Inhaled nitric oxide (iNO) is used to treat acute pulmonary hypertension and to improve pulmonary ventilation/perfusion relationships in critically ill adults and children. The effects of iNO have always been considered to be restricted to the lungs as it is metabolized before it leaves the pulmonary circulation. In volunteer studies no effects are seen in systemic haemodynamics. However, a recent study of the effects of iNO on phenylephrine-induced pulmonary hypertension in anaesthetized pigs found that iNO might have renal effects. In the control animals, where iNO was given to anaesthetised normal pigs, a marked diuresis was found and could not be accounted for by any changes in global haemodynamics.

We studied the renal effects of iNO in humans to determine if a similar effect occurred.

Methods and Results
Five healthy non-smoking male volunteers aged 18–41 yr and weighing 75–90 kg were studied. Approval was obtained from Central Oxford Research Ethics Committee and the subjects gave written consent. The experiment consisted of three 2-h phases: a control phase with subjects breathing room air normally, a middle phase breathing an NO/air mixture through a mask, and a second control phase breathing air normally.

Initially subjects voided their bladders, mean arterial pressure was measured and 150 ml water was drunk. After each hour, mean arterial pressure was measured, urine volume was recorded on voiding, urine was sampled and 150 ml water was drunk. In the middle of each phase blood samples were taken for plasma separation. Urine and plasma samples were frozen for later analysis for creatinine, sodium and potassium.

For the middle 2-h phase subjects were fitted with a leak-free face mask connected to a non-rebreathing valve. Nitric oxide (1000 vpm in N₂) was mixed with air to an inspired concentration of 40 vpm. The mixture was delivered at 12 litres min⁻¹ via reservoir bags and a reservoir tube. Inspired NO concentrations were monitored continuously with a chemiluminescence analyser.

On a separate day subjects returned for the control study, with the same plan, when air was breathed through the mask and apparatus during the middle phase.

Creatinine clearances and fractional and total sodium excretions were calculated for each 2-h phase using standard formulae. Urine volumes and mean arterial pressure were averaged for each of the 2-h phases.

Because of the large variation in urine volumes between subjects, volumes and calculated variables depending on them were corrected to relative values by dividing the values for a subject in a particular study period by the value obtained in the first control phase.
Variables were tested using a paired two-tailed ‘t’-test and differences were taken to be significant for P-values less than 0.05. No corrections were made for multiple comparisons.

The results are given in Table 1. Inhalation of nitric oxide increased urine volume which decreased after iNO was discontinued and was not seen in the control experiments. Absolute and fractional sodium excretion (FENa) remained unchanged during the nitric oxide phase, compared with a reduction in the control experiments. Creatinine clearance and arterial pressure did not change over time in both nitric oxide and control experiments.

Comment

These data suggest that in normal volunteers iNO is associated with a modest diuresis and a slight natriuresis. This is the first time that this has been reported in humans.

In the control experiment, urinary sodium and FeNa decreased with time, whilst urine output and creatinine clearance remained stable. This is probably because the subjects were adjusting to the constraints of drinking 150 ml water each hour. A longer period of controlled fluid intake before the study would have been preferable.

With nitric oxide, a diuresis was evident through the iNO phase. Urinary sodium and FeNa were maintained as iNO was inhaled. When compared to the progressive decrease observed in the control experiments, this suggests that iNO increases urinary sodium excretion and FeNa. The absence of a change in creatinine clearance implies that there was no change in glomerular filtration rate (GFR) and, with no change in mean arterial blood pressure, the global haemodynamics appear unaltered. The diuresis thus arose because of the natriuresis, and so the effects of iNO appear to be tubular in nature, affecting sodium resorption along the nephron, rather than vascular or glomerular. These findings are subtly different from those reported by Troncy and colleagues in pigs which suggested iNO was inducing changes in glomerular blood flow.

iNO cannot leave the lung in its native state and it is therefore unlikely that NO is having a direct effect on the kidney. Its principle metabolite, nitrate, has been shown to be a diuretic, but only at very high concentrations, far above those predicted for this study.

An alternative explanation would be for NO to be acting on the angiotensin converting enzyme (ACE) in the lungs. Small doses of angiotensin II that do not affect the arterial pressure have been shown to reduce total and fractional sodium excretion and urine volume without any change in GFR, and blockade of this system would result in the opposite effects, which is what we have observed here. So, if iNO was inhibiting ACE, angiotensin II levels would decrease to cause the observed results.

The nitric oxide donor sodium nitroprusside inhibits ACE in vitro, as does shear stress to blood vessel walls, both possibly through NO release. ACE itself has several cysteine residues whose thiol groups would be able to react with NO to modulate its activity. This would support an ACE inhibition theory, but in the absence of better data and without angiotensin II measurements, this is highly speculative, and the effects seen could equally be related to changes in anti-diuretic hormone levels.

This study used quite high concentrations of iNO to induce a modest change in renal salt and water handling. Both the mechanism and clinical relevance remain to be determined.

References

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