Pulmonary hypertension associated with benfluorex exposure

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Published on April 20, 2012 as doi: 10.1183/09031936.00188611

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Abstract (194 words)

Benfluorex was marketed in France until 2009, despite its similar pharmacological properties with fenfluramine and its derivatives known to be a cause of pulmonary arterial hypertension.

The aim of this study is to report clinical and haemodynamic characteristics of patients suffering of pulmonary hypertension associated with benfluorex exposure identified by the French pulmonary hypertension network.

Eighty five cases of pulmonary hypertension associated with benfluorex exposure were identified by the French pulmonary hypertension network from June 1999 to March 2011. Of these, 70 patients had confirmed pre-capillary pulmonary hypertension. The median duration of exposure was 30 months, with a median of 108 months between start of exposure and diagnosis of the pulmonary vascular disease. 33% of all patients also had prior exposure to fenfluramine or dexfenfluramine, and an additional risk factor for pulmonary hypertension was identified in 20/70 (30%) patients with pre-capillary pulmonary hypertension. A quarter of patients in this current series showed co-existing pulmonary hypertension and mild to moderate cardiac valve involvement.

The results of our study, together with the accumulated data regarding the known toxic effects of fenfluramine and dexfenfluramine, strongly suggest that benfluorex exposure is a potent trigger for pulmonary arterial hypertension

Key words:

Benfluorex, anorectic agents, fenfluramine derivates, pulmonary hypertension, valvular heart disease
Introduction

Pulmonary arterial hypertension (PAH) is a rare condition characterised by a progressive increase in pulmonary vascular resistance that leads to eventual right heart failure (1, 2). An aetiological link between exposure to anorectic agents and PAH has been demonstrated for nearly half a century. In the most recent pulmonary hypertension (PH) guidelines, these cases are included in the group of PAH induced by drugs or toxins exposure (3).

Two years after the amphetamine derivative aminorex became commercially available in Switzerland, Germany and Austria, a dramatic increase in the number of cases of so-called “primary” PH was observed (4, 5). Compelling geographic and temporal evidence supported a causal role for aminorex in this epidemic. Following these events, a working group of the World Health Organization convened the first world congress on PH in 1973. The subsequent publication of the Executive summary document of the congress provided, for the first time, a consensus on the clinical and pathological classification of the disorder (6).

Norfenfluramine is a metabolically active product of fenfluramine and its derivatives. Exposure to norfenfluramine is known to be associated with both cardiac valvular dysfunction and PAH. Mounting evidence indicates that serotonin contributes to the pathophysiology of PH by promoting proliferation of pulmonary arterial smooth muscle cells and adventitial fibroblasts (7). Recent data suggest that fenfluramine and its derivatives can induce pulmonary vascular remodelling through a direct action on the serotonin pathway (8).

Fenfluramine has been commercially licensed in Europe since 1963 as anorectic agent. The fenfluramine derivative dexfenfluramine was first made available in France in 1985 (9). During the 1980s and 90s, fenfluramine and its derivatives were
widely prescribed throughout Europe. However, a link between fenfluramine exposure and the development of PAH was first suspected in 1981 (10). In 1992, Roche et al reported a case series of patients that developed PAH after exposure to dexfenfluramine (11). The following year, Brenot et al reported that approximately 20% of patients referred for evaluation of PAH at the Hôpital Antoine Béclère in Clamart, France, had a history of exposure to fenfluramine and/or one or more of its derivatives (12). The observation that patients exposed to anorexigenic agents, in particular fenfluramines, were at increased risk of PAH was subsequently confirmed in the International Primary Pulmonary Hypertension Study (13). Further evidence of the association was provided by data from the Surveillance Of Pulmonary Hypertension In America (SOPHIA) (14). Finally, fenfluramine and dexfenfluramine were withdrawn from the french market in 1997.

