Drug-induced pulmonary arterial hypertension: a recent outbreak

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ABSTRACT Pulmonary arterial hypertension (PAH) is a rare disorder characterised by progressive obliteration of the pulmonary microvasculature resulting in elevated pulmonary vascular resistance and premature death. According to the current classification PAH can be associated with exposure to certain drugs or toxins, particularly to appetite suppressant intake drugs, such as aminorex, fenfluramine derivatives and benfluorex. These drugs have been confirmed to be risk factors for PAH and were withdrawn from the market. The supposed mechanism is an increase in serotonin levels, which was demonstrated to act as a growth factor for the pulmonary artery smooth muscle cells. Amphetamines, phentermine and mazindol were less frequently used, but are considered possible risk factors, for PAH. Dasatinib, dual Src/Abl kinase inhibitor, used in the treatment of chronic myelogenous leukaemia was associated with cases of severe PAH, potentially in part reversible after dasatinib withdrawal. Recently, several studies have raised the issue of potential endothelial dysfunction that could be induced by interferon, and a few cases of PAH have been reported with interferon therapy. PAH remains a rare complication of these drugs, suggesting possible individual susceptibility, and further studies are needed to identify patients at risk of drug-induced PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a rare disease defined by elevated mean pulmonary arterial pressure (PAP) $\geqslant$25 mmHg, which leads to an increase in pulmonary vascular resistance, right cardiac failure and then death [1]. In the current classification of pulmonary hypertension (PH) (table 1), PAH is defined as "group 1" and can be idiopathic, heritable or associated with different conditions including connective tissue disease, congenital heart disease, HIV infection, portal hypertension and also exposure to toxins/drugs [2]. All these subgroups of PAH share common alterations in the signalling pathways and broadly similar histological findings, *i.e.* intense remodelling of non-muscularised pulmonary arteries [2]. The first "outbreak" of PAH occurred in 1965 in Switzerland, Germany and Austria and has been associated with an anorectic intake, aminorex [3, 4]. After that, improvement in medical awareness and the diagnosis of the disease allowed us to identify additional drugs associated with an increased risk for the development of PAH. In the European Respiratory Society/European Society of Cardiology, guidelines for diagnosis and treatment of PH drugs and toxins are classified based upon their risk of inducing PAH into four categories

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TABLE 1 Updated clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension
- 1.1 Idiopathic pulmonary arterial hypertension
- 1.2 Heritable
  - 1.2.1. *BMPR2*
  - 1.2.2. *ALK1*, *endoglin* (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drug- and toxin-induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart diseases
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2. Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders splenectomy
- 5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BMPR2: bone morphogenetic protein receptor, type II; *ALK1*: activin receptor-like kinase 1 gene. Reproduced from [2] with permission from the publisher.

(table 2): 1) definite: aminorex, fenfluramine, dexfenfluramine or benfluorex; 2) possible: cocaine, phenylpropanolamine, chemotherapeutic agents or selective serotonin reuptake inhibitors (SSRI); 3) likely: amphetamines/methamphetamines or L-tryptophan; and 4) unlikely: cigarette smoking, oral contraceptives or oestrogens [5]. The current knowledge and recent advances on drug-induced PAH will be discussed later on in this review.

Anorexigen-associated PAH

Appetite suppressant drugs were the first well-established risk factors for the development of PAH [6, 7]. First, all aminorex then fenfluramine derivatives, and more recently benfluorex, have been used in the treatment of obesity, and associated with PAH. Fenfluramine derivatives like aminorex are potent serotonin (5-HT) uptake inhibitors and they interact directly with the 5-HT transporter [8]. In PAH elevated levels of 5-HT may act as a growth factor for pulmonary artery smooth muscle cells, thus contributing to the development of the disease [9–11].

Aminorex

In 1967, only 2 years after the introduction of the anorexigen drug aminorex on the market in Switzerland, West Germany and Austria, an epidemic of PAH was observed [4]. During this period, nearly 60% of the diagnosed patients had a history of aminorex intake that allowed us to recognise the temporal and geographical relationships between the use of the drug and PAH development [3, 12]. Furthermore, this epidemic significantly decreased 2 years after the withdrawal of aminorex. These patients were found to have precapillary PH with typical plexiform arteriopathy upon histological examination and a severe prognosis: 10 years after the epidemic, half of the patients died, usually of right heart failure [3].

