Pulmonary Pharmacology & Therapeutics 28 (2014) 1–8

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

Review

The impact of drug–drug interactions on pulmonary arterial hypertension therapy

Rocco Ciracì, Giampaolo Tirone, Francesco Scaglione*

Department of Medical Biotechnologies and Translational Medicine, Milan, Italy

ARTICLE INFO

Article history:
Received 4 November 2013
Received in revised form
8 January 2014
Accepted 12 January 2014

Keywords:
PAH
Combination therapy
DDIs

ABSTRACT

In clinical practice, pulmonary arterial hypertension (PAH) requires co-administration of multiple drugs to act on several pathogenic mechanisms; chronic pathologic conditions induce the onset of other concomitant diseases that need additional therapies. Combination treatment could exploit a synergism between administered drugs, increasing the effectiveness of the treatment and allowing dose reductions of the individual agents with a subsequent lower risk of toxicity. Conversely, concomitant administration of drugs may cause drug–drug interactions (DDIs), compromising treatment efficacy or increasing side effects, with a negative influence on disease progression. The choice of treatment is based on the fact that PAH is not caused by a single mechanism and that several syndromes, genetic abnormalities and environmental factors predispose to disease; therefore it is very likely that the use of treatments acting on a single pathway are not significantly effective. Moreover PAH is also frequently associated with other diseases that require concomitant clinical therapy. In this review we focused on the pharmacological treatment in PAH and related DDIs, evaluating alterations in drug transport, absorption, metabolism and excretion. This detailed analysis may be useful in clinical practice, as a better prediction of adverse events caused by DDIs in PAH improves the efficacy of combination therapy, resulting in reduced health care costs.

1. Introduction

PAH is a serious disease characterized by proliferation of endothelial and smooth muscle cells as well as the increased deposition of extracellular matrix, with a consequent reduction of luminal space in the pulmonary vasculature and an increase in pulmonary vascular resistance and arterial pressure [1].

In clinical practice PAH, as with many chronic disorders, requires co-administration of multiple drugs to act on several pathogenic mechanisms; chronic pathologic conditions induce the onset of other concomitant diseases that need additional therapies. Combination treatment could exploit a synergism between administered drugs, increasing the effectiveness of the treatment and allowing dose reductions of the individual agents with a subsequent lower risk of toxicity. Conversely, concomitant administration of drugs may lead to a higher risk of DDIs, compromising treatment efficacy or increasing side effects, with a negative influence on disease progression.

DDI is defined as “The pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effect of the two agents when given alone” [2].

Currently, treatment of PAH, that is either disease specific or non-specific, aims to improve survival, symptoms and quality of life. Conventional therapy acts on three established molecular pathways of PAH pathophysiology: prostacyclin and analogues, endothelin receptor antagonists (ERAs) and phosphodiesterase type 5 (PDE5) inhibitors. Patients are also treated with supportive therapies such as warfarin, diuretics, digoxin, calcium channel blockers and supplemental oxygen [3].

The choice of treatment is based on the fact that PAH is not caused by a single mechanism and that several syndromes, genetic abnormalities and environmental factors predispose to disease; therefore it is very likely that the use of treatments acting on a single pathway is not significantly effective. Many patients tend to have a suboptimal response to treatment, others require more

Abbreviations: PAH, pulmonary arterial hypertension; DDI, drug–drug interaction; ERAs, endothelin receptor antagonists; PDE5, phosphodiesterase type 5; OATP, organic anion transporting polypeptide; MDR1, multidrug resistance protein 1; AUC, area under curve; CYP450, cytochrome p450; cAMP, cyclic adenosine monophosphate; NO, nitric oxide; cGMP, cyclic guanosine monophosphate; ET, endothelin; UGTs, uridine 5′-diphosphate glucuronosyltransferases; CysA, cyclosporine A; Rif, rifampicin; ADME, absorption, distribution, metabolism, and elimination; PK, pharmacokinetics; PD, pharmacodynamics.

* Corresponding author. via Vanvitelli 32, Milan, Italy. Tel.: +39 02 50317073.
E-mail address: francesco.scaglione@unimi.it (F. Scaglione).

1094-5539/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pupt.2014.01.004

drugs to control the disease. Moreover PAH is also frequently associated with other diseases that require concomitant clinical therapy.

The aim of this review is to address DDIs observed in patients suffering from PAH, analyzing sites of drug action, transport, metabolism and elimination mechanisms, since DDIs result in the alteration of drug ADME. This detailed analysis is crucial to a better prediction of adverse events caused by DDIs in PAH, and reducing the number of interactions will increase the chance of successful combination therapy, increasing the effectiveness of treatment and reducing health care costs.

2. Drug–drug interactions in PAH

Each compound that interferes with drug metabolizing enzymes, as well as influx or efflux transporters, may induce alterations of the ADME of another co-administered drug, changing its efficacy and safety. This frequently occurs when treating patients with multiple concomitant drugs.

