Letter to the Editor | http://dx.doi.org/10.3349/ymj.2011.52.5.869 pISSN: 0513-5796, eISSN: 1976-2437 | Yonsei Med J 52(5):869-870, 2011 | YMJ

RE: Pulmonary Hypertension Associated with Use of Phentermine?

Ed J. Hendricks[1] and Richard B. Rothman[2]

[1]Center for Weight Management, 2510 Douglas Boulevard, Suite 200, Roseville, California;
[2]Belite Medical Center, 3923 Old Lee Highway, Suite 61A, Fairfax, Virginia, U.S.A.

Received: March 30, 2011
Accepted: May 27, 2011
Corresponding author: Dr. Ed J. Hendricks, Center for Weight Management, 2510 Douglas Boulevard, Suite 200, Roseville, California 95661, USA.
Tel: 916-772-1191, Fax: 916-773-0498
E-mail: edhendricks@surewest.net

· The authors have no financial conflicts of interest.

Dear Sir,

Recently Bang, et al.[1] reported a case of a 29 year-old obese woman who was hospitalized with pulmonary arterial hypertension (PAH) and a history of having taken phentermine hydrochloride 37.5 milligrams daily for 35 days. Since common etiologies of PAH were excluded by the patient's history, examination procedures, and hospital course, the authors suggest this is the first case of phentermine-induced PAH. We suggest instead this is a case of idiopathic pulmonary arterial hypertension (IPAH) rather than PAH secondary to therapeutic phentermine.

The authors suggest, based on one case report, that phentermine mono-therapy produces the same increase in incidence of PAH previously seen in patients treated with fenfluramine mono-therapy and in patients treated with a combination of fenfluramine and phentermine. However, a survey of 95 European cases of PAH by Abenhaim, et al.[2] found that of the 30 patients that had a history of taking anorexic agents, 24 had taken a fenfluramine, but none had taken phentermine. Moreover, Rich, et al.,[3] in a North American prospective study in which 579 patients with pulmonary hypertension were studied, found that the odds ratios for an association of pulmonary hypertension and fenfluramine to be 7.5, an odds ratio for a similar association for phentermine of 0.6, and concluded that fenfluramines, but not phentermine are risk factors for PAH. Since fenfluramines were taken off-market in 1997 there have been no subsequent reports linking PAH or IPAH to anorectic medicines. Hence the literature does not support the contention of Bang, et al. that phentermine mono-therapy has caused an increased incidence of secondary PAH similar to that caused by fenfluramine.

Physicians in other countries may not be aware that phentermine has long been the most widely used anti-obesity medicine in the United States. A recent survey of United States obesity treatment specialists found that for 97%, phentermine was their first choice among the available anti-obesity drugs.[4] The majority of physicians surveyed reported they prescribed phentermine long-term in any patient provided the medicine was effective and produced no intolerable side effects. The longest duration of phentermine therapy reported in the literature has been forty years with no serious adverse effects.[5] The survey confirmed that most specialists have employed doses higher than the maximum dose of 37.5 milligrams daily recommended by the U.S. Food and Drug Administration (FDA)-approved label. There are other reports of the safe use of higher doses.[4,6-9] Thus, in spite of continued widespread use of phentermine for longer durations and higher doses than rec-

ommended by the FDA-approved label, there is no report of an increased incidence of pulmonary hypertension due to phentermine in the U.S. The incidence of IPAH is approximately one case per million per year in the general population. Since phentermine is so widely used, it is reasonable to expect an occasional patient diagnosed with IPAH will coincidently have taken phentermine.

PAH and IPAH are characterized by an increase in pulmonary vascular resistance due to progressive obliteration of pulmonary arterioles, which in turn are induced by pulmonary arteriole smooth muscle cell proliferation and arteriolar vasoconstriction with accompanying inflammation and thrombosis. One hypothesis to explain fenfluramine-induced PAH is that fenfluramine releases 5-hydroxytryptophan (5-HT) via the 5-HT transporter (SERT), and that the increased concentration of plasma 5-HT provokes pulmonary vasoconstriction and pulmonary arterial smooth muscle cell proliferation.[10] However, recent data raises questions about this hypothesis.[11] 5-HT is also thought to play a central role in the pathogenesis of IPAH. Bang, et al. imply that phentermine is active as a serotonin transporter producing increases in 5-HT levels, and therefore has the potential to cause PAH. However, Rothman, et al.[12] have shown previously that phentermine has considerably less potent SERT substrate activity, and is considerably less effective in elevating plasma 5-HT compared to fenfluramine, and compared to the commonly abused stimulants methamphetamine and 3,4-methylenedioxymethamphetamine. In another study Rothman, et al. found that phentermine produced minimal increases in 5HT, insufficient to provoke pulmonary arteriolar smooth muscle proliferation.[13] These studies suggest that it is unlikely phentermine could induce PAH by the mechanism proposed by Bang, et al.

In summary we suggest that phentermine, after 52 years of widespread use has proven to be both effective and safe. Historically, an association between phentermine monotherapy and PAH has been suggested but confirming evidence has not appeared. Currently, while we have few effective pharmacologic agents to include in obesity treatment, patients and physicians are fortunate to have phentermine available. Bang, et al. are correct in noting the absence of long-term, dose ranging, clinical trials with phentermine; we concur that such trials are needed and should be conducted. Meanwhile, while we await trials, phentermine treatment should not be withheld from the obese because of fear of theoretical but unproven adverse effects.

REFERENCES

1. Bang WD, Kim JY, Yu HT, Cho SS, Jang JY, Oh CM, et al. Pulmonary hypertension associated with use of phentermine. Yonsei Med J 2010;51:971-3.
2. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med 1996;335:609-16.
3. Rich S, Rubin L, Walker AM, Schneeweiss S, Abenhaim L. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. Chest 2000;117:870-4.
4. Hendricks EJ, Rothman RB, Greenway FL. How physician obesity specialists use drugs to treat obesity. Obesity (Silver Spring) 2009;17:1730-5.
5. Frank A. The long-term management of obesity with continuing pharmacotherapy. Obes Res 2004;12:1821-7.
6. Douglas A, Douglas JG, Robertson CE, Munro JF. Plasma phentermine levels, weight loss and side-effects. Int J Obes 1983;7:591-5.
7. Haddock CK, Poston WS, Foreyt JP, DiBartolomeo JJ, Warner PO. Effectiveness of Medifast supplements combined with obesity pharmacotherapy: a clinical program evaluation. Eat Weight Disord 2008;13:95-101.
8. Hendricks EJ, Greenway FL. A study of abrupt phentermine cessation in patients in a weight management program. Am J Ther 2011;18:292-9.
9. Rothman RB. Treatment of obesity with "combination" pharmacotherapy. Am J Ther 2010;17:596-603.
10. MacLean MR, Dempsie Y. Serotonin and pulmonary hypertension--from bench to bedside? Curr Opin Pharmacol 2009;9:281-6.
11. Rothman RB, Cadet JL, Dersch CM, McCoy MT, Lehrmann E, Becker KG, et al. Altered gene expression in pulmonary tissue of tryptophan hydroxylase-1 knockout mice: implications for pulmonary arterial hypertension. PLoS One 2011;6:e17735.
12. Rothman RB, Baumann MH. Methamphetamine and idiopathic pulmonary arterial hypertension: role of the serotonin transporter. Chest 2007;132:1412-3.
13. Zolkowska D, Rothman RB, Baumann MH. Amphetamine analogs increase plasma serotonin: implications for cardiac and pulmonary disease. J Pharmacol Exp Ther 2006;318:604-10.