Inorganic Nitrate for Blood Pressure Lowering?

To the Editor:

Kapil et al. reported that potassium nitrate ingestion lowers blood pressure (BP) in human subjects. Peak plasma nitrate (NO₃⁻) and nitrite (NO₂⁻) concentrations increased up to 35- and 4-fold, respectively. Increased plasma cGMP levels suggests that the depressor action of nitrate is mediated by the NO/cGMP cascade, respectively. Increased plasma cGMP levels suggests that the depressor action of nitrate is mediated by the NO/cGMP cascade, presumably after reduction of NO₃⁻ to NO₂⁻ and its reduction to NO. Using ¹⁵NO₃⁻, we provided evidence for ¹⁵NO₃⁻ to ¹⁵NO₂⁻ reduction in humans. Similar results were obtained for ¹⁵NO₃⁻ and S-[¹⁵N]nitroso-N-acetylcysteine ethyl ester in male rabbits (Figure).

Oral administration of isosorbide dinitrate (ISDN) (0.13 mmol daily) and pentaerythritol tetranitrate (PETN) (0.25 mmol daily) increased moderately plasma concentration of NO₃⁻ (1.2- and 1.4-fold, respectively) and NO₂⁻ (2.2- and 1.8-fold, respectively) in young subjects.3

Organic nitrates (R-ONO₂), inorganic salts of NO₃⁻ and NO₂⁻, and thionitrites (R-SNO) seem to lower BP through similar mechanisms, but their pharmacokinetics and pharmacodynamics differ considerably. The single dose of 0.32 to 0.45 mmol NO₃⁻/kg is up to 60 times the mean daily endogenous NO synthesis rate in healthy subjects and up to 36 times the therapeutic ISDN and PETN dose.3 NO₃⁻ required for BP lowering results in very high and long-lasting extracellular and intracellular NO₃⁻ and NO₂⁻ concentrations, which may, in turn, exert toxic, mutagenic, and carcinogenic effects. NO₃⁻ and NO₂⁻ are actively transported in various cells including the nephron.2 High millimolar tissue concentrations of NO₃⁻ may induce acidosis in mammalian cells.4 Also, elevation of methemoglobin, oxidative stress, and glutathione consumption may ensue.

Ingestion of NO₃⁻-rich foods or cheap NO₃⁻ salts for NO-mediated BP lowering is tempting. However, ingestion of large NO₃⁻ amounts carries serious risks because of the unpredictable harmful potential of the NO₃⁻/NO₂⁻/NO/NH₃ system. Before NO₃⁻ supplementation can be applied clinically for BP lowering, efficacy and safety needs to be demonstrated in large clinical

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**Figure.** A–C, Pharmacokinetics of orally administered ¹⁵NO₃⁻ (A), ¹⁵NO₂⁻ (B), and S-[¹⁵N]nitroso-N-acetylcysteine ethyl ester (S¹⁵NACET) (C) to rabbits. D, BP effect of intravenous S¹⁵NACET in a rabbit. Data are mean±SD from duplicate analyses (A and B) in one rabbit each or from three rabbits (C).
studies. However, these trials cannot exclude an increased NO$_3^-$/NO$_2^-$-induced cancer risk.$^5$

Disclosures

None.

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5. Erdman SE, Rao VP, Poutahidis T, Rogers AB, Taylor CL, Jackson EA, Ge Z, Lee CW, Schauer DB, Wogan GN, Tannenbaum SR, Fox JG. Nitric oxide and TNF-$
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