Drug-induced heart valve disease: a blind spot for cardiologists

ABSTRACT

- **Exposure to *benfluorex* (Mediator°), a drug marketed in France from 1976 to late 2009, caused hundreds of deaths, in particular from heart valve disease.**

- **Very few cases of heart valve disease due to Mediator° were reported before the drug was withdrawn from the French market, but many cases now known to be due to Mediator° were detected before late 2009.**

- **Before the withdrawal of Mediator°, many cardiologists attributed these drug-induced valve disorders to other causes, often rheumatic heart disease, even though rheumatic fever had long since become very rare in France.**

- **Servier, the company that used to market Mediator°, and the French Health Products Agency were late in informing healthcare professionals of its probable, and then established, effects on heart valves.**

- **For decades, French cardiology textbooks did not specifically describe drug-induced heart valve disease. Yet reports of heart valve disease linked to the use of Mediator°-like amphetamine appetite suppressants had been published in the scientific literature since the late 1990s.**

In France, exposure to *benfluorex* (Mediator°), a drug marketed from 1976 to 2009, harmed thousands of patients and killed hundreds by inducing pulmonary arterial hypertension (PAH) and/or heart valve disease (1). This disaster was brought to light thanks to the tenacity of Irène Frachon, a pulmonologist from Brest (1,2). With a few notable exceptions such as Georges Chiche in Marseille, cardiologists as a group played no major role in revealing this link, despite their front-line role in diagnosing heart valve disease with echocardiography (2,3). When cardiologists diagnosed heart valve disease, to what extent did they consider a link with *benfluorex*?

Drug-induced heart valve disease misattributed to other causes

Cases of *benfluorex*-related heart valve disease had in fact been diagnosed before the drug's market withdrawal in late 2009, but they had been attributed to other causes. This is suggested by the timing of the 6743 cases of heart valve disease linked to *benfluorex* that were reported to the French pharmacovigilance system or pharmaceutical companies (4). For example, among over 2800 cases of heart valve disease diagnosed before 2010 and subsequently linked to *benfluorex*, only 30 reports were submitted before this date and mentioned *benfluorex* (3,4).

Many cardiologists had not considered a link with benfluorex. A survey, conducted between 2012 and 2015 and described in a thesis in the field of history and sociology of science, explored the practices of French cardiologists involved in the care of *benfluorex*-exposed patients (**a**)(2). This qualitative study did not involve a representative sample of the total population of cardiologists in France. About two-thirds of the 173 cardiologists who completed the survey said they remembered having had consultations with patients taking *benfluorex* before the disaster became public. Most of these cardiologists reported that before 2009 (the year Mediator° and other *benfluorex*-containing products were withdrawn from the French market), they had never suspected a link with a drug when they detected heart valve disease. Furthermore, few cardiologists spontaneously mentioned medication as a possible cause of heart valve disease (2).

Often diagnosed as rheumatic heart disease by cardiologists. When the cardiologists who responded to this survey detected heart valve disease before 2009-2010, they diagnosed rheumatic heart disease (valve damage subsequent to acute rheumatic fever) three times more often than drug-induced heart valve disease (2). According to an article published in a specialised cardiology journal in 2014 (all quoted excerpts in this article are our translations), "*before 2009, and even now*", cardiologists have often mistaken the drug-induced heart valve disease they observed for rheumatic heart disease and, when surgery was performed, descriptions of excised valves referred to "*presumed acute rheumatic fever*" (5). For example, Marie-Christine Malergue, a cardiologist who has been a member of the expert panel on *benfluorex* for the French National Office for Compensation for Medical Accidents (ONIAM) since 2014, reported that she

a- *The author of the thesis sent a questionnaire to over 4000 of the 6000 cardiologists practising in France between 2012 and 2015. 173 completed questionnaires were received and included in the thesis, 72 of which had been collected in 2012 and 101 in 2014-2015 (ref 2).*

had previously been "*convinced that these cases of heart valve disease* [linked to Mediator°] *were degenerative (which does not really mean much) or, more often, rheumatic heart disease*" (2,6).

Despite the rarity of rheumatic fever in high-income countries. The incidence of acute rheumatic fever in high-income countries has declined since World War II (5). *Prescrire* reported in 1990 that locally acquired acute rheumatic fever had virtually disappeared in France (7). The proportion of cases of heart valve disease due to rheumatic heart disease has fallen markedly since the 1970s (2). Meanwhile, the incidence of drug-induced heart valve disease has increased since the 1960s, especially since the market introduction of amphetamine appetite suppressants (2,5,6).

After the Mediator° disaster was brought to public attention, it was calculated that there was a less than 0.2% chance of heart valve disease being rheumatic heart disease, when detected in a person exposed to *benfluorex* and born in France in 1960 (8). According to a 2013 article, valve disease can only reasonably be diagnosed as rheumatic heart disease in a patient with a documented episode of acute rheumatic fever, generally during childhood (9).