Benfluorex is a benzoate ester that shares similar structural and pharmacologic characteristics with dexfenfluramine and fenfluramine. The active and common metabolite of each of these molecules is norfenfluramine, which itself has a chemical structure similar to that of the amphetamines. Given its pharmacological properties, benfluorex would be expected to have similar toxic effects to the fenfluramine derivatives. However, benfluorex was not subjected to the same restrictions as the fenfluramine derivatives in 1997 in France, at least in part because it was approved as an agent for treatment of diabetes and the metabolic syndrome and not an anorexigen. As a result, and in spite of case reports, benfluorex remained available in France until November 2009, until compelling data were brought from a case-control study by Frachon et al highlighting the potential cardiotoxic effects, even though it had been withdrawn from commercial use in other European countries several years prior previously (15, 16). Between 1976 and 1980, benfluorex has been marketed in other
European countries including Spain, Greece, Portugal and Italy. Withdrawal of benfluorex in Spain and Italy occurred in 2003 and 2004, respectively, due to the occurrence of cardiac valvulopathy.

We have previously reported a small series of patients with PAH that had prior exposure to benfluorex (17). The aim of the current study was to establish the clinical and haemodynamic characteristics and outcomes of patients identified by the French PH network with prior exposure to benfluorex and confirmed PH.

**Patients and Methods**

**Patients**

All patients with PH and a prior history of exposure to benfluorex that were assessed at the French PH referral centre or one of its associated competent centres were evaluated. Accordingly, all 25 hospitals comprising the French national PAH network, which was established in 2004 as part of the orphan disease program, were involved in the study. Data was centrally collected and analysed at the French referral centre for severe PH (Hôpital Antoine Béclère, Univesité Paris-Sud, Clamart). According to French legislation, ethics committee agreement and provision of informed consent are not required for retrospective collection of data corresponding to current practice. The database was, however, compiled anonymously within the restrictive requirements of the Commission Nationale Informatique et Liberté, the organisation dedicated to privacy, information technology, and civil rights in France.
PH was defined as a mean pulmonary arterial pressure (mPAP) \( \geq 25 \text{mmHg} \). All patients had undergone initial screening by transthoracic echocardiography and were subsequently sent to a competent centre for suspected PH without evident sign of left cardiac disease. A right heart catheterisation was systematically performed during the initial assessment in order to confirm the diagnosis of PH, clarify its mechanism and determine its severity.

The type of PH was defined according to the ERS/ESC guidelines (18). Precapillary PH was defined as mPAP \( \geq 25 \text{mmHg} \) and pulmonary capillary wedge pressure (Pcwp) \( \leq 15 \text{mmHg} \). Mixed pre- and post-capillary PH was defined as mPAP \( \geq 25 \text{mmHg} \), \( \text{Pcwp} > 15 \text{mmHg} \) and transpulmonary gradient (TPG = mPAP-Pcwp) \( > 12 \text{mmHg} \). Post-capillary PH was defined as mPAP \( \geq 25 \text{mmHg} \), \( \text{Pcwp} > 15 \text{mmHg} \) and TPG \( \leq 12 \text{mmHg} \).

In line with current guidelines, all patients in whom the diagnosis of PH was confirmed by right heart catheterisation underwent extensive investigations in order to identify additional possible risk factors for PH (congenital heart disease, portopulmonary hypertension, human immunodeficiency virus (HIV) infection, connective tissue disease, chronic thrombo-embolic PH, chronic obstructive or restrictive lung disease, systolic or diastolic left heart disease, haemoglobinopathies etc…).

Details of anorexigen exposure (benfluorex and/or others) were gathered by detailed clinical history either at time of initial work-up or \textit{a posteriori} depending on each case. The date of onset, the date of last use and the cumulative months of use were established after patient’s interview and confirmed after collecting written prescriptions when available.

\textbf{Clinical, functional and haemodynamic assessment at baseline evaluation}
Clinical characteristics included age, sex, weight (kg), height (m), body mass index (BMI) (weight/height², kg/m²) and cardiovascular risk factors (history of diabetes mellitus, hypertension and dyslipidemia) were collected from baseline evaluation. Functional status of patients was assessed by modified New York Heart Association (NYHA) functional class and 6-minute walk distance (m). Standard right-heart catheterisation and acute vasodilator challenge were performed in all patients for diagnostic confirmation. Patients were classified as acute responders according to the current criteria (19).

Baseline clinical characteristics of patients with benfluorex-induced PAH were compared to those of patients from the French referral centre with fenfluramine-induced PAH previously reported by Souza, et al (20).

**Genetic Studies**

Thirteen patients with benfluorex induced PAH were assessed for *BMPR2* germline mutation as previously described (21).

