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 (NO$_3^-$) and nitrite (NO$_2^-$) concentrations increased up to 35- and 4-fold, respectively. Increased plasma cGMP levels suggest that the depressor action of nitrate is mediated by the NO/cGMP cascade, presumably after reduction of NO$_3^-$ to NO$_2^-$ and its reduction to NO. Using $^{15}$NO$_3^-$, we provided evidence for $^{15}$NO$_3^-$ to $^{15}$NO$_2^-$ reduction in humans. Similar results were obtained for $^{15}$NO$_3^-$ and S-$^{15}$N-nitroso-N-acetylcysteine ethyl ester in male rabbits (Figure). Oral administration of isosorbide dinitrate (ISDN) (0.13 mmol daily) and pentaerythrityl tetranitrate (PETN) (0.25 mmol daily) increased moderately plasma concentration of NO$_3^-$ (1.2- and 1.4-fold, respectively) and NO$_2^-$ (2.2- and 1.8-fold, respectively) in young subjects.

Organic nitrates (R-ONO$_2$), inorganic salts of NO$_3^-$, 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 NO$_3^-$/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. NO$_3^-$ required for BP lowering results in very high and long-lasting extracellular and intracellular NO$_3^-$ and NO$_2^-$ concentrations, which may, in turn, exert toxic, mutagenic, and cancerogenic effects. NO$_3^-$ and NO$_2^-$ are actively transported in various cells including the nephron. High millimolar tissue concentrations of NO$_3^-$ may induce acidosis in mammalian cells. Also, elevation of methemoglobin, oxidative stress, and glutathione consumption may ensue. Ingestion of NO$_3^-$-rich foods or cheap NO$_3^-$ salts for NO-mediated BP lowering is tempting. However, ingestion of large NO$_3^-$ amounts carries serious risks because of the unpredictable harmful potential of the NO$_3^-$/NO$_2^-$/NO/NH$_3$ system. Before NO$_3^-$ supplementation can be applied clinically for BP lowering, efficacy and safety needs to be demonstrated in large clinical

Figure. A–C, Pharmacokinetics of orally administered $^{15}$NO$_3^-$ (A), $^{15}$NO$_2^-$ (B), and S-$^{15}$N-nitroso-N-acetylcysteine ethyl ester (SNACET) (C) to rabbits. D, BP effect of intravenous SNACET 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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