Drug-induced valve disease and considerations of benefit versus risk

Jeffrey S. Borer* 

The Howard Gilman, Institute for Heart Valve Diseases, State University of New York Downstate Medical Center, 635 Madison Avenue, New York, NY 10022

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This editorial refers to ‘Frequency of drug-induced valvular heart disease in patients previously exposed to benfluorex: a multicentre prospective study’, by C. Tribouilloy et al., on page 3580

Data from epidemiological studies, and a single randomized trial, have plausibly suggested that a variety of amphetamine-related molecules can cause valvular morphological lesions and variable degrees of valvular dysfunction.1–10 Though a causal relationship has not been unequivocally proven, cellular mechanisms have been defined that may account for such a relationship.11,12 However, early in the experience with the phentermine–fenfluramine combination that sensitized the medical community to such problems,1 the frequency of valve involvement probably was markedly overstated. Indeed, at the height of the concern, when several very small series suggested that the majority of exposed patients developed valve disease, five patients (as large as some of the published series) were referred to me after moderately long exposure to seek evidence of valve disease; none was apparent in any. Importantly, the involved drugs all were approved for specific benefits, e.g. weight reduction for morbidly obese persons who might suffer from orthopaedic, psychological, cardiovascular, and other deprivities in part because of their body weight, and diabetes control for patients in whom glucose metabolic abnormalities could have several unwanted and potentially preventable consequences. In all such situations, the appropriateness of the therapies must be determined on the basis of a judgement of putative benefits vs. putative risks. Since the benefits and the risks of the amphetamine-related therapies are intrinsically different, the relationship between benefit and risk is impossible to quantify rigorously and must be based on the judgement of experienced observers. Therefore, it is essential to quantify, as precisely as possible, the benefits and the risks. Benefits often are reasonably quantified by randomized, appropriately controlled trials enabling comparison of groups receiving and not receiving therapy. Even here, however, the effort to preclude potential confounders that could lead to ambiguous interpretation of randomized trials often leads to inclusion only of patients who may not be fully representative of the larger populations that may use the therapies. Thus, it can be useful to supplement clinical trials with observational studies or ‘real-world’ trials not rigorously excluding all confounders to understand benefits more completely. Conversely, trials designed to test for benefits generally are deficient in defining risks. The primary reason is that, by the time a therapy is sufficiently developed so that it can undergo trials for regulatory approval, i.e. Phase III studies, earlier smaller studies must reassure manufacturers, investigators, and regulators that adversities are not likely to outweigh benefits. Consequently, adverse events and, most importantly, serious adverse events that are potentially importantly morbid or lethal, are relatively uncommon in Phase III clinical trials, precluding credible quantitative comparison of adversity vs. benefit.

For example, in the area examined by the study by Tribouilloy et al., i.e. the frequency of valve abnormalities associated with benfluorex,11 a prospective randomized positively controlled trial previously was performed involving 846 diabetic patients randomly allocated to treatment (423 benfluorex, 423 pioglitazone) for ~1 year.7 The impact on cardiac valve function was prospectively considered, but only 683 patients had at least one baseline and one post-baseline echocardiogram, essential for rigorously testing the impact of therapy on valves, and only 615 (73%) of these were evaluable for morphology and function on at least one valve (310 benfluorex, 305 pioglitazone). The presence of baseline echocardiograms was very important: prior to therapy, approximately half the patients had morphological valve abnormalities and 84% had at least mild valve dysfunction (largely regurgitation). Without the pre-therapy data, on-therapy results would have been very difficult to interpret. During the study, new morphological valve abnormalities occurred in only 12 patients (8 benfluorex, 4 pioglitazone), resulting in wide confidence intervals and lack of statistically significant differences; new valve regurgitation or regurgitation increasing by at least one grade during study was more convincingly different (82 (27%) benfluorex vs. 33 (11%) pioglitazone, P<0.0001) but, importantly, these emergent findings were overwhelmingly mild. Only five patients [two receiving benfluorex and three receiving pioglitazone (P = 0.64)] reached echocardiographic grade 2 regurgitation and none manifested moderate or severe regurgitation or any valvular stenosis. Tribouilloy and his co-workers also undertook a

* Corresponding author. Tel: +1-212-289-7777, Fax: +1-212-426-4353, Email: canadad45@aol.com

