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Letter to the Editor

Pharmacovigilance: Learnings from pergolide

As the debate about what constitutes good pharmacovigilance practice swells, I would like to reflect on what has been learnt from studies with the anti-Parkinson drugs, pergolide and cabergoline and consider what impact this learning has on pharmacovigilance practice.

In January of this year, two publications in the NEJM reported findings of an increased risk of valvular heart disease (VHD) in people receiving clinical doses of pergolide or cabergoline [1,3]. These publications come some 10 years after the withdrawal of Fen-Phen, the anti-obesity drug, which was withdrawn for causing the same pathology. As Brian Roth summarises in his NEJM commentary [5], we can now probably safely say that 5HT2b receptor activation is a key culprit in mediating pergolide and cabergoline-induced valvular pathology.

It now becomes very important to define what actions we should take as a result of this emergent biology. One should certainly incorporate screening for 5HT2b agonist activity into the development of new drug candidates. However, the question that then naturally arises is what decision can be made if indeed a new drug candidate possesses activity at this receptor. The recent NEJM papers allow us to make other important observations that are relevant here. Firstly, they highlight that some drugs possessing 5HT2b receptor activity, such as lisergide, do not cause VHD. Secondly, they show that some patients can quite safely take pergolide and cabergoline without developing this condition. Indeed, subsequent letters to NEJM Editor [1,4] confirm this. Thus, these observations clearly define that 5HT2b receptor activity, while a key factor for mediating VHD, is likely only to mediate risk, not causation. There are likely to be many other factors involved in the development of this complex condition, such as individual genotype and other pharmacology. From these publications alone, the observation that VHD can be seen in patients not taking pergolide and cabergoline suggests that there are other contributing factors. Indeed, amantadine (a compound lacking 5HT2b activity) was reported in the NEJM paper by Schade et al. [3], to increase incidence of cardiac-valve regurgitation. Moreover, if we look beyond these recent publications, the wider literature reports in the order of 50 drugs that have associated incidence of VHD in human. Those drugs have diverse pharmacological properties, affecting more than 200 different proteins. Many of those proteins are known to reside in the heart valves. Although the evidence is not as compelling as for 5HT2b, these proteins could also be considered risk factors for VHD. Clearly there is a lot more to understand to clarify individual risk in patients taking these medications and further epidemiological and/or genotyping studies would help to validate the role of these proteins in triggering VHD in susceptible individuals. Thus, while it is prudent to include 5HT2b in drug screens, at this stage, one cannot justify making go-no-go decisions on any observation that any new drug candidate possesses activity at this molecular target for VHD.

The greatest opportunity in this advance of our molecular understanding of drug-induced VHD resides in being able identify potential risk in new drug candidates and then tailor pharmacovigilance studies to looking specifically for early signs of VHD induced by such molecules. Once we know where to attribute risk in any new candidate molecule, one can focus on harnessing all the clinical knowledge surrounding that potential adverse event to design more informed pharmacovigilance studies. Thus, how might our advancing clinical understanding of VHD be used to help the early identification of possible drug-induced VHD? Analysis of the medical literature and label data sheets for the marketed drugs known to cause VHD allows us to assess the possible utility of known signs of VHD. For example, two of the most commonly reported side effects of drugs known to cause VHD are dizziness and dyspnoea. This is consistent with their recognition as clinical signs of VHD. On the surface, the lack specificity of both dyspnoea and dizziness might seem to preclude their use in this setting. However, in combination with other factors, signals can be sharpened. Thus, any increase in the incidence of dyspnoea and dizziness by a new drug with a known molecular risk (indicated by its known interaction with 5HT2b) might be considered biologically significant, particularly if one could eliminate other causes of dizziness or dyspnoea and build in a consideration of other known environmental risk factors such as smoking and age or any knowledge of the molecular risk of any co-prescribed medicines in those patients. Much of this information is known. Having the capability to harness it in order to gather a deep clinical understanding about VHD will allow signals to be detected in a scientifically driven way and allows further risk to be evaluated more systematically across different patient groups.

Identifying molecular risk factors such as 5HT2b has been a great advance but that advance will only make impact on patient safety if we use that knowledge, together with the wealth of clinical knowledge to define robust pharmacovigilance plans. In a recent press conference, the FDA set a firm objective to strengthen the 'science that supports its medical product safety system at every stage of the product life cycle from pre-market testing and development through post-market surveillance and risk management'. I believe this case study provides a good illustration of how we might begin to approach this. The endeavour cannot be without significant commitment on behalf of the regulatory and industry communities, but in reality, this is no different to the effort that goes into understanding the clinical condition that the drug is intended to treat.

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