Evaluation of nitrogen dioxide scavengers during delivery of inhaled nitric oxide

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Summary
We have analysed the ability of three nitrogen dioxide absorbing materials (soda lime, noXon and zeolite) to act as nitrogen dioxide scavengers during delivery of inhaled nitric oxide. Different mixtures of gas were produced in a ventilator (Servo Ventilator 300) and passed through an inspiratory tube. Concentrations of nitrogen dioxide and nitric oxide were measured in the distal part of the tube, with and without the gas having passed through a canister containing the different filter materials. Our findings indicated that nitrogen dioxide was absorbed effectively by all filter materials but that there was re-formation of nitrogen dioxide from nitric oxide and oxygen in or immediately after the canister. This initial production of nitrogen dioxide was very rapid and could not be prevented by the use of scavengers. Thus soda lime and zeolite had no practical effect as scavengers in this delivery system, and the effect of noXon was very slight. (Br. J. Anaesth. 1998; 81: 404–408)

Keywords: pharmacology, nitric oxide; gases non-anaesthetic, nitric oxide; gases non-anaesthetic, nitrogen dioxide; ventilation, mechanical; equipment, scavenging devices

Inhalation of nitric oxide has been shown to reduce pulmonary artery hypertension and improve oxygenation in patients with acute lung injury. However, inhaled nitric oxide is potentially toxic because of its rapid oxidation to nitrogen dioxide. Nitrogen dioxide reacts with water to form nitric and nitrous acids which can cause lung injury.

The amount of nitrogen dioxide formed during inhalation of nitric oxide depends on the concentrations of oxygen and nitric oxide, and the contact time between the two. In order to decrease the concentration of nitrogen dioxide in the inspired gas, it has been recommended that the concentration of inhaled nitric oxide and oxygen be minimized, the time of contact between them reduced as much as possible and the concentration of nitric oxide be kept constant throughout the inspiratory phase. It has also been claimed that the concentration of inspired nitrogen dioxide can be decreased by the use of nitrogen dioxide-absorbing materials, but the value of such scavengers is a matter of debate.

In this study, we have determined the value of three different materials in absorbing nitrogen dioxide in a system for delivery of inhaled nitric oxide.

Methods
Figure 1 shows the experimental layout for administering and measuring concentrations of nitric oxide and nitrogen dioxide.

A Servo Ventilator 300 (Siemens-Elema AB, Solna, Sweden) with a gas module delivering nitric oxide from a stock gas tank of nitric oxide–nitrogen was used to supply different mixtures of nitric oxide and oxygen. A gas flow regulating valve, built on the same gas regulating principle as oxygen and air valves, injects nitric oxide into the inspiratory limb. All three valves are microprocessor-controlled to provide a flow that is rapidly adjusted (ms) in proportion to the main ventilatory flow (flow proportional). This regulatory system maintains the concentration of nitric oxide almost constant during inspiration and expiration, despite changes in minute ventilation, oxygen concentration, mode of ventilation (pressure-regulated, volume-regulated), inspiratory time, pause time, frequency, etc.

A paediatric silicon tube, 0.85 m in length, attached to the ventilator and a canister (diameter 0.07 m, height 0.075 m, volume 290 ml) containing the nitrogen dioxide absorbing material, was connected to the tube by an adapter. The same canister was used for all three materials to minimize differences in volume-dependent absorption and to standardize the deadspace volume on each side of the canister during the tests.

Concentrations of nitric oxide and nitrogen dioxide were measured using electrochemical fuel cells (CiTiceLs, City Technology Ltd, City Technology Centre, Portsmouth, UK) and a chemiluminescence analyser (ML 9841A Monitor Laboratories, LS Lear Siegler, Measurement Controls Corporation, Englewood, CO, USA) after the tube and canister. To avoid contamination with room air, we added a 0.85-m tube after the monitors, and the system was open to atmospheric air to avoid pressure dependency (fig. 1). Two measuring techniques were used to avoid systematic error, but the values obtained with the electrochemical fuel cells were used in the tables and figures.

The chemiluminescence analyser and electrochemical fuel cells were calibrated with dry calibration gas containing nitric oxide (82.2 ppm 2%) and nitrogen dioxide (6.7 ppm 2%) in nitrogen (AGA...
The chemiluminescence analyser is zeroed automatically. The electrochemical fuel cells were zeroed with dry air. The system was flushed with nitric oxide–nitrogen four times to eliminate interference from nitrogen dioxide formed and trapped in the high pressure tubing.

