Eur Respir J 2011; 38: 510–511
DOI: 10.1183/09031936.00075211

EDITORIAL

Whistleblowers

M. Humbert*,#,¶, G. Simonneau*,#,¶ and A.T. Dinh-Xuan+

The term whistleblower comes from the phrase ''blow the whistle'', which refers to a whistle being blown by a policeman or a referee to indicate an activity that is illegal or a foul [1]. Recently, whistleblowers have disseminated valuable information to the community through new media outlets, such as WikiLeaks. In medicine, whistleblowers serve to shed light on side-effects of drugs and, occasionally, improprieties that have yet to be highlighted or investigated. Since the 1960s, such whistleblowers have made public the unacceptable cardiovascular risks of the appetite suppressants aminorex, fenfluramine, dexfenfluramine, and benfluorex [2–14]. These drugs had few (if any) beneficial clinical effects; however, they significantly increased the risk of life-threatening complications such as pulmonary arterial hypertension (PAH) and/or valvular heart diseases.

One of the main objectives of the *European Respiratory Journal* (*ERJ*) is to provide updates for its readership on new therapeutic developments in the field of respiratory diseases. In doing so, the *ERJ* must of course provide a balanced view, highlighting not only the benefits of new treatments but also important potential adverse effects. The *ERJ* and its predecessor, the *Bulletin Européen de Physiopathologie Respiratoire,* have been an important platform for whistleblowers with respect to the field of cardiopulmonary medicine. Since the landmark review published by GURTNER [2] describing the links between PAH and the appetite suppressant aminorex, several original articles published in the *ERJ* have emphasised the major pulmonary vascular and valvular heart complications of fenfluramine derivatives [3, 8, 9, 11, 12]. These articles have clarified the cardiovascular risks associated with the use of these agents and demonstrated the fenfluramine-like cardiovascular side-effects of benfluorex. Indeed, recognition of this association led eventually to a complete ban of benfluorex from the market in France and resulted in a major medical and political scandal in France, emphasising the need to reassess the working procedures of French (and European) pharmacovigilance systems [15].

In addition to helping to bring to light the link between PAH and certain drugs and toxins, several studies published in the *ERJ* have also highlighted important side-effects of PAH-specific therapies [16–22]. European post-marketing surveillance of the endothelin receptor antagonist, bosentan, confirmed that the incidence and severity of elevated aminotransferase levels in clinical practice was similar to that reported in clinical trials and confirmed the need for monthly monitoring of liver transaminases in patients treated with this agent [16]. On a more serious note, cases of severe (and sometimes fatal) idiosyncratic liver failure have been reported with sitaxentan, another endothelin receptor antagonist used in the treatment of PAH, leading to the withdrawal of this agent from the market worldwide in December 2010 [17–21]. This also prompted an amendment to the most recent guidelines published jointly by the European Society of Cardiology and the European Respiratory Society [22, 23].

In order to help improve detection of potential drug-induced pulmonary vascular diseases, it is important to stress the critical importance of obtaining of a detailed history of a given individual's current and prior drug exposure. In a recent issue of the *ERJ*, DUMITRESCU *et al.* [24] reported a case of PAH induced by dasatinib, a tyrosine kinase inhibitor (TKI) that has proven to be a life-saving treatment in patients with chronic myelogenous leukaemia. Although TKIs are usually well tolerated, these agents nonetheless exhibit systemic toxicity [24–28]. Pulmonary complications, in particular pleural effusions, have been reported more frequently with dasatinib use compared with other TKIs [25]. In addition, isolated case reports have suggested that PAH may be a potential complication of dasatinib use [24, 26, 27]. On April 18, 2011, the French drug regulatory agency AFSSAPS revealed that 13 cases of pulmonary hypertension had been identified in dasatinib-treated patients in France [28]. These cases are currently being investigated further and the agency has made it a point of emphasis that prescribers should monitor for the possible development of pulmonary hypertension in dasatinib-treated patients [28]. As reported by DUMITRESCU *et al.* [24], such cases of pulmonary hypertension occur after several months of exposure and may be, at least in part, reversible. This suggests a direct and specific effect of dasatinib on the pulmonary vasculature. Although clinical improvement was generally observed after withdrawal of dasatinib, some patients remained symptomatic and showed persistent haemodynamic impairment several months after discontinuation of this agent [28]. Clearly, further studies are needed in order to better understand dasatinib-induced pulmonary hypertension in humans.

In order to obtain additional important clinical data and also improve reporting of adverse drug effects in the future, the conducting of more so-called ''pragmatic'' trials could be invaluable. Such trials serve to further evaluate therapeutic approaches (both investigative and established) by testing the impact of pharmacological interventions in cohorts of patients deemed more representative of those encountered in day-to-day clinical practice. When performed properly, these trials can

*Université Paris-Sud, Faculté de Médecine, Kremlin-Bicêtre, #Assistance Publique–Hôpitaux de Paris, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Béclère, Clamart, ¶INSERM U999, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, and +Dept of Cardiopulmonary Medicine, Cochin Hospital, University Paris Descartes, Paris, France.

