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CORRESPONDENCE

Amfepramone does not cause primary pulmonary hypertension

To the Editor:

The article by ABRAMOWICZ *et al.* [1] should show the first case of primary pulmonary hypertension (PPH) associated with the use of amfepramone (diethylpropion), an anorectic drug, and BMPR2 mutation. In my opinion, the relationship between amfepramone and the rise of PPH in this case is unproven.

BMPR2 mutation is related to PPH without use of anorectics. Autosomal dominant germline mutations in BMPR2 have been identified in ~55% of familial cases and in 25% of patients with negative family history [2].

There are three different types of anorectic drugs: fenfluramines (fenfluramine and dexfenfluramine), serotonin releasers; noradrenergic agents (*i.e.* amfepramone), noradrenaline releasers; and sibutramine, a noradrenaline and serotonin reuptake inhibitor [3].

It is true that BMPR2 mutations combined with exposure to fenfluramine derivatives increase the risk of developing PPH, but the mechanisms of the lesions, with any probability, are associated with the serotoninergic pathway [4–6]. Amfepramone is a noradrenaline releaser and not a serotonin stimulant.

However, after ABENHAIM *et al.* [7] showed a correlation between anorectics and PPH, a second much larger study was performed in the USA [8]. This study showed that: 1) only the use of fenfluramines for $\geqslant$6 months remained associated with the diagnosis of PPH; and 2) when only recent users of fenfluramines (*i.e.* those using them in the 6 months preceding diagnosis) were counted as exposed, the associated adjusted odds ratios from the logistic regression that reflected the directions of associations were higher.

Therefore: 1) Abramowicz′s patient had a mutation, which could, *per se*, cause PPH; 2) there are no data that amfepramone causes PPH; 3) a direct relationship between noradrenergic pathway and PPH has never been supposed; 4) the exposure to anorectic drug was too short; and 5) the period between amfepramone use and the onset of symptoms is too long.

Considering this case, if we use the common algorithms for the assessment of adverse drug reactions [9–11], the result is unlikely. It is very difficult to be able to suppose that the use of amfepramone could have any relationship, even indirectly, in the rise of primary pulmonary hypertension.

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From the authors:

We appreciate G. Di Sacco′s comments and acknowledge the limitations of the single-case association we report [1]. However, we believe it is worthy of attention. Our patient is interesting as she took amfepramone only, without fenfluramine, which is uncommon. Amfepramone-only cases are indeed so scarce that the study by ABENHAIM *et al.* [2] and similar studies could not confirm or rule out an association with primary pulmonary hypertension (PPH).

G. Di Sacco is being merely semantic when quoting a BMPR2 mutation *per se* as a cause of PPH. Indeed, the penetrance of the mutation is so low, 10–20%, that we must conclude that some other factors are necessary for PPH to develop.

Our patient developed PPH after use of amfepramone on a short-term basis, as is reported for BMPR2 mutation carriers after fenfluramine [3]. Indeed, you expect to find some BMPR2 mutation carriers in PPH patients without anorexigen use. However, the frequency of BMPR2 mutations observed in PPH after fenfluramine use was much larger than in the general population [2].

This favours a model where fenfluramine is a possible trigger of primary pulmonary hypertension in BMPR2 mutation carriers. Our single-case observation is consistent with this model.

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