patients with PAH who recovered their normal haemodynamic function were safely withdrawn from EPO with the aid of an exercise stress test.

1. Introduction

Epoprostenol (EPO) was the first therapy to be approved for the treatment of pulmonary arterial hypertension (PAH). In 20 years since the introduction of EPO, which was approved in 1999 in Japan, the survival of patients with PAH has greatly improved compared to the era before the development of this disease-specific treatment [1]. Several effective oral PAH-specific drugs are currently available. Furthermore, upfront triple combination therapy has dramatically improved the prognosis of PAH [2]. There have been some cases in which haemodynamics normalised for a certain period under EPO infusion.

There is a paucity of published data on how to safely transit patients on ambulatory EPO drip infusion to oral therapy in the event of complications and problems during parenteral administration of prostacyclins, including frequent bloodstream infections, inability to set an adequate dosage of EPO or intolerable side effects such as severe thyroid disorder and unpleasant vasodilatory symptoms. EPO withdrawal and transition to subcutaneous or oral prostacyclin alternatives in selected patients with PAH have also been reported. However, the criteria for withdrawal or decrease in the amount of EPO remain unclear [3,4].

In contrast, exercise pulmonary hypertension (pH) is considered to reflect early pulmonary vascular disorder and may be used to evaluate the degree of pulmonary vascular abnormality in patients with very mild PH [5]. In patients with PAH who recovered near-normal haemodynamics and were eligible for EPO withdrawal, a near-normal exercise response would signify an achievement of reverse remodelling of the pulmonary arteries and healed vascular dysfunction.

We report our experience with patients who achieved normalised haemodynamics at rest and succeeded in weaning the EPO dosage to termination using the exercise stress test.

2. Methods

A retrospective review was performed on consecutive patients with PAH treated at our hospital (2009–2019) who were successfully weaned off EPO. This study complied with the Declaration of Helsinki and was

* Corresponding author at: Department of Cardiovascular Medicine, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan.
E-mail address: ayumigoda@ks.kyorin-u.ac.jp (A. Goda).

https://doi.org/10.1016/j.ijcard.2021.11.041
Received 20 July 2021; Received in revised form 16 October 2021; Accepted 15 November 2021
Available online 17 November 2021