TABLE 2 Risk factors for and associated conditions of pulmonary arterial hypertension

Definite	**Possible**
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St John's Wort
Toxic rapeseed oil	Chemotherapeutic agents
Benfluorex	Selective serotonin reuptake inhibitors
Dasatinib	Pergolide
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-Tryptophan	Oestrogen
Methamphetamines	Cigarette smoking

Reproduced and modified from [5].

Fenfluramine and derivatives

In the 1980s, several case reports suggested a possible relationship between the use of fenfluramine derivatives and PAH [13]. In the 1990s, an initial retrospective study supported a possible role of fenfluramine derivatives as risk factors for PAH development [14]. The results of the International Primary Pulmonary Hypertension Study demonstrated a strong association between PAH and the use of anorexic drugs, mainly derivatives of fenfluramine [15]. In a French study, SIMONNEAU *et al.* [7] reported the characteristics of 62 patients with fenfluramine-induced PAH (61 females). The interval between the onset of dyspnoea and that of drug intake was 49±68 months. The majority of patients used fenfluramine derivatives for at least 3 months: about half of the patients used dexfenfluramine alone; 27% used fenfluramine in association with amphetamines; 11% used fenfluramine alone; and 8% used both drugs [7]. When compared with sex-matched PAH patients not exposed to fenfluramine, patients with fenfluramine-induced PAH had the same clinical presentation at diagnosis, comparable haemodynamics and were treated with the same available drugs and had a broadly similar prognosis (50% overall survival at 3 years) [7]. By contrast, the fenfluramine-induced PAH group was characterised by a higher age and body mass index and fewer patients proportionately with an acute vasodilator response [7]. More recently, SOUZA *et al.* [16] have shown that patients with fenfluramine-induced PAH may be carriers of bone morphogenetic protein receptor type 2 (*BMPR2*) mutations, a similar proportion (22.5%) has been reported in sporadic PAH. Interestingly, patients carrying *BMPR2* mutations had a significantly lower duration of exposure to fenfluramine than patients without any mutations [16]. The median survival was 6.4 years, with no significant difference between fenfluramine-induced PAH and a control group of idiopathic and heritable PAH patients. Duration of fenfluramine exposure showed no relation to survival [16]. Fenfluramine derivatives were banned from commercial use in 1997.

In conclusion, fenfluramine-induced PAH patients share clinical, functional, haemodynamic and genetic features with idiopathic PAH patients, as well as similar overall survival rates. These observations suggest that fenfluramine derivatives may act as a trigger for PAH without influencing its clinical course [7, 16].

Benfluorex

Benfluorex is a benzoate ester that shares similar structural and pharmacological characteristics with fenfluramine derivatives. The active and common metabolite of each of these molecules is norfenfluramine, which itself has a chemical structure similar to that of amphetamines. The commercial product, put on the market in 1976 as a treatment for diabetes and metabolic syndrome, has mainly been prescribed in France (5 million patients exposed). Benfluorex was not marketed as an anorexigen, therefore, it could evade the restrictions imposed in late 1990s after the proven association between fenfluramine derivatives and PAH or cardiac valvular diseases. In 2009, a case series provided evidence of possible cardiotoxic effects of benfluorex [17]. In addition, a case-control study demonstrated that benfluorex is associated with valvular heart diseases, and premature deaths [18]. Recently, the French PAH Network reported 85 cases of PH associated with benfluorex exposure diagnosed between 1998 and 2011 and among them 70 patients with PAH [19]. The median delay between initiation of benfluorex exposure and diagnosis of PAH was 108 months and the median duration of exposure was 30 months. Interestingly, a third of the patients had prior exposure to fenfluramine derivatives and an additional risk factor for PAH was identified in 20 out of the 70 PAH patients [19]. Approximately 25% of the patients showed coexisting PAH and mild-to-moderate valvular heart disease. Given, that benfluorex shares the same active metabolite as fenluramine derivatives, it is highly probable that benfluorex triggers PAH [19].