Reports of drug-induced heart valve disease since the 1960s. The charges brought against the drug company Servier in the Mediator° trial include concealing some of the drug's adverse effects, while the French Health Products Agency is accused of failing to inform patients and healthcare professionals of these effects, and taking too long to withdraw the drug from the market (10). Although specific information about the effect of *benfluorex* on heart valves was lacking, drug-induced heart valve disease had already been described, and there were reasons to suspect *benfluorex* might have this effect.

The first article to mention a link between heart valve disease and a drug, namely the ergot-derived antimigraine drug *methysergide*, was published in the 1960s (6). The first article indicating a link between heart valve disease and fenfluramines was published in 1997 in the *New England Journal of Medicine,* and involved patients taking *fenfluramine* combined with *phentermine* (2,6). That same year, marketing authorisation for *dexfenfluramine* and *fenfluramine*, both marketed by Servier and both suspected of damaging heart valves, was suspended in France and revoked in the United States (2,11).

Benfluorex, also marketed by Servier, was described in the 1970s as chemically similar to *fenfluramine* (12,13). *Prescrire* mentioned its chemical similarity to *fenfluramine* and *dexfenfluramine* in the 1990s (14). In 2003, *Prescrire* reported that a case of heart valve disease linked to the use of *benfluorex had been* published in detail in Spain (15). In 2006, *Prescrire* expressed surprise that a 2005 French pharmacovigilance review on *benfluorex* had not looked at heart valve disease, given its similarity to *fenfluramine* and the cases of heart valve disease observed with *fenfluramine* (16).

Differences between cardiologists in their knowledge of Mediator° and their prescribing behaviour. Some of the cardiologists surveyed for the above-mentioned thesis were unaware of Mediator°'s authorised indication: mainly as an adjunct in the treatment of diabetes. More than three-quarters of the cardiologists surveyed mentioned diabetes, but one-quarter thought it was indicated for weight loss, whereas this was an off-label use. Few cardiologists reported having prescribed Mediator°. Twelve of the cardiologists surveyed reported they did not know that *dexfenfluramine*, a drug similar to *benfluorex*, had been withdrawn from the market in 1997 (2).

Other cardiologists in the study were more knowledgeable. About one-third of them had deprescribed *benfluorex* at least once before 2009 due to its lack of efficacy and potential harm due to its similarity to *dexfenfluramine*, or after they had read *Prescrire* (2). The thesis does not specify whether these particular cardiologists had reported or even detected heart valve disease in patients exposed to *benfluorex*.

To further illustrate that it was possible to suspect *benfluorex* in cases of heart valve disease before late 2009, the first case in a patient taking *benfluorex* alone was reported to the French pharmacovigilance system in 1999 (by the cardiologist Georges Chiche in Marseille), and the first case report describing heart valve disease linked to Mediator° (reported to the Toulouse Regional Pharmacovigilance Centre) was published in 2006 (1-3).

Why drugs were overlooked as the cause of valve disease

The cardiologist and ONIAM expert Marie-Christine Malergue referred to her own past difficulty with attributing heart valve disease to a drug as "*diagnostic wandering*" (6). Some of the reasons for this difficulty, also experienced by other cardiologists, were general factors, such as shortcomings in the pharmacology education received by doctors, trivialisation of the use of Mediator° while it was marketed, and alleged concealment of the drug's true nature, one of the charges brought against Servier (6,17). But other reasons relate specifically to the field of cardiology and cardiologists' education.

Belated description of drug-induced heart valve disease in textbooks. The author of the thesis states that, for about 40 years, cardiologists could not have learned to distinguish between rheumatic heart disease and drug-induced heart valve disease from the cardiology textbooks she examined (2). In the textbooks available before 2009, signs later considered specific to drug-induced heart valve disease were initially described as features of rheumatic heart disease, and later as resembling rheumatic heart disease (2,5,6).

Cardiologists themselves have described how this led to "*the transmission of distorted academic knowledge*" (5). For example, on describing the

knowledge transmitted by leading authorities in the field, Marie-Christine Malergue cites "*Professor Acar's famous phrase: 'mitral stenosis with fusion is the hallmark of acute rheumatic fever' (…) therefore any mitral disease with commissural fusion was rheumatic heart disease, until it was discovered that drug-induced mitral valve disease also led to commissural fusion*" (6).

Drug-induced heart valve disease was not therefore described specifically in cardiology textbooks, despite the development and improvement of echocardiography, a first-choice technique for detecting valve disease, during the 1970s to 1990s (2,5). Cardiologists continued to interpret the drug-induced heart valve disease they observed on echocardiography as a variant of a previously common condition, rheumatic heart disease, rather than the emergence of a new condition caused by a drug (2).

Knowing the specific echocardiographic signs. Another difficulty is due to the similarities shared by rheumatic and drug-induced valve disease, and the fact that the signs of drug-induced valve disease "*are not always detectable on transthoracic echocardiography*" (2,5,6,8). There are however echocardiographic differences between the two conditions. According to Marie-Christine Malergue, although it takes time to learn, "*the features* [of heart valve disease due to Mediator®] *become highly specific and fairly easily identifiable over time*" (**b**)(6).