Alteration in both drug metabolizing enzyme levels and drug transporters is the most important mechanism leading to changes in pharmacokinetic parameters, including bioavailability, clearance, volume of distribution and half-life, causing alterations in drug plasma concentration (AUC). Inhibition of drug metabolizing enzymes and/or drug uptake into the liver following an interaction may induce an elevation in plasma concentration due to a decrease in hepatic and biliary clearance that can lead to serious adverse effects and toxicity if the dose is not reduced. Conversely, induction of metabolizing enzymes and/or efflux transporters may increase the drug's elimination and attenuate its pharmacological effect as a result of decreased drug exposure. In these cases an increase in dose may be needed to achieve the desired pharmacological effect. In contrast to inhibition, which represents nearly immediate response, induction is a slowly regulated process that follows chronic exposure to a drug. Indeed it is considered an adaptive response of the organism aimed to protect against xenobiotics by increasing the detoxification enzymes activity (Fig. 1).

As already mentioned previously, combination therapy is commonly used in clinical practice for patients suffering from PAH. Thus, it is likely that one drug may alter the PK/PD of another by modulating CYP isoenzymes activity. The most commonly detected interactions involve cytochrome p450 oxidases (CYP450), in particular CYP3A or CYP2C families [4,5], furthermore, drug's PK can be affected by the rate of absorption, distribution into bodily parts and clearance, as well as by biotransformation. Therefore, the action that some drugs have on transport mechanisms in the liver and intestine, for example on OATP transporters [6], is also clinically relevant.

The section below shows the main interactions observed in patients treated with prostacyclin analogues, phosphodiesterases-5 inhibitors and endothelin receptor antagonists.

Table 1
PK/PD interaction of prostacyclins and analogues: concomitant administration with drugs acting on platelet function can increase a risk of bleeding, through a synergic effect.

Drug	Interaction	Effect	Clinical relevance
Prostacyclin and analogues	Synergism with anticoagulants, platelet inhibitors, thrombin inhibitors	Platelet aggregation inhibition	Risk of bleeding Recommended monitoring of platelet function

2.1. Prostacyclin and analogues

Prostacyclin is able to increase levels of cyclic adenosine monophosphate (cAMP), acting as a potent pulmonary and systemic vasodilator. Prostacyclin also has antiproliferative effects and inhibits platelet aggregation.

In PAH, prostacyclin synthase activity is reduced with a consequent lowering of prostacyclin levels in pulmonary vessels; therefore prostanoid replacement therapy has been studied in clinical trials in the last decades with some good results, particularly with prostacyclin/epoprostenol or analogues such as treprostinil and iloprost [7,8].

Since prostacyclin is characterized by a very short half-life, the analogues are delivered by continuous intravenous (epoprostenol) or subcutaneous (treprostinil) infusion, or administered by frequent inhalations (iloprost) [9].

Prostacyclins don't have specific DDIs as they are metabolized via β-oxygenation in mitochondria and don't follow the cytoplasmic cytochrome P450 pathway. However, their action may potentiate the risk of bleeding in patients treated with other drugs acting on platelet function such as anticoagulants, platelet inhibitors, thrombin inhibitors or agents that potentially cause thrombocytopenia. Precise monitoring of platelet function is sufficient to manage prostacyclin combination therapy [10].

No other DDIs are reported (Table 1).

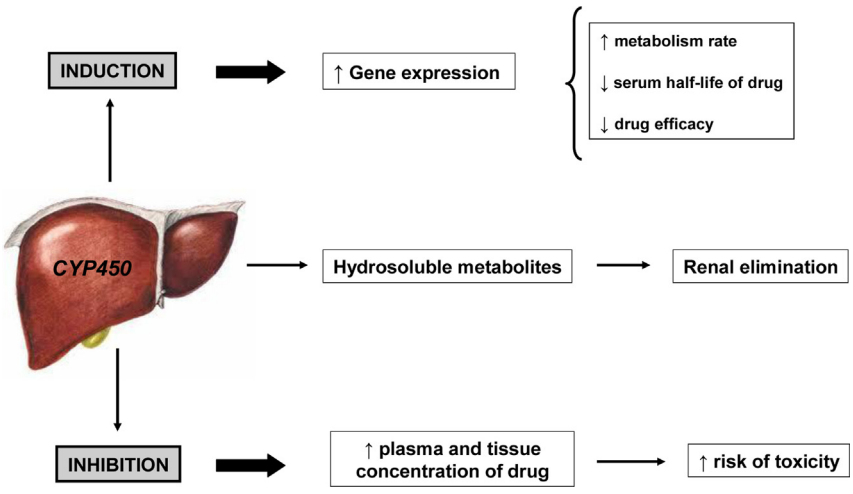

Fig. 1. Consequences of induction and inhibition mechanisms on pharmacological properties of a drug.