**Assessment for associated valvular heart disease**

Transthoracic echocardiography was used to identify and describe associated mitral and/or aortic valve insufficiency and/or morphological valvular abnormalities. Valve morphology and function was assessed according to current recommendations(22). A valvular regurgitation was classified as mild, moderate, moderate to severe or severe, based on qualitative, semi-quantitative, and quantitative methods, as recommended. Concerning mechanism, valve movement was considered to be restrictive when valvular mobility was reduced (22). Mitral orifice area was
measured by planimetry using two dimensional echocardiography of the according to the recommendations of European Society of Cardiology (23).

Statistical analysis
All continuous data are presented as mean±SD or median (interquartile range) as appropriate. Comparison between continuous data was performed using an unpaired t-test. A Chi-squared test was used for group data comparison.
Results

Number of cases of PH associated with benfluorex exposure identified by the French PH network

The first case of pre-capillary PH in a patient with prior exposure to benfluorex was referred to the French PH referral centre in June 1999. In total, between June 1999 and March 2011, 85 cases of PH associated with benfluorex exposure were diagnosed throughout the French PH network. Of these, the diagnosis was established at the national referral centre in 30 patients and at satellite centres in 55 patients. Only 9 cases were evaluated for the first time between 1999 and 2005. In the remaining 76 cases, the diagnosis of PH was established between 2006 and 2011 (figure 1).

Among the 85 cases referenced in this study, 5 cases were yet published by Bondon-Guitton et al (24) and 4 other cases by Boutet et al (17).

In 70 patients, PH was established as ‘pure’ pre-capillary PH (i.e. without an associated post-capillary component). Thirteen patients had ‘mixed’ pre- and post-capillary PH (as evidenced by a TPG >12 mmHg). Two patients were established as having post-capillary PH without a pre-capillary component. We accordingly deemed that these two patients did not have pulmonary vascular disease per se.

Clinical characteristics

The median patient age was 62 years. Males comprise 22% of the total cases. The median value for BMI was 30 kg/m². At time of diagnosis of PH, 58% of patients were known to have diabetes mellitus, 44% had dyslipidemia and 56% had systemic hypertension. At least one of these three cardiovascular risk factors was present in 80% of patients.
**Benfluorex exposure**

The median duration of exposure to benfluorex in our patient population was 30 months. It was not possible to accurately establish the duration of benfluorex exposure in 12 patients. The median interval between date of first exposure to benfluorex and date of diagnosis of PH was 9 yrs. Seventeen patients were regarded as current users at the time of diagnosis. Finally, for the other patients, median latency between last exposure and the diagnosis of PH was 5 years. Twenty eight patients (33%) reported exposure to fenfluramine or dexfenfluramine in addition to benfluorex. In all cases, exposure to the fenfluramine derivatives was prior to benfluorex exposure.

**Characteristics of patients with “pure” pre-capillary PH**

The majority of patients evaluated in our network had “pure” pre-capillary PH (n=70, 82%). At time of diagnosis, 83% (58/70) of patients had dyspnoea that was moderate to severe (NHYA functional class III to IV). Median 6-minute walk distance was 319 meters. The haemodynamic profile of this cohort is summarised in Table 1. A positive vasodilator response to inhaled nitric oxide (NO) was observed in 4 patients (5.7%). Among the 70 patients with pre-capillary PH, an additional risk factor for PH was identified in 21 patients: 5 cases of connective tissue disease, 3 cases of chronic obstructive pulmonary disease and 1 of idiopathic pulmonary fibrosis, 4 cases of distal chronic thromboembolic PH (CTEPH) and 3 cases of proximal CTEPH, 2 cases of cirrhosis, 1 case of sickle cell disease, 1 case of familial PAH and 1 case of abnormal pulmonary venous return.
The current cohort of patients with pre-capillary PH and benfluorex exposure was compared to those patients from the French registry with PAH and prior exposure to fenfluramine derivatives (12) (Table 1). Those with benfluorex were approximately 10 years older at time of diagnosis. The proportion of males with a history of benfluorex exposure (male to female ratio 1:3) was greater than that exposed to fenfluramine derivatives (male to female ratio 1:19). The median duration of exposure to benfluorex was markedly longer compared that of the fenfluramine derivatives. The median interval between initial drug exposure and PAH diagnosis was non-significantly longer among patients taking benfluorex compared to those that had been exposed to fenfluramine derivatives. Compared to patients that had taken fenfluramine derivatives, patients with benfluorex exposure exhibited slightly less severe hemodynamic abnormality (PVR values approximately 25% lower).

