Inorganic nitrate ingestion decreases blood pressure and improves vascular compliance in healthy volunteers

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The endothelium has emerged as a key regulator of vascular homeostasis and its dysfunction has been identified as a key pathogenic phenomenon in cardiovascular disease. The hallmark of endothelial dysfunction is impaired endothelium-dependent vasodilatation: a response known to be mediated by nitric oxide (NO). Our previous studies have demonstrated that oral ingestion of inorganic nitrate inhibits the endothelial dysfunction caused by an ischaemia-reperfusion injury in the forearm of healthy volunteers. Ingestion of inorganic nitrate elevates blood and tissue levels of nitrite through bioconversion in the entero-salivary circulation, and then nitrite is converted to NO in the circulation, and it is this phenomenon that is thought to underlie the beneficial effects in humans.\(^1,2\) However, whether inorganic nitrate might improve endothelial function per se in the absence of a pathogenic stimulus is yet unknown.

All studies were approved by the local Research Ethics Committee. We conducted a randomised, double-blind, crossover study in 14 healthy volunteers to determine the effects of oral inorganic nitrate (8mmol KNO\(_3\) capsules, Martindale Pharmaceuticals, UK) versus placebo (8mmol KCl capsules, Martindale Pharmaceuticals, UK) on endothelial function. To determine endothelial function, flow-mediated dilatation (FMD) in response to reactive hyperaemia of the brachial artery was measured using ultrasound according to standard procedures,\(^3\) prior to and 3h following capsule ingestion. In addition, blood pressure (BP) was measured according to British Hypertension Society guidelines using a validated device (7051T, Omron Corporation, Japan) and pulse wave velocity (PWV) determined by assessment of waveforms between the carotid and femoral arteries using a Vicorder device (Vicorder, Skidmore Ltd, UK). Finally, blood and urine samples were collected for chemiluminescence analysis of plasma and urinary [nitrite] and [nitrate] prior to and 3h following capsule ingestion.

Inorganic nitrate supplementation had no effect on endothelial function in healthy volunteers (6.9±4.1% pre- to 7.1±4.0% post-KNO\(_3\)). Despite this, there was a significant elevation of plasma [nitrite] (0.4±0.1 \(\mu\)mol/L pre- to 0.7±0.2 \(\mu\)mol/L post-KNO\(_3\), \(p<0.0001\)), plasma [nitrate] (31.1±16.0 \(\mu\)mol/L pre- to 214.9±67.2 \(\mu\)mol/L post-KNO\(_3\), \(p<0.0001\)), urinary [nitrate] (0.2±0.1 \(\mu\)mol/L pre- to 0.5±0.4 \(\mu\)mol/L post-KNO\(_3\), \(p<0.0001\)) and urinary [nitrate] (1429.0±776.9 \(\mu\)mol/L pre- to 11410.0±8072.0 \(\mu\)mol/L post-KNO\(_3\), \(p<0.0001\)). In addition these changes in nitrate and nitrite were associated with a decrease in systolic BP (116.9±14.3mmHg pre- to 112.1±12.8mmHg post-KNO\(_3\), \(p<0.01\)) and PWV (6.5±0.5 m/s pre- to 6.2±0.4 post-KNO\(_3\), \(p<0.0001\)). In contrast KCl capsules had no effect on any of the parameters measured.

These findings demonstrate that although inorganic nitrate ingestion does not alter endothelial function per se, it does appear to improve blood flow, in combination with a reduction in blood pressure. It is likely that these changes are due to the production of NO that likely directly relaxes vascular smooth muscle and therefore decreases pulse wave velocity.

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References