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comparative study, involving diabetic patients already exposed to benfluorex, which was begun after marketing cessation and aimed to assess the prevalence of valve abnormalities among those previously exposed. All French physicians were invited to join the study, which required referring patients who received benfluorex for echocardiography. Unfortunately, no pre-therapy echocardiogram was available, precluding assessment of treatment-emergent valve abnormalities. The study included 376 patients who had been exposed to benfluorex for \( \sim 3 \) years (mean); 376 diabetic patients who had not received the drug during the same interval were selected as controls. Propensity matching was also undertaken, reducing the population for comparison to 293 patients in each group. The critical element of study design, that all study subjects needed to have been referred by their physicians for an echocardiogram, clearly was a potential source of bias, but, importantly, the results of this comparative study were relatively similar to those of the prospective randomized trial: benfluorex exposure was associated with \( \sim 33\% \) regurgitant valves, the great majority mild and none severe. Though prospective randomized superiority trials of therapeutic efficacy have important limitations for assessing adversities, other options exist. Non-inferiority trials can be performed, to define precisely the relationship of adversities with one strategy vs. another, exemplified by the ongoing Food and Drug Administration (FDA)-mandated PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen) trial of relative cardiovascular adversities among non-steroidal anti-inflammatory drugs, but such studies can be ethically difficult to justify, quite large to provide adequate power, and present
recruitment difficulties. Alternatively, observational studies of consecutively treated patients can provide a ‘real-world’ worst-case estimate of adversity. Within the latter category, a rich source of potential data is offered by the growing development of large insurance databases, including the massive national health service databases available in several countries. The study by Tribouilloy et al. is an example of the latter. Though it includes the patients in the earlier study by Tribouilloy et al. and required voluntary referral of all included patients for echocardiography, additional non-diabetic patients were identified in the database and included, for a total of 835 exposed patients. Mean exposure duration again was 3 years, but was longer (mean 55 months) in the 6.8% of the population in whom morphological valve abnormalities ‘specific’ for benfluorex exposure were found, consistent with the morphological findings in the prospective, randomized trial. The likelihood of valve abnormality was, in fact, directly related to exposure duration, as well as to female gender and smoking, and inversely related to body mass index (BMI). Of the 57 patients who manifested morphological abnormalities, most had trace or mild regurgitation, and approximately one-third were moderate, but none was severe.

When added to the earlier studies relating valve disease to amphetamine-related drugs and specifically to benfluorex, the study of Tribouilloy et al. is consistent with several tentative conclusions. First, the frequency of valve abnormalities is relatively modest and most abnormalities are no more than mild. However, since the earlier national database study of Weill et al. suggested that patients exposed to the drug require valve surgery at a rate that is 3-fold that of unexposed patients, it is not possible to conclude that exposures never result in serious adverse events. Nonetheless, the rate of valve surgery with this drug is very low, estimated at $\approx 0.028\%/\text{year}$. Secondly, though the natural history of valve lesions associated with drug exposure remains undefined, the similarity of the prevalence in the 1 year randomized trial and the 3 year database study suggests that disease proceeds relatively slowly. Thus, perhaps regular echocardiographic assessment could identify patients who respond adversely to the drug before irreversible damage occurs, enabling many patients to gain benefit with acceptable risk. This inference would depend, of course, on the natural history of the condition and, particularly, on the likelihood that recovery is possible after exposure cessation, a possibility that has been suggested. Moreover, the risk markers identified in the present study (exposure duration, lower BMI, female gender, and smoking) further suggest that patients predisposed to respond with valve alterations may be identifiable and, if the drug were available, could be discouraged from its use.

The overarching conclusion from these data is that precise delineation of cardiovascular risk is critical if decisions about acceptability of risk/benefit relationships are to be made for non-cardiovascular drugs with potential cardiovascular risks. Thus, for example, if prior experience suggests the possibility of valve disease with a drug that has potentially important non-cardiac benefits, development of new drugs of related structure should involve plans for pre-therapy, as well as on-therapy, cardiac assessment so that patients are not inappropriately denied the benefits of potentially useful therapies.

**Conflict of interest:** J.S.B. has consulting and investigator relationships with multiple drug and device manufacturers. However, for the purposes of this editorial, only one is of particular relevance. He is a consultant to Servier Laboratoires, Paris, France, manufacturer of benfluorex, although he has never consulted on this particular drug.

**References**