The presence of a $BMPR2$ mutation was evaluated in 13 sporadic cases of pre-capillary PAH exposed to benfluorex. In total, 2 patients carried a $BMPR2$ mutation (15%). Furthermore, we identified a patient with familial PAH and exposure to benfluorex (unfortunately, $BMPR2$ mutation has not yet been sequenced in this patient).

**Characteristics of patients with mixed pre- and post-capillary PH**

Evidence of mixed pre- and post-capillary PH was observed in 13/85 (16%) patients. Nine of these individuals had systemic hypertension, itself a risk factor for diastolic left ventricle dysfunction. Individual data for these patients are shown in Table 2.

**Mitral and/or aortic valvular heart disease**
Mitral and/or aortic valvular heart disease was identified by echocardiography among 23 of the 83 patients (28%) with either pre-capillary or mixed pre- and post-capillary PH. The proportion of patients with evidence of associated cardiac valvulopathy was greater among patients with mixed pre- and post-capillary PH compared to patients with “pure” pre-capillary PH (7/13, 54%, versus, 16/70, 23% respectively; p=0.02). There was evidence of significant mitral valve disease in 10 patients and significant aortic valve disease in 7. Mixed aortic and mitral valve disease was identified in 6 individuals. Morphological abnormalities compatible with benfluorex toxicity have been described in 7 patients (8.2%). Details regarding valvular heart disease involvement are summarised in Table 3.

**Outcomes**

Median time of follow-up was 10 months. The majority of patients diagnosed with pre-capillary PH are currently treated by one or more specific PAH therapeutic agents (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors or prostacyclin analogues). At time of last follow-up, 8 patients had died. Two patients had undergone lung transplantation of whom one patient died in the immediate post-operative period.
Discussion

From June 1999 to March 2011, we identified 85 cases of PH associated with benfluorex exposure in the French PH network. Of these, 70 patients had confirmed pre-capillary PH. Approximately one quarter of all patients also had exposure to fenfluramine or dexfenfluramine, and an additional risk factor for PH was identified in one third of patients. From 2006 onward, we observed annual increase in the number of cases of PH associated with benfluorex exposure. The majority of study subjects were overweight or obese and the presence of at least one other major risk factor for cardiovascular disease was identified in 80%. This finding is not surprising however, as patients with these co-morbidities correspond to the population for whom benfluorex was in general prescribed. Interestingly, we observed a relatively high proportion of patients (26%) that had both PH and aortic and/or mitral valve disease which findings may be also accounted for norfenfluramine toxicity. This is in marked contrast to the findings of previous French and US studies of patients with fenfluramine exposure or its derivatives that showed increased incidences of either isolated PAH (12) or isolated valvular heart disease, respectively (25).

Baseline clinical and functional characteristics of benfluorex-associated PH patients were broadly similar to the cohort of PAH patients exposed to fenfluramine and its derivatives (20). However, with regard to length of drug exposure, some differences were also apparent between these populations. In particular, the median duration of exposure to benfluorex was significantly longer than that reported with fenfluramine and its derivatives. This difference is most likely due to the fact that benfluorex was generally prescribed as a long-term treatment for overweight patients
that had diabetes and/or metabolic syndrome. In contrast, fenfluramine and its derivatives were exclusively used as anorexigens and in general treatment was prescribed on a short-term basis (generally less than 6 months) (20). Benfluorex, as fenfluramine and dexfenfluramine is metabolized into norfenfluramine a 5-HT2B agonist (26). Whereas dexfenfluramine is given once a day (60 mg), recommended treatment by benfluorex is three times per day (450 mg). These dexfenfluramine and benfluorex usual dosages lead to the same plasmatic concentration of norfenfluramine (50 ng/mL) (27). However, most of benfluorex exposed patients had a prescribed dosage at 300 mg or even 150 mg per day, leading to a norfenfluramine plasmatic concentration lower than in fenfluramine users (28). Interestingly, despite the longer median duration of benfluorex treatment, no significant difference in the interval between the initial drug exposure and date of PH diagnosis was observed between the two populations. The observation that patients exposed to benfluorex were older and showed a less marked female preponderance compared to fenfluramine and its derivatives is likely accounted for by the different therapeutic indications of the respective agents corresponding to two different populations (20).