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Amphetamines

Amphetamines, methamphetamines and cocaine are considered to be risk factors for PAH, based on case reports and pharmacological similarities to fenfluramine [2, 20–23]. The largest retrospective study on amphetamines and their role in the development of PAH was performed by CHIN *et al.* [24] between 2002 and 2004. The authors analysed the proportion of stimulant use (amphetamines, methamphetamines, or cocaine) in 340 patients with idiopathic PAH, chronic thromboembolic PH (CTEPH) or PAH associated with other risk factors. A history of stimulant use was found in 28.9% of patients with a diagnosis of idiopathic PAH, compared with 3.8% of patients with PAH and a known risk factor, and 4.3% of patients with CTEPH. After adjustment for differences in age, patients with idiopathic PAH were about 10 times more likely to have used stimulants than patients with PAH associated with other risk factors, and eight times more than patients with CTEPH [24]. Another interesting finding of the study is the high rates of stimulant use in patients with HIV infection and as the mechanisms behind this particular form of PAH are still unclear the use of stimulant substances might play a role [24]. Methamphetamines and amphetamines act more potently on norepinephrine and dopamine transporters and barely affect the serotonin transporter [25]. Nevertheless, both serotonin and norepinephrine have vasoconstrictive and growth modulating effects on smooth-muscle cells, suggesting a possible involvement of methamphetamines and amphetamines in the development of PAH [25–27].

Phentermine

Phentermine is an anorexigen approved for short-term use as a treatment for obesity. Phentermine stimulates the secretion of noradrenalin in the central nervous system, and suppresses appetite by regulating the β-adrenergic receptors [28]. In the 1980s, the association between fenfluramine and phentermine became the gold standard for treating obesity. After 1997 when fenfluramine derivatives were banned by the Federal Drug Administration (FDA), phentermine could still be prescribed for short periods of time in specific situations. In the analysis in 2000 by RICH *et al.* [29], phentermine was not retained as a potential risk factor for PAH; however, the long history of concomitant use with fenfluramine cannot completely exclude a role in the development of PAH.

Mazindol

Mazindol is an amphetamine-like appetite suppressant and stimulant agent used in the treatment of narcolepsy and obesity. Recently, a case of partially reversible PAH associated with mazindol intake was reported [30]. However, in a larger series of 139 patients treated with mazindol, no cases of PAH were reported, but only 45 patients underwent cardiac echography [31]. Because of its mechanism, periodic cardiovascular examinations should be offered to patients treated with mazindol.

Dasatinib-induced PAH

Tyrosine kinase inhibitors (TKI), and particularly imatinib, revolutionised the treatment of chronic myelogenous leukaemia (CML) [32]. The platelet derived growth factor (PDGF) pathway has been clearly demonstrated to be involved in the development of the animal model of PH and in human PAH. Interestingly, imatinib, a TKI that could inhibit the PDGF receptor, has been discussed as a potential treatment for PAH [33]. Dasatinib is a TKI with markedly higher affinity for BCR/ABL kinase in comparison with imatinib (~300-fold) and it inhibits a large number of kinases including the Src family kinases. Dasatinib is approved as a second-line treatment in imatinib resistant CML and recent data suggested that dasatinib may have higher efficacy in newly diagnosed CML than imatinib. In this context, it was quite paradoxical that cases of PAH were reported with the use of dasatinib [34–36]. Recently, we published a series of nine cases of dasatinib-induced PAH from the French PAH Network [37]. These patients were characterised by a female predominance. By contrast with anorexigen-associated PAH, all cases occurred during treatment with dasatinib [37]. Median delay between initiation of dasatinib and PAH diagnosis was 34 months (range 8–48 months). At diagnosis, most patients had severe clinical, functional and haemodynamic impairment, some of them requiring vasoactive drugs and management in the intensive care unit [37]. Clinical and functional improvements were usually observed after discontinuing dasatinib; however, some patients required specific PAH treatment. Acute vasodilator response was observed in only one out of nine patients, suggesting that isolated acute vasoconstriction may not represent the main mechanism of dasatinib-induced PAH. Indeed, the majority of patients failed to demonstrate complete haemodynamic recovery and two patients died at follow-up [37]. No predictive factor (including clinical comorbidities or *BMPR2* genetic status) of dasatinib related-toxicity was detected in this study. Authors estimated the lowest incidence of PAH in patients exposed to dasatinib at 0.45%. Interestingly, all patients had previously received imatinib before dasatinib and six patients had received nilotinib after dasatinib discontinuation without PAH recurrence. This suggests that pulmonary vascular toxicity induced by dasatinib is probably molecule-related and not class-related. There are many hypotheses behind this