Three types of nitrogen dioxide absorbing materials were studied: (i) soda lime (Viosorb, MIE, Medical and Industrial Equipment, Falcon Road, Souton Industrial Estate, Exeter, Devon, UK) which has a variable undetermined grain size and a density of 0.82 g ml⁻¹. The colour indicator used was ethyl violet; (ii) noXon (Hoechst AG, Frankfurt, Germany), which contains a polymeric material (polyphenylensulphide), has a grain size of 0.7–2 mm and a density of 0.4 g ml⁻¹; (iii) Zeolite 518, 4 Ångstrom (Grace, Worms, Germany), a naturally occurring and synthetic group of minerals with a framework consisting of interlocking tetrahedrons of SiO₄ and AlO₄. It has a grain size of 1 mm and a density of 0.78 g ml⁻¹.

In the first series of experiments the ventilator was set to deliver nitric oxide 40, 70 and 100 ppm at an FIO₂ of 0.9. The gas source was a high pressure cylinder (160 bars) of nitric oxide in nitrogen (1001 ± 20 ppm) (AGA AB, Lidingö, Sweden). A low minute volume (1 litre min⁻¹) was used to provide the highest possible nitrogen dioxide production. In the second series of experiments the nitric oxide–nitrogen stock gas cylinder was exchanged for a calibration gas cylinder containing nitrogen dioxide–nitrogen 196 ppm (Air Liquide Gas AB, France). This cylinder was connected to the nitric oxide valve which was set to deliver nitrogen dioxide 10 ppm at an FIO₂ of 0.21.

Nitric oxide and nitrogen dioxide concentrations were measured during the experiments with and without the canister in place.

The production of nitrogen dioxide was calculated according to the following equation, which describes the concentration of nitrogen dioxide in the delivery system:

\[
[\text{NO}_2] = k_A [\text{NO}] + k_B [\text{NO}]^2 + k_C [\text{O}_2] + k_D [\text{NO}] [\text{O}_2] + k_E [\text{NO}] [\text{O}_2] [\text{O}_2]
\]

were nitrogen dioxide [NO₂] and nitric oxide [NO] concentrations are in parts per million (ppm), oxygen concentration [O₂] is in percentage, and contact time (t) is in seconds. The rate constants are \(k_A = 5.12 \times 10^{-3}\), \(k_B = 1.41 \times 10^{-6}\) and \(k_C = 0.86 \times 10^{-4}\). Contact time of nitric oxide and oxygen was calculated by dividing the volume of the paediatric tube and adapter by mean gas flow. The calculated values are given in figure 2 A–C, showing the expected approximate concentration of nitrogen dioxide at different concentrations of nitric oxide in the delivery system without a filter.

Absorption of nitrogen dioxide (concentration of nitrogen dioxide before (without) the filter–concentration of nitrogen dioxide after the filter, divided by the concentration of nitrogen dioxide before the filter) and transformation of nitrogen dioxide to nitric oxide (concentration of nitric oxide after the filter–concentration of nitric oxide before (without) the filter) divided by concentration of
nitrogen dioxide before (without the filter) were calculated when nitrogen dioxide–nitrogen was delivered and expressed as a percentage.

Results

**ABSORPTION OF NITROGEN DIOXIDE IN NITROGEN**

All three materials absorbed nitrogen dioxide effectively. Zeolite absorbed almost all nitrogen dioxide (table 1).

**TRANSFORMATION OF NITROGEN DIOXIDE TO NITRIC OXIDE**

NoXon was the only material that transformed nitrogen dioxide to nitric oxide (table 2).

**ABSORPTION OF NITROGEN DIOXIDE PRODUCED BY OXIDATION OF NITRIC OXIDE**

Soda lime decreased the concentration of nitric oxide by 6.6% and of nitrogen dioxide by 4.9% at the highest nitric oxide concentration. Concentrations of nitrogen dioxide were always higher with soda lime than without, at comparable concentrations of delivered nitric oxide (fig. 2a).

NoXon decreased the concentration of nitric oxide by 12.1% and of nitrogen dioxide by 17.5% at the highest nitric oxide concentration, but the concentration of nitrogen dioxide was still higher with noXon than without, at comparable concentrations of nitric oxide. At set concentrations of nitric oxide 40 and 70 ppm, concentrations of nitrogen dioxide were reduced by noXon at comparable concentrations of delivered nitric oxide (fig. 2b).

Zeolite decreased the concentration of nitric oxide by 70–80% and nitrogen dioxide by 84–94% (fig. 2c).

Discussion

One of the problems with administration of nitric oxide is spontaneous and continuous oxidation of nitric oxide to the more toxic nitrogen dioxide. Nitrogen dioxide scavengers can reduce the concentration of nitrogen dioxide in inspired gas and it has been recommended that they should be used during inhalation of nitric oxide. Soda lime has been tested by several authors with variable results.10–13 Our study supports and explains the finding that nitrogen dioxide scavengers have a limited role to play.

We tested three nitrogen dioxide scavenging materials and showed that they all effectively absorbed nitrogen dioxide from a nitrogen dioxide–nitrogen stock gas. However, the situation changed when we tried to scavenge nitrogen dioxide