Iron Supplementation in ACE Inhibition as a Treatment for Cough: Is It Really Inoffensive?

To the Editor:

I enjoyed learning from the article by Lee et al.1 about the possible relationship between ACE-inhibitor cough and the NO synthase (NOS) system. During the past decade, there has been some accumulation of data relating NOS to cardiovascular diseases and endocrinic effects. This enzyme, which is usually expressed in skeletal muscle and vascular endothelium, when knocked out in eNOS−/− mice has been shown to cause not only hypertension but also insulin resistance and hyperlipidemia, metabolic derangements not found in other hypertension model mice and rats.2 Sustained hyperinsulinaemia in rats was shown to cause insulin resistance, hypertension, and impairment of eNOS activity. Further inhibition of eNOS by a specific inhibitor in these rats increased the severity of their systolic blood pressure (from 134 to 158 mm Hg with insulin alone and to 175 mm Hg with extra eNOS inhibition).3 A further study by Duffy et al.4 published a few months ago, found in patients with coronary disease, a decrease in forearm resistance of vessels when treated by an iron chelator (deferoxamine). This effect was abolished by eNOS inhibitor and was not achieved by nitroprusside or other antioxidants.

In light of these new publications and other accumulative data in the past few years relating to major role of eNOS in cardiovascular morbidity and possibly the groundstone for the understanding of the etiology of the metabolic and vascular X syndrome, one may ponder about the advantages of giving hypertensive patients mega doses of iron or any other NOS inhibitors as a treatment or in research while increasing the risk of coronary heart disease.

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Response

Dr Lev has asked if there is anything to comment on regarding the association between NO synthase (NOS) and hypertension. As far as we know, the association between in vivo NO production by NOS and hypertension has been demonstrated in some animal studies, but there is a lack of evidence about the association in humans.1 Despite this fact, we understand that there can be some anecdotal concerns on inhibition of NOS that may bring about increase in blood pressure.

However, as we have pointed out in our report, there were no significant changes in blood pressure in our subjects with hypertension by iron supplementation, and no other significant side effects, including cardiovascular ones, were noted with the medication. We think that the amount of iron our subjects received was not large enough to bring about any detrimental effects. Although if higher doses of iron will be needed, concern on increment of long-term cardiovascular effects with iron accumulation may be substantial as we do not know the appropriate dose of iron for complete abolishment of ACE inhibitor-induced cough yet (near-complete disappearance occurred in 3 among 10 subjects). But that is a subject that needs further studies.

A more important point is that although the inhibition of cough by iron supplementation was substantial in our study, the association between this phenomenon and NOS inhibition still needs further confirmation. We think that this sort of concern should be brought about after further studies have revealed the true mechanism behind this phenomenon, as there may well be other explanations of it.

Dr Lev has also asked us to comment on the ethical point of view regarding the “high” dose of iron to patients with hypertension. As we have pointed out above and in our paper, we have reviewed the changes in blood pressure in our patients with hypertension and found out no significant changes in any of them. Although it is true that the dose of iron we administered is higher than the daily requirement, we do not consider it to be of a “mega” dose that can lead to significant accumulation of iron. In fact, as we have revealed in our paper, the ferritin levels of our hypertensive patients increased slightly after the 4-week administration of iron, but the change did not show any statistical significance.

Furthermore, our study was ethically approved by the ethical committee of our institute, not to mention the fact that all of our subjects gave informed consent agreeing to inclusion in our study.

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