It was only after 2009 that features specific to drug-induced valve disease were described as such in cardiology textbooks (2). The author of the thesis found references to drug-induced heart valve disease, and *benfluorex* as a causative agent, in textbooks dating from 2012 and 2014. They contributed to the belated standardisation of knowledge about drug-induced heart valve disease due to *benfluorex*. This knowledge was also disseminated by the French Society of Cardiology and the French National Authority for Health, but only after news of the disaster became public (2).

Scientific publications not seen or not remembered. Various reasons have been put forward as to why drug-induced heart valve disease was overlooked. The case reports published in the *New England Journal of Medicine* in 1997 and 1998, describing heart valve disease linked to fenfluramines, went "*relatively unnoticed*" in France, because fenfluramines were immediately withdrawn from the market worldwide after their publication (2,5,6,11).

Another postulated reason is that healthcare professionals remembered the high risk of pulmonary arterial hypertension (PAH) associated with amphetamine appetite suppressants, but not the risk of valve damage (5,6). The risk of PAH had already been shown as of the 1960s and 1970s with *aminorex* (not marketed in France), before it was described in the 1990s with *dexfenfluramine* and *fenfluramine* (6).

Yet another possible reason relates to the fact that many of the cardiologists in the survey reported that they did not often read medical or scientific journals (**c**)(2).

Biased continuing education. Many of the cardiologists surveyed reported that they often or very often kept informed by reading medical journals distributed free of charge by pharmaceutical companies (2). In addition, many of them often relied on pharmaceutical companies for continuing education. Fewer than 20 of the 173 respondents said they never accepted offers of funding from pharmaceutical companies. Conference attendance was funded by pharmaceutical companies in a great many cases (2).

The influence of pharmaceutical companies on cardiologists was not the focus of this thesis (2). However, the established link between industry gifts and health professionals' decisions means that it is worth considering corporate influence as one of the reasons for overlooking the first warnings about drug-induced heart valve disease, and those associated with *benfluorex* in particular (2,18-20).

Seek out reliable sources of information, and remember to consider the patient's medication

Almost all of the cardiologists who took part in this survey reported asking patients what drugs they were taking (2). But when heart valve disease was detected, they rarely suspected that a drug was responsible. The number of cases of heart valve disease reported in patients exposed to *benfluorex* suggests that any one cardiologist would have seen only a small number of patients with valve disease caused by this drug. But the fact that these cases were attributed on a massive scale to another cause cardiologists considered probable is disquieting, and shows that drugs were a "blind spot" for the profession at the time.

b- *The cardiologist Marie-Christine Malergue mentions several echocardiographic features specific to the heart valve disease induced by Mediator®: "restriction of the mitral leaflets and subvalvular apparatus, thickened appearance of the aortic cusps with "rolling" of the free edges, central aortic regurgitation with a diastolic cusp defect, "drumstick" appearance of the mitral leaflets, commissural fusion, rare calcification (…). Histological analysis of an excised valve is the gold standard for confirming drug-related heart valve disease but is rarely available, (…) endocardial fibrosis of the leaflets and chordae, preserved valve architecture, a fibrotic layer (…) as if the valve had been dipped in glue…" (ref 6).*

c- *The French Health Products Agency stated in early 1998 that "only a few cases of usually moderate left heart regurgitation" linked to fenfluramine or dexfenfluramine had been reported. However, 30 cases were reported in Belgium between late 1994 and mid-1997. In 1998, Prescrire mentioned the possibility that some cases in France may have been mistaken for rheumatic heart disease (ref 23).*

Patients exposed for too long. The failure to recognise the link between heart valve disease and Mediator° meant that these cases were not reported as suspected adverse drug reactions, pharmacovigilance organisations were slow to react, and patients were exposed to the drug for too long (2). A review of cases of heart valve disease linked to *benfluorex* reported up to 2015 showed that exposure to *benfluorex* continued after diagnosis of heart valve disease in 1861 cases, i.e. 29% of all the reports analysed. Half of these patients remained exposed for at least 27 more months (4).

Since this disaster came to light, the growing body of scientific literature on drug-induced heart valve disease has led to an increase in the proportion of applicants that ONIAM has recognised as victims of Mediator° (**d**)(9,6,21). Yet many cardiologists surveyed between 2012 and 2015 for the thesis on the Mediator° disaster still considered that too much had been made of it in the media, and even that its importance as a public health issue had been exaggerated (2).

When confronted with a health problem, particularly one with no known cause, healthcare professionals would do well to consider and systematically investigate the possibility of toxicity, especially drug toxicity, so as to avoid exposing the patient to the suspected drug any longer, if possible, and to limit these harmful effects in other patients (22).

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***d-** Victims still struggle to have their disease recognised when seeking compensation, especially when the claim is dealt with in the courts (ref 2).*

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