phenomenon, and no clear answer to date. One hypothesis is that by inhibiting Src, which plays a critical role in smooth muscle cell proliferation and vasoconstriction, dasatinib alters the proliferation/antiproliferation equilibrium at the endothelial and pulmonary arterial smooth muscle level [38]. In addition, all other molecular targets specific to dasatinib might be involved, but further research must be done to understand the exact mechanisms involved.

In conclusion, a large inhibition spectrum and lack of specificity of TKIs may be responsible for unexpected toxicities, even at the pulmonary vascular level.

Interferon-associated PAH

The interferons (IFNs) comprise an evolutionary conserved family of secreted proteins that participate as extra-cellular messengers in a wide variety of responses, including antiviral, antiproliferative, immunomodulatory and developmental activities that act to maintain homeostasis and in-host defence [39]. IFNs are classified as helical cytokines and categorised as type I or type II according to their physical and functional characteristics. Type I IFNs include α (leukocyte), β (fibroblast), τ and ω subtypes, which were likely to have arisen from a common ancestral gene.

IFN-α

IFN-α has been used extensively in the treatment of hepatitis viruses, but also in haematological, nephrological, and dermatological malignancies. The association of IFN-α and ribavirin has been considered to be the current standard of care for hepatitis C in the last decades [40, 41]. Side-effects associated with IFN therapy have been reported, including transient flu-like symptoms to serious effects, such as cardiac arrhythmias, cardiomyopathy, renal and liver failure, polyneuropathy, and myelosuppression. Several pulmonary side-effects have been reported including asthma exacerbation, pleural effusion, sarcoidosis, cryptogenic organising pneumonia, bilateral pulmonary infiltrates [42]. DHILLON *et al.* [43] presented four cases of PAH occurring in patients treated with IFN-α for hepatitis C infection. Three of them were non-cirrhotic and two patients were post-liver transplant with an uncomplicated postsurgical course. Portopulmonary hypertension and other causes of PH had been systematically ruled out. Although most of the side-effects disappear 24 months after the discontinuation of IFN-α, in these 4 cases PAH was not reversible. As experimental investigations in sheep showed that IFN-α can stimulate the thromboxane cascade, which resulted in transient PAH [44], the authors suggest, as potential mechanisms, the acceleration of a previously subclinical phenomenon caused by other factors, such as human herpes virus 8, hepatitis C virus itself, or a previously unrecognized genetic predisposition [43, 45].

IFN-β

IFN-β is an extra-cellular protein mediator of host defence and homeostasis. IFN-β has well-established direct antiviral, antiproliferative and immunomodulatory properties. Recombinant IFN-β is approved for the treatment of relapsing–remitting multiple sclerosis. At present there are two cases of patients with multiple sclerosis who have developed possible PAH after IFN-β therapy [46, 47].

In conclusion therapies with IFN-α and -β may be associated with an increased risk for the development of PAH and future studies are needed to evaluate their full impact on pulmonary haemodynamics.

Conclusion

At the beginning of the 21st century drug-associated PAH remains a clinical problem. After worldwide alerts concerning anorexigens, many drugs were suspected to be risk factors for PAH [48]. However, it remains a great challenge to confirm the imputability of a drug, because PAH is always a rare complication occurring only in a very small proportion of exposed patients (usually $<1\%$). Close interactions between national drug regulatory agencies, national PH networks and PAH patient associations may represent a possible solution for detecting new, potential, drugs that are capable of inducing PAH and for launching global alerts if necessary.

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