Compared to the cohort with fenfluramine exposure, patients exposed to benfluorex that had PH showed a less marked hemodynamic impairment as evidenced by lower levels for mPAP and PVR. We also observed the same proportion of patients that had a positive response after acute vasodilator testing (5.7%) as has been described in other studies of patients with idiopathic PAH(19). The same proportion of such “responders” was also reported in populations exposed to fenfluramine and its derivatives (20).
A relatively high proportion of patients in our study had at least one other potential risk factor for the development of PH (30%). As previously discussed, these patients were typically obese. Although obesity is not a known independent risk factor for PAH (13), it is nonetheless associated with other conditions that themselves predispose to other forms of PH, such as obstructive sleep apnoea, chronic thrombo-embolic disease and left heart disease. In addition, some patients had other associated condition that may promote the development of PAH (like portal hypertension or systemic sclerosis). Similarly, The Surveillance of North American Pulmonary Hypertension reported a high rate of anorexigen use in “secondary” PH too (11.4%) (29). These observations suggested that multiple risk factors for PH may have additive effects.

A quarter of the overall cohort patients with benfluorex exposure and PH had as a risk factor additional prior exposure to fenfluramine or one of its derivatives for a median duration of 11 months. In all cases, exposure to the fenfluramine derivatives was prior to benfluorex exposure. Time between start of fenfluramine use and PH diagnosis was 21 years (6-36 years) that is much higher than what has been described in the French patients who developed fenfluramine-associated PAH (9, 20). Furthermore, hemodynamic characteristics of patients exposed to both benfluorex and fenfluramine or its derivates were not different from those of patients exposed to benfluorex only (data not shown). None of these data can suggest that combined exposure was more harmful than benfluorex exposure alone. These observations corroborate the hypothesis that the additional exposition to benfluorex was likely to trigger the occurrence of the pulmonary vascular disease in these patients. However, one cannot exclude a priming effect of initial fenfluramine exposure.
Interestingly, the presence of \textit{BMPR2} mutations has been examined in 13 patients and resulted in 2 patients with mutated genes. This proportion is similar to what is found in population of patients with idiopathic PAH or fenfluramine associated PAH\cite{20, 30, 31}. This finding corroborates the concept that benfluorex-induced PAH shares also genetic predisposition features with idiopathic PAH. These observations underscore the complex nature of PAH pathogenesis. Anorexigens may precipitate pulmonary vascular disease in patients with predisposing factors or underlying conditions associated with higher risk to develop PH. Anorexigen use could play a role of trigger in both populations.

Furthermore, hemodynamic evaluation identified some patients with mixed pre- and post-capillary PH. The majority of these patients had systemic hypertension, a known risk factor for the development of diastolic left ventricle dysfunction which itself can contribute to increases in PAP. Approximately half of these patients had associated valvular heart disease, a factor that likely also contributed to the post-capillary component of PH observed in this subgroup. In these patients, we can not exclude that benfluorex could have also played a role in the precapillary component of PH.

Prior exposure to appetite suppressants is now firmly established as aetiologically relevant for the development of both cardiac valvular disease and PAH. Hitherto, however, published series have not described the co-existence of both these cardiovascular complication following exposure to anorexigens. In France, fenfluramine and its derivatives were removed from the market following an epidemic of PAH in the late 1980s and early 1990s. However, cardiac valvular disease were
rarely reported following exposure to this class of drug in France (12). In contrast, severe cardiac valvulopathy was the first cardio-vascular side effect described in patients in the US that had been prescribed combination fenfluramine/phentermine (“fen-phen”), the latter agent being an amphetamine derivative (25).

