Antioxidant Effect of Lercanidipine

To the Editor:

We were surprised by the effects of lercanidipine reported by Taddei et al1 on the plasma antioxidant capacity, with the ferric reducing (antioxidant) power (FRAP) value increasing from 305.0±31.3 to 435.7±142.9 μmol/L. Typical FRAP values for human plasma usually range from 800 to 1200 μmol/L.2 The apparently low baseline values may be related to the use of ascorbic acid or Trolox3,4 (rather than a solution of ferrous ions) as calibrator without correcting for their stoichiometric factor, which is 2.0 in the FRAP assay. However, it is more difficult to explain the almost 50% increase in plasma FRAP values after lercanidipine treatment. We have found that lercanidipine itself has no in vitro antioxidant effect in the FRAP assay, but it does undergo extensive first-pass metabolism, and some metabolites could have a direct antioxidant effect. The peak plasma concentration (C max) of S-lercanidipine is, at most, around 15 μmol/L,3,4 and although the C max for total metabolites was >40 times higher than that of the parent drug,5 this still amounts to <1 μmol/L of total metabolites. Even if each molecule of metabolite could scavenge several radicals, it is highly unlikely that this would have any appreciable direct effect on the plasma FRAP value. Similarly, captopril has virtually no contribution to plasma FRAP in vivo, despite having in vitro antioxidant activity.6

In contrast, plasma ascorbic acid at normal plasma concentrations (40 to 60 μmol/L) contributes about 15% of the total FRAP value. Bilirubin and α-tocopherol each contribute about 5%, plasma proteins 10%, and uric acid around 60% to the FRAP value.2 Lercanidipine is unlikely to cause a substantial change in any of these parameters. Renal function was not affected according to the serum creatinine data (for which units are presumably μmol/L rather than mg/dL as presented).1

Antioxidant effects have been shown with some lipophilic calcium antagonists such as lercanidipine, but this is probably related to their accumulation within membranes or by virtue of their pharmacological effects on calcium channels, rather than a major effect on the total plasma antioxidant power.2,3 Amlodipine showed antioxidant activity in hepatic microsomal membranes which appeared to be a nonreceptor-mediated effect due to the biophysical interactions with the membrane lipid bilayer.9

We might speculate that the apparent change in FRAP could be an artifact, as several antioxidants are unstable ex vivo, especially in EDTA plasma.10 Pre-analytical loss could have resulted in low results being obtained in basal samples, rather than high levels in post-treatment samples. Blood samples might also have been taken some time after the infusions of vitamin C when plasma ascorbic acid concentrations were still elevated. The large SD values of 10% to 30% for the mean plasma FRAP also suggest perhaps some pre-analytical change or analytical problem.

These comments do not detract from the main finding in the study and the elegant demonstration of how treatment with lercanidipine can reverse the endothelial dysfunction associated with hypertension. However, they do serve to illustrate how it can be difficult to interpret apparent changes in some parameters in the absence of a control group.

Brian Tomlinson
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

Iris F.F. Benzie
Ageing and Health Section
School of Nursing
The Hong Kong Polytechnic University


Response

The issues raised by Tomlinson and Benzie with regard to our paper1 fall into 2 areas: (1) criticism of low plasma ferric reducing antioxidant power (FRAP) in our hypertensive population and (2) lack of explanation for lercanidipine-induced increase in plasma FRAP.

Concerning the first issue, we have consistently found low plasma levels of FRAP in patients with essential hypertension.2,3 This is probably related to the presence of increased oxidative stress in patients with essential hypertension, since in healthy subjects (n=40) we found greater plasma FRAP values (685±343 μmol/L) as compared with hypertensive patients.3 We are aware that these values are still lower than those quoted by Tomlinson and Benzie (normal plasma values of FRAP ranging from 200 to 1200 μmol/L).4 However, apart from the methodological points raised by Tomlinson and Benzie, it must be underlined that their values were detected in Chinese individuals, a population not comparable to Caucasians.

On the second issue, it is quite unexpected that lercanidipine has no in vitro effects on FRAP. The FRAP assay is based on the ferric/ferrous reaction and an antioxidant such as vitamin C can increase FRAP by releasing an electron and undergoing oxidation.4 It is worth noting that the dihydropyridine ring can also release an electron and undergo oxidation, a mechanism similar to that exerted by vitamin C.5 Therefore a direct effect of lercanidipine on FRAP would be expected.

However, a conceivable negative effect of acute exposure to lercanidipine in vitro conditions does not necessarily exclude a positive effect of chronic administration of lercanidipine in humans (ie, in totally incomparable clinical conditions). Dihydropyridine compounds, including lercanidipine, have a well-established direct antioxidant activity by accumulation within membranes.5,6 In line with this possibility, in our study we...
observed a clear decrease in specific markers of oxidation such as plasma lipoperoxides and isoprostanes.1 When markers of oxidation decrease, this usually indicates a depressed production of oxygen free radicals. If the production of oxygen free radicals decreases, this causes a parallel decrease in the amount of oxidized antioxidants, since antioxidants can reduce free radical concentration by undergoing oxidation. Thus, it is very likely that lercanidipine-induced increase in plasma FRAP values could be a logical and expected consequence of the direct effect of lercanidipine on oxygen free radical production.

Stefano Taddei  
Agostino Virdis  
Lorenzo Ghiadoni  
Daniele Versari  
Guido Salvetti  
Armando Magagna  
Antonio Salvetti  
Department of Internal Medicine  
University of Pisa  
Pisa, Italy

Antioxidant Effect of Lercanidipine
Brian Tomlinson and Iris F.F. Benzie

Hypertension. 2003;42:e10-e11; originally published online September 2, 2003;
doi: 10.1161/01.HYP.0000091372.14174.89
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/42/4/e10

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/