Questioning the Cardioprotective Effect of Bromocriptine Treatment

To the Editor:
I read with interest the paper “Centrally Mediated Effects of Bromocriptine on Cardiac Sympathovagal Balance” by Drs Franchi, Lazzeri, Barletta, Ianni, and Mannelli, which was published in July 2001.1 The authors cite a report by Przuntek et al published in 1992 that suggested that bromocriptine treatment lessened mortality in patients with Parkinson disease. The authors presumed that this putative cardioprotective effect can be related to withdrawal of cardiac sympathetic activity leading to fewer life-threatening ventricular arrhythmias. Unfortunately, the authors failed to mention that since 1992, long-term studies in Australia2 and France3 have failed to replicate the findings cited in the Przuntek paper. The Australian and French studies were of 10-year durations and found no evidence of a cardioprotective effect from bromocriptine.

Over the past 25 years, bromocriptine has been studied in the treatment of clinical indications such as acromegaly, hyperprolactinemia, postpartum lactation suppression, cocaine craving, and diabetes mellitus, in addition to Parkinson disease. Rather than a cardioprotective effect, bromocriptine shares with other ergot alkaloids the property of vasoconstriction, with the potential for serious cardiotoxicity.3 Over the years, investigations have shown that bromocriptine has active metabolites4 that persist in the body for up to 120 hours. Hydroxylated metabolites of bromocriptine have been found to be effective in reducing prolactin in rats.5 Dr. Franchi and colleagues did not investigate pharmacologically active bromocriptine metabolites.

Finally, medical journals have recognized the need for objectivity in the publication of clinical research findings.11 In reply to the letter by Dr D.J. Petro referring to our article “Centrally-mediated effects of bromocriptine on cardiac sympathovagal balance” published in Hypertension, July 2001,1 I would like to point up the following issues:

1. The design and the results of the study were chiefly aimed at evaluating the effects (peripherally and centrally, as well) of acute bromocriptine administration on the cardiac sympathovagal balance. The influence of long-active metabolites of the drug lies outside our specific purpose. Moreover, the references cited by Dr Petro (Reavill et al, 1980,2 Valente et al, 19975) referred only to data obtained in experimental animals.
2. The potential role for serious tissue injuries caused by the vasoconstrictive effects of bromocriptine (Watson et al, 1992;4 Przuntek et al) we evaluated the drug effects after an acute and not chronic administration and with healthy subjects rather than in disease conditions.” In the same section, we also observed that, “The increase in LF component, observed after acute oral bromocriptine, seems to be in disagreement with those arrived at by these authors. In the same section, we also observed that, “The increase in LF component, observed after acute oral bromocriptine, seems to be in disagreement with those arrived at by these authors. The increase in LF component, observed after acute oral bromocriptine, seems to be in disagreement with those arrived at by these authors. The increase in LF component, observed after acute oral bromocriptine, seems to be in disagreement with those arrived at by these authors.

Denis J. Petro
Arlington, Virginia

been advanced by us in the conclusions. We invite Dr Petro to carefully reread the arguments discussed in the article. Furthermore, in the Australian and French studies, the cardioprotective effect of bromocriptine was not the aim of the investigation. In particular, Montastruc et al,10 made a comparison between levodopa and bromocriptine administration, particularly with respect to overall mortality, and in the cohort by Hely et al,9 the most common cause of death was pneumonia. Thus, I think that no conclusion can nor should be drawn about the cardioprotective effect of bromocriptine on the basis of those studies.

4. Finally, about the need to include an acknowledgment section, I want to bring to your attention the following items: (a) the research was fully performed in our Institution (Department of Internal Medicine, University of Florence); (b) only institutional research funds were employed and no other sources of financial assistance were provided; and (c) bromocriptine is a well-known and freely available drug. Moreover, Davidoff et al,10 who recently strengthened the need of objectivity, were referring only to clinical trials. We did not perform a clinical trial, and in such a situation, as Dr Davidoff said, “the Authors can stand behind the published results.” Therefore, so can we.

Franco Franchi
Dipartimento di Medicina Interna
Università degli Studi di Firenze
Florence, Italy


Response

We are responding to several points made by Dr Majima in regard to our recent article in Hypertension.1

(1) Dr Majima wanted us to provide an explanation for the –7 mm Hg drop in mean blood pressure (MBP) from the pretreatment period to Week 1 (Figure 1 in our article). This request was surprising, because (a) the difference was not statistically significant, (b) it’s usual to observe such a variation in BP within a few days after surgically installing the telemetry device, as previously reported,2 and (c) by the end of Week 1 and 2 we were expecting instead a 40- to 50-mm Hg increase in BP as reported by Dr. Majima’s group.3

As we stated in our article, MBP was 115±3 mm Hg in normal Brown Norway rats compared with 118±3 mm Hg in Brown Norway Katholiek (BNK) rats. Hence, there is also no difference between the 2 strains in terms of BP, similar to Dr Majima’s data.3 Our BP values were about 12 to 14 mm Hg higher than Dr Majima’s, but that’s normal because we measured BP in the United States with our equipment, whereas Dr Majima’s were done in Japan with their equipment.

(2) As we indicated in the article, Dr Majima visited our laboratory in an attempt to reconcile the different findings between our study and his, but we were not able to do so. We included him in the acknowledgments as a way of expressing our gratitude for his generous assistance. Thus, there is no letter to this effect, as we merely wished to acknowledge his courtesy to us. It does not seem logical to me that it would be necessary for us to first write to Dr Majima and ask for his permission to thank him for helping us. Moreover, the Editorial Board of Hypertension never asked us to provide them with any documentation regarding this matter.

In our article we stated “…(1) normal BN rats were given a subcutaneous infusion of Ang II or high salt diet alone or combined with iCatibant… and (2) BNK rats were given a subcutaneous infusion of a nonpressor dose of Ang II or high salt diet… we were unable to reproduce any of their findings or those of Madeddu et al.” There was a mistake, and we should have stated “(1) normal BN rats were given high salt diet alone or combined with iCatibant… and (2) BNK rats were given a subcutaneous infusion of a nonpressor dose of Ang II or high salt diet... we were unable to reproduce any of their findings or those of Madeddu et al.” Dr Majima did not participate with us in the protocol dealing with the effect of icatibant infusion on the pressor effect of Ang II in normal BN rats. Dr Majima stated that the original results were confirmed while participating with us on a protocol involving BNK rats infused with vehicle or subpressor dose of Ang II. That is wrong, because when we administered a subpressor dose of Ang II, systolic blood pressure was slightly higher in BNK rats compared with rats given vehicle; however, direct arterial MBP in awake and restrained rats was similar in both groups. For that reason, we opted for telemetry for feasibility and explained the rationale for its use in our paper.
Questioning the Cardioprotective Effect of Bromocriptine Treatment
Denis J. Petro

_Hypertension_. 2002;39:e16-e17

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 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/39/2/e16

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/