CORRESPONDENCE: M. Humbert, Service de Pneumologie, Hôpital Antoine Béclère, 157 rue de la Porte de Trivaux, 92140 Clamart, France. E-mail: marc.humbert@abc.aphp.fr

come up with unforeseen benefits as well as unforeseen adverse effects of new treatments [29, 30]. In any case, one must re-emphasise the need to declare all side-effects of drugs to local pharmacovigilance agencies and pharmaceutical companies, which should themselves regularly examine and, where necessary, update their practices. This should lead to periodically revised recommendations for a better and safe use of drugs as needed. Whistleblowers should intervene when the systems in place fail to accurately and effectively inform and/or react when a risk has been identified.

STATEMENT OF INTEREST

Statements of interest for M. Humbert and G. Simonneau can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

REFERENCES

1 Wikipedia. Whistleblower. http://en.wikipedia.org/wiki/Whistleblower Date last accessed: April 25, 2011.
2 Gurtner HP. Pulmonary hypertension, ''plexogenic pulmonary arteriopathy'' and the appetite depressant drug aminorex: post or propter? *Bull Europ Physiopath Resp* 1979; 15: 897–923.
3 Pouwels HM, Smeets JL, Cheriex EC, *et al.* Pulmonary hypertension and fenfluramine. *Eur Respir J* 1990; 3: 606–607.
4 Brenot F, Hervé P, Petitpretz P, *et al.* Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 1993; 70: 537–541.
5 Abenhaim L, Moride Y, Brenot F, *et al.* Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 335: 609–616.
6 Connolly HM, Crary JL, McGoon MD, *et al.* Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; 337: 581–588.
7 Simonneau G, Fartoukh M, Sitbon O, *et al.* Primary pulmonary hypertension associated with the use of fenfluramine derivatives. *Chest* 1998; 114: Suppl. 3, 195S–199S.
8 Delcroix M, Kurz X, Walckiers D, *et al.* High incidence of primary pulmonary hypertension associated with appetite suppressants in Belgium. *Eur Respir J* 1998; 12: 271–276.
9 Humbert M, Deng Z, Simonneau G, *et al.* BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. *Eur Respir J* 2002; 20: 518–523.
10 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
11 Souza R, Humbert M, Sztrymf B, *et al.* Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J* 2008; 31: 343–348.
12 Boutet K, Frachon I, Jobic Y, *et al.* Fenfluramine-like cardiovascular side-effects of benfluorex. *Eur Respir J* 2009; 33: 684–688.
13 Frachon I, Etienne Y, Jobic Y, *et al.* Benfluorex and unexplained valvular heart disease: a case-control study. *PLoS One* 2010; 5: e10128.
14 Weill A, Païta M, Tuppin P, *et al.* Benfluorex and valvular heart disease: a cohort study of a million people with diabetes mellitus. *Pharmacoepidemiol Drug Saf* 2010; 19: 1256–1262.
15 Mullard A. Mediator scandal rocks French medical community. *Lancet* 2011; 377: 890–892.
16 Humbert M, Segal ES, Kiely DG, *et al.* Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007; 30: 338–344.
17 Lavelle A, Sugrue R, Lawler G, *et al.* Sitaxentan-induced hepatic failure in two patients with pulmonary arterial hypertension. *Eur Respir J* 2009; 34: 770–771.
18 Hoeper MM. Liver toxicity: the Achilles' heel of endothelin receptor antagonist therapy? *Eur Respir J* 2009; 34: 529–530.
19 Hoeper MM, Olsson KM, Schneider A, *et al.* Severe hepatitis associated with sitaxentan and response to glucocorticoid therapy. *Eur Respir J* 2009; 33: 1518–1519.
20 Corris PA, Langleben D. The Achilles heel of endothelin receptor therapy for pulmonary arterial hypertension. *Eur Respir J* 2010; 35: 460–461.
21 Lee WT, Kirkham N, Johnson MK, *et al.* Sitaxentan-related acute liver failure in a patient with pulmonary arterial hypertension. *Eur Respir J* 2011; 37: 472–474.
22 Galiè N, Hoeper MM, Gibbs JS, *et al.* Liver toxicity of sitaxentan in pulmonary arterial hypertension. *Eur Respir J* 2011; 37: 475–476.
23 Galiè N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.
24 Dumitrescu D, Seck C, ten Freyhaus H, *et al.* Fully reversible pulmonary arterial hypertension associated with dasatinib treatment for chronic myeloid leukemia. *Eur Respir J* 2011; 38: 218–220.
25 Bergeron A, Rea D, Levy V, *et al.* Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. *Am J Respir Crit Care Med* 2007; 176: 814–818.
26 Rasheed W, Flaim B, Seymour J. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukemia. *Leuk Res* 2009; 33: 861–864.
27 Mattei D, Feola M, Orzan F, *et al.* Reversible dasatinib-induced pulmonary arterial hypertension and right ventricle failure in a previously allografted CML patient. *Bone Marrow Transplant* 2009; 43: 967–968.
28 Agence française de sécurité sanitaire des produits de santé. Sprycel© (dasatinib): risque d'hypertension arterielle pulmonaire – Lettre aux professionels de santé. www.afssaps.fr/Infos-de-securite/Lettres-aux-professionnels-de-sante/Sprycel-R-dasatinib-risque-d-hypertension-arterielle-pulmonaire-Lettre-aux-professionnels-de-sante Date last modified: April 18, 2011. Date last accessed: April 25, 2011.
29 Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008; 337: a2390.
30 Ware JH, Hamel MB. Pragmatic trials – guides to better patient care? *N Engl J Med* 2011; 364: 1685–1687.