Fatal pulmonary arterial hypertension associated with phenylpropanolamine exposure

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CASE REPORT

Exogenous substances such as the appetite suppressant fenfluramine are known to be causally related to the development of pulmonary arterial hypertension (PAH). In these cases, the clinical course as well as the pulmonary vascular disease pathologically is indistinguishable from idiopathic PAH. Other exogenous substances, such as amphetamines, cocaine, and meta-amphetamines, have been considered to be potential risk factors for inducing PAH. SOPHIA (the study of pulmonary hypertension in America), in addition to confirming previous reports of a causal association between the appetite suppressant fenfluramine and PAH, unexpectedly found a significantly increased risk for the development of PAH with exposure to over-the-counter antiobesity agents containing phenylpropanolamine. The first case is reported of fatal PAH in a child heavily treated with cold remedies containing phenylpropanolamine, which, in addition to the results of SOPHIA, strengthens the hypothesis that phenylpropanolamine is a risk factor for the development of PAH.

SOPHIA (the study of pulmonary hypertension in America) unexpectedly found a significantly increased risk for the development of pulmonary arterial hypertension (PAH) with exposure to over the counter antiobesity drugs containing phenylpropanolamine.1 We report here a case of idiopathic PAH in a young boy who had a very high exposure to phenylpropanolamine in brompheniramine/phenylpro (Dimetapp, Wyeth Consumer Healthcare, Madison, New Jersey, USA) that strengthens this association of phenylpropanolamine and PAH.

CASE REPORT

A 7.5 year old boy was hospitalised with pneumonia seven days before his death in May 1999. On admission he was also noted to have thrombocytopenia, abdominal pain, and a history of two syncopal episodes with exertion the previous week. Echocardiography was remarkable for severe tricuspid regurgitation with an estimated pulmonary artery systolic pressure of 105 mm Hg. He also had significant right ventricular dysfunction, right ventricular hypertrophy, and a flat interventricular septum consistent with severe PAH. An ECG showed right axis deviation and right ventricular hypertrophy. Chest radiography was remarkable for bilateral peripheral infiltrates, enlarged central pulmonary arteries, and right ventricular enlargement. His complete blood cell count was remarkable for a white cell count of 21 500 per μl with a differential of 64% polymorphonuclear cells, 22% lymphocytes, and 11% monocytes. His haemoglobin was 13.2 g/dl, haematocrit 37% and a platelet count of 6 mm in the first hour. His family history was unremarkable—that is, there was no family history of pulmonary hypertension, connective tissue disease, congenital heart defects, or haematological abnormalities. The patient died during cardiac catheterisation. On necropsy, he was found to have grade III Heath-Edwards pulmonary vascular changes and endarteritis consistent with severe PAH.

Medical history was remarkable for frequent visits to his paediatrician: at least 40 outpatient visits from December 1992 through December 1998. These visits were for upper respiratory tract infections, sinusitis, and otitis media. He was treated with multiple courses of antibiotics, as well as with Dimetapp containing phenylephrine in brompheniramine on at least 35 occasions—that is, at least five times a year. The Dimetapp was used for a minimum of four days with each course of treatment, for a cumulated exposure of at least four months with a total cumulative phenylpropanolamine dose of at least 5 g.

DISCUSSION

Classic and severe pulmonary arteriopathy developed in a young child with a history of chronic ingestion of Dimetapp containing phenylephrine in brompheniramine. Phenylephrine in brompheniramine is a synthetic sympathomimetic amine that was commonly found in appetite suppressants and in cold and cough remedies until it was removed from the market in 2000 due to the risk of haemorrhagic stroke associated with phenylpropanolamine exposure. Case reports,2 as well as the case controlled haemorrhagic stroke study reported in 2000,3 support the role of phenylpropanolamine in appetite suppressants, as well as possibly in cold and cough remedies, as an independent risk factor for haemorrhagic stroke. Dimetapp subsequently was re-released with pseudoephedrine replacing the phenylpropanolamine. Exogenous substances such as the appetite suppressants fenfluramine and dexfenfluramine are known to be causally related to the development of PAH.4 In these cases, the clinical course as well as the pulmonary vascular disease...

Abbreviations: PAH, pulmonary arterial hypertension; SOPHIA, study of pulmonary hypertension in America
pathologically is indistinguishable from cases of idiopathic PAH in which no apparent cause can be determined. Other exogenous substances, such as amphetamines and L-tryptophan, and agents such as cocaine and meta-amphetamines, have been considered to be potential risk factors for inducing PAH. SOPHIA, in addition to confirming previous reports of a causal association between the appetite suppressant fenfluramine derivatives and PAH, also showed a significant association between PAH and over-the-counter antiobesity agents containing phenylpropanolamine. We report the first case of fatal PAH in a child heavily treated with cold remedies containing phenylpropanolamine, which, in addition to the results of SOPHIA, strengthens in our view the hypothesis that phenylpropanolamine is a risk factor for the development of PAH.

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