In this issue of Hypertension is an article from several investigators in Stockholm, primarily of the Lundberg and Weitzberg groups at the Karolinska Institutet, which addresses one aspect of the potential use of orally ingested nitrite ions as therapies in humans for various diseases or, perhaps in food or food supplements, for some general improvement in cardiovascular or metabolic parameters. The most significant finding of this work is that pretreatment with a proton pump inhibitor, esomeprazole, to minimize gastric acidification blunts the measured effects of 0.3 mg/kg of sodium nitrite on lowering systolic blood pressure by about ±6 mm Hg maximally. These findings are consistent with previous work from this group on the importance of the entero-salivary pathway of nitrate reduction to nitrite and then the nonenzymatic metabolism of nitrite in the acidic stomach to form various nitrite derivatives, including NO itself. Further, recent work from Pinheiro et al in Sao Paolo, Brazil, has shown similar effects in administration of sodium nitrite to rats.

Thus, these results are relevant to the potential confounding effect of proton pump inhibitor use in studies of nitrate/nitrite administration in food or as drugs to patients or populations. Moreover, there is a recent literature suggesting that proton pump inhibitors can increase the likelihood of adverse cardiovascular events or even mortality in at-risk populations by 25% to 100%. Thus, the hypothesis implicit in the current article is that proton pump inhibitor administration blunts beneficial effects of usual nitrate and nitrite consumption in food, including the effects of certain drugs used in these patient groups. Although these studies are not all consistent, the effects are large enough to cause some clinical concerns and the impetus to search for the possible mechanisms involved. The new studies demonstrate that the effect of esomeprazole is not because it changes the NO signaling pathway but, unlike the results from rat studies, does not suggest involvement of S-nitrosothiol formation in the antihypertensive effect.

Less clear-cut results from this new work relate to 2 other important questions related to potential nitrite/nitrate pharmacological uses: (1) whether there are marked differences in the effects of oral versus infused ions and (2) whether lowering of blood pressure is to be expected and its role, if any, in the potential beneficial effects of these agents. The new report surprisingly finds that the effect on systolic blood pressure is limited to the oral doses and that intravenous doses that achieve comparable blood levels of nitrite ions do not have such an effect, suggesting some important biochemical activation in the stomach or portal circulation. However, one should be aware that the total oral dose, which is expected to be almost entirely absorbed, seems to be >10 times that of the maximal total infused nitrite dose. Perhaps, technical problems related to the blood measurements, such as the kinetics of dose responses, have contributed to this apparent paradox. Indeed, many other studies have shown robust cardiovascular effects of infused nitrite in normal volunteers and those with various illnesses.

Of related importance is the question of whether nitrite ions should be expected to affect blood pressure at physiological or pharmacological doses. At higher doses, adverse effects such as methemoglobin formation and precipitous circulatory changes can occur. The literature on pharmacological studies of nitrate and nitrite administration, in human beings and in animal models, is inconsistent, with a wide range of results with respect to blood pressure changes. The consensus seems to be that small decreases in systolic blood pressure may be expected in human populations. (In the presence of cell-free hemoglobin, such as in acute or chronic hemolytic anemias, these effects are likely to be blunted.) However, in view of the fact that NO seems to primarily increase blood flow in most tissues and organs studied and that measured blood pressure (systolic, diastolic, or mean arterial) is a composite of changes in peripheral vascular resistance and cardiac output and is subject to many other agonists and antagonists—some of which may change rapidly in compensation for pharmacological administrations, the complexity of clinical results reported up to now is perhaps not surprising. Further, some effects of NO may be immediate, whereas others, such as increases in numbers or sizes of tissue microvessels and mitochondria, may only occur with chronic administration.

Equally important is the fact that potential benefits of circulating NO or nitrite ions may include other processes, such as inhibition of platelet reactivity and blood clotting, or even complex metabolic pathways, rather than primarily blood pressure lowering. For these reasons, continued clinical studies of nitrate and nitrite administration in humans, at a range of doses and routes of administration, are necessary to

See related article, pp 23–31

Acid Test for Nitrite Pharmacology
Barbora Piknova, Alan N. Schechter

© 2016 American Heart Association, Inc.
Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.116.08222
DOI: 10.1161/HYPERTENSIONAHA.116.08222

Acid Test for Nitrite Pharmacology
Barbora Piknova, Alan N. Schechter

See related article, pp 23–31

In this issue of Hypertension is an article from several investigators in Stockholm, primarily of the Lundberg and Weitzberg groups at the Karolinska Institutet, which addresses one aspect of the potential use of orally ingested nitrite ions as therapies in humans for various diseases or, perhaps in food or food supplements, for some general improvement in cardiovascular or metabolic parameters. The most significant finding of this work is that pretreatment with a proton pump inhibitor, esomeprazole, to minimize gastric acidification blunts the measured effects of 0.3 mg/kg of sodium nitrite on lowering systolic blood pressure by about ±6 mm Hg maximally. These findings are consistent with previous work from this group on the importance of the entero-salivary pathway of nitrate reduction to nitrite and then the nonenzymatic metabolism of nitrite in the acidic stomach to form various nitrite derivatives, including NO itself. Further, recent work from Pinheiro et al in Sao Paolo, Brazil, has shown similar effects in administration of sodium nitrite to rats.

Thus, these results are relevant to the potential confounding effect of proton pump inhibitor use in studies of nitrate/nitrite administration in food or as drugs to patients or populations. Moreover, there is a recent literature suggesting that proton pump inhibitors can increase the likelihood of adverse cardiovascular events or even mortality in at-risk populations by 25% to 100%. Thus, the hypothesis implicit in the current article is that proton pump inhibitor administration blunts beneficial effects of usual nitrate and nitrite consumption in food, including the effects of certain drugs used in these patient groups. Although these studies are not all consistent, the effects are large enough to cause some clinical concerns and the impetus to search for the possible mechanisms involved. The new studies demonstrate that the effect of esomeprazole is not because it changes the NO signaling pathway but, unlike

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Molecular Medicine Branch, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD.
Correspondence to Alan N. Schechter, Molecular Medicine Branch, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, 9000 Rockville Pike, Bldg 10, Room 9N312, Bethesda, MD 20892, E-mail aschecht@helix.nih.gov or Barbora Piknova, Molecular Medicine Branch, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, 9000 Rockville Pike, Bldg 10, Room 9N312, Bethesda, MD 20892, E-mail piknovab@niddk.nih.gov
establish whether these agents can enter medical use beyond the still well-tested injunction that we should all eat maximal amounts of green leafy vegetables and related foods.

However, it must be remembered that nitrate and nitrite administration (green box in upper right of Figure) are always competing with levels of these ions from dietary ingestion and from synthesis from arginine by the 3 NO synthase enzymes. Furthermore, as also shown in the Figure, several oxidative and reductive pathways are now known to interconvert these species and NO itself. Clearly, developing a pharmacology for nitrite will not be simple.

Sources of Funding

This study was supported by National Institutes of Health.

Disclosures

A.N. Schechter is a coinventor on a patent to the National Institutes of Health for therapeutic uses of nitrite ions. The other author reports no conflicts.

References


Acid Test for Nitrite Pharmacology
Barbora Piknova and Alan N. Schechter

Hypertension. 2017;69:13-14; originally published online October 31, 2016;
doi: 10.1161/HYPERTENSIONAHA.116.08222

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/69/1/13

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/