Interestingly, a quarter of patients in the current series showed co-existing PH and mild to moderate cardiac valve disease. This finding could be explained at least in part by the longer duration of exposure to benfluorex. The concomitant development of both these cardio-vascular side effects, as was found in our population, strengthens the hypothesis that these toxicities were directly attributable to fenfluramine-like cardio-vascular effects of benfluorex exposure. No particular factor could be attributed to the relatively high proportion of patients that had both PH and valvular cardiac disease. Interestingly, the proportion of patients with cardiac valvular structural abnormalities identified in our series is strikingly similar to the incidence of valvular dysfunction that was observed in the unpublished “REGULATE” study undertaken by Servier Pharma of patients exposed to benfluorex who were evaluated at baseline and after 12 months by echocardiography (32). The objective of the REGULATE study was to compare during 52 weeks the efficacy and safety of two “anti-diabetic” oral treatments (benfluorex versus pioglitazone). It included 847 patients with type 2 diabetes. Results, based on the comparison of echocardiography at baseline and after 1 year of treatment, showed statistically significant of functional valvular abnormalities in patients treated by benfluorex in comparison with patients treated with pioglitazone (26.5% vs 10.9%, p <0.0001). Morphological abnormalities of the valves were also observed twice as often with benfluorex (2.6% vs 1.3%, p <0.264). The findings of this industry-sponsored study, in conjunction with results from a separate case-control study by Frachon et al that also highlighted the potential
cardiac toxicity of benfluorex, led directly to its withdrawal in 2009 from the French market (15).

The first case investigated at the French PH referral centre of a patient with prior exposure to benfluorex who developed PAH was documented in 1999 (17). Thereafter, a relatively small number of cases were identified during the period 1999-2005. In contrast, a dramatic increase in the number of the cases was observed from 2006 onwards. The reasons for the observed latter increase in incidence are unclear but may be related to the fact that between its initial approval in 1976 and the mild 1990s, the numbers of patients prescribed benfluorex remained relatively low. However, following the withdrawal from the market of several popular anorexigens, sales of benfluorex rose substantially. Indeed, approximately two thirds of the total sales of benfluorex in France were recorded during the period 2000-2009, which is a temporal argued for benfluorex imputability (33). The French national fund of health insurance reported that 200,000 to 300,000 patients per year were exposed to benfluorex between 2006 and 2009 and that 7 millions boxes of benfluorex have been sold every year during this period. In addition, a greater awareness among clinicians of the potential toxic effects of benfluorex following publication of the initial series by Boutet et al and publications of reports in the press may also have contributed to the increased incidence observed towards the end of our study (17).

To include an optimum number of benfluorex-exposed patients, we did solicit all centres of the French pulmonary hypertension (PH) network, in order to identify from their records all PH cases associated with benfluorex exposure before PH diagnosis. The retrospective analysis of data is a limitation of this report as it does not guarantee an optimal identification of all patients especially before the creation of the French PH network. Another limitation of this study is that benfluorex exposure history was
collected by the patients themselves. We were not able to validate systematically drug exposure through medical charts or pharmacy records.

In conclusion, the revelations about the cardio-vascular side effects of benfluorex led to an embarrassing political and medical scandal in France and highlighted significant deficiencies in the French pharmacovigilance system (16, 34). The results of our present study, together with the accumulated data regarding the known toxic effects of fenfluramine and dexfenfluramine, strongly suggest an aetiological link between benfluorex exposure and the development of PAH. Although an additional larger case-control study would be required to further strengthen hypothesis of a pathogenic role of benfluorex in the development of PAH, it is unlikely such a study will ever be undertaken given that this agent has now been withdrawn from the market. As PAH is an unequivocal severe consequence of cardio-vascular toxicity of several drugs and toxins, one should investigate in great detail all cases referred for so-called unexplained PAH in order to identify whether a toxic exposure may have acted as a trigger for PAH (35).
Acknowledgements

The authors thanks the following members of PAH network who have contributed to the conduct of this study: Azzedine Yaïci, Delphine Natali, Florence Parent, Laurence Rottat (Clamart), Laurent Têtu (Toulouse), Sébastien Renard (Marseille), Jean-François Cordier (Lyon), Pascal De Groote (Lille), Romain Magnier (Caen), Ari Chaouat (Nancy), Matthieu Canuet (Strasbourg), Jocelyn Inamo (Martinique), Céline Chabanne (Rennes).

We thank also Dermot S. O’Callaghan who contributed to the writing of this article.
Table 1. Baseline clinical, functional and hemodynamic data of patients with benfluorex-associated PAH. Comparison with cohort of patients with fenfluramine and dexfenfluramine-associated PAH.

<table>
<thead>
<tr>
<th></th>
<th>Benfluorex</th>
<th>Dexfenfluramine &amp; Fenfluramine</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>70</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Age, years (median [IQR])</td>
<td>61 [51-71]</td>
<td>52 [44-59]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (Female:Male) ratio</td>
<td>3.1</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m² (median [IQR])</td>
<td>30 (26-34)</td>
<td>27 (24-33)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Delay between first anorexigen exposure and PAH diagnosis, months (median [IQR])</td>
<td>108 [60-144]</td>
<td>78 [43-140]</td>
<td>NS</td>
</tr>
<tr>
<td>Anorexigen exposure duration, months (median [IQR])</td>
<td>30 [12-70]</td>
<td>6 [3-12]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA-FC, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 (17%)</td>
<td>15 (14%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>52 (74%)</td>
<td>71 (65%)</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>6 (9%)</td>
<td>23 (21%)</td>
<td></td>
</tr>
<tr>
<td>6MWD, m (median [IQR])</td>
<td>319 [209-372]</td>
<td>250 [121-355]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hemodynamics (mean±SD):</td>
<td></td>
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</tr>
<tr>
<td>RAP, mmHg</td>
<td>9±5</td>
<td>11±6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>47±11</td>
<td>60±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pcwp, mmHg</td>
<td>10±4</td>
<td>9±3</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.4±0.6</td>
<td>2.2±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>PVRi, mmHg/L/min/m²</td>
<td>17±8</td>
<td>26±11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

List of abbreviations: NYHA FC: New York Heart Association functional class; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; Pcwp: pulmonary capillary wedge pressure; PVRi: pulmonary vascular resistance index; SD: standard deviation; IQR: interquartile range

*: Comparison between continuous data was performed using an unpaired t-test. A Chi-squared test was used for group data comparison.
Table 2. Individual characteristics of patients with mixed pre- and post-capillary hypertension

<table>
<thead>
<tr>
<th>n°</th>
<th>systemic hypertension</th>
<th>associated valvular insufficiency</th>
<th>RAP mmHg</th>
<th>s/d-mPAP mmHg</th>
<th>Pcwp mmHg</th>
<th>TPG mmHg</th>
<th>PVRi, mmHg/L/min/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>mild mitral insufficiency</td>
<td>14</td>
<td>105/40-65</td>
<td>29</td>
<td>36</td>
<td>11.2</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>mild aortic insufficiency</td>
<td>15</td>
<td>60/28-40</td>
<td>18</td>
<td>22</td>
<td>6.7</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>mild aortic and moderate mitral insufficiency</td>
<td>12</td>
<td>95/44-63</td>
<td>23</td>
<td>40</td>
<td>23.3</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>mild mitral insufficiency</td>
<td>18</td>
<td>101/29-55</td>
<td>26</td>
<td>29</td>
<td>9.7</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>11</td>
<td>58/22-38</td>
<td>16</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>mild aortic and moderate mitral insufficiency</td>
<td>9</td>
<td>65/34-47</td>
<td>31</td>
<td>16</td>
<td>6.6</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>No</td>
<td>17</td>
<td>73/37-52</td>
<td>24</td>
<td>28</td>
<td>8.2</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>No</td>
<td>18</td>
<td>70/22-41</td>
<td>19</td>
<td>22</td>
<td>7.6</td>
</tr>
<tr>
<td>9</td>
<td>No</td>
<td>No</td>
<td>29</td>
<td>88/41-59</td>
<td>19</td>
<td>40</td>
<td>13.8</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>No</td>
<td>15</td>
<td>82/37-55</td>
<td>27</td>
<td>28</td>
<td>6.9</td>
</tr>
<tr>
<td>11</td>
<td>Yes</td>
<td>No</td>
<td>14</td>
<td>94/28-50</td>
<td>28</td>
<td>22</td>
<td>10.6</td>
</tr>
<tr>
<td>12</td>
<td>Yes</td>
<td>moderate aortic and mild mitral insufficiency</td>
<td>8</td>
<td>67/27-45</td>
<td>22</td>
<td>23</td>
<td>5.9</td>
</tr>
<tr>
<td>13</td>
<td>Yes</td>
<td>mild mitral insufficiency</td>
<td>11</td>
<td>75/25-49</td>
<td>22</td>
<td>27</td>
<td>9.6</td>
</tr>
</tbody>
</table>

List of abbreviations: RAP: right atrial pressure; s/d-mPAP: systolic/diastolic-mean pulmonary artery pressure; Pcwp: pulmonary capillary wedge pressure; TPG: transpulmonary gradient; PVRi: pulmonary vascular resistance index.
Table 3. Associated valvular heart diseases in patients assessed for PH associated with benfluorex

<table>
<thead>
<tr>
<th>Type of valvular dysfunction</th>
<th>Grade</th>
<th>Morphological abnormalities</th>
<th>Type of associated PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Aortic</td>
<td>mild</td>
<td>-</td>
<td>mixed</td>
</tr>
<tr>
<td>2 Mitral</td>
<td>mild</td>
<td>-</td>
<td>mixed</td>
</tr>
<tr>
<td>3 Mitral</td>
<td>mild</td>
<td>-</td>
<td>mixed</td>
</tr>
<tr>
<td>4 Mitral and Aortic</td>
<td>moderate mild</td>
<td>Mitral valves sclerosis</td>
<td>mixed</td>
</tr>
<tr>
<td>5 Mitral</td>
<td>mild</td>
<td>Mitral valves thickening</td>
<td>mixed</td>
</tr>
<tr>
<td>6 Mitral and Aortic</td>
<td>mild moderate</td>
<td>-</td>
<td>mixed</td>
</tr>
<tr>
<td>7 Mitral and aortic</td>
<td>mild moderate</td>
<td>-</td>
<td>mixed</td>
</tr>
<tr>
<td>8 Mitral</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>9 Aortic</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>10 Aortic</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>11 Mitral</td>
<td>trivial</td>
<td>Reduced mobility of anterior leaflet of mitral valve</td>
<td>precapillary</td>
</tr>
<tr>
<td>12 Aortic</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>13 Mitral and aortic</td>
<td>mild mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>14 Mitral</td>
<td>moderate</td>
<td>Mitral valves prolapse</td>
<td>precapillary</td>
</tr>
<tr>
<td>15 Mitral</td>
<td>moderate</td>
<td>Thickening of anterior and posterior leaflets of mitral valve + thickened chordae</td>
<td>precapillary</td>
</tr>
<tr>
<td>16 Mitral</td>
<td>moderate to severe</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>17 Mitral and aortic</td>
<td>mild mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>18 Aortic</td>
<td>mild</td>
<td>Aortic leaflets change</td>
<td>precapillary</td>
</tr>
<tr>
<td>19 Mitral and aortic</td>
<td>moderate mild</td>
<td>Mitral valve sclerosis</td>
<td>precapillary</td>
</tr>
<tr>
<td>20 Aortic</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>21 Mitral</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>22 Mitral and aortic</td>
<td>NP NP</td>
<td>-</td>
<td>precapillary</td>
</tr>
<tr>
<td>23 Mitral</td>
<td>mild</td>
<td>-</td>
<td>precapillary</td>
</tr>
</tbody>
</table>
Figure 1. Number of newly-diagnosed benfluorex-associated PH patients per year between 1999 and March 2011.
**Figure 2.** Type of benfluorex-associated pulmonary hypertension identified between 1999 and March 2011.

- Pulmonary hypertension (mPAP ≥ 25 mmHg) \( n = 85 \)
  - Post-capillary pulmonary hypertension (Pcwp > 15 mmHg; TPG ≤ 12 mmHg) \( n = 2 \)
  - Pre-capillary pulmonary arterial hypertension (Pcwp ≤ 15 mmHg) \( n = 70 \)
  - Mixed pre- and post-capillary hypertension (Pcwp > 15 mmHg; TPG ≥ 12 mmHg) \( n = 13 \)

mPAP: mean pulmonary arterial pressure; Pcwp: pulmonary capillary wedge pressure; TPG: transpulmonary gradient (=mPAP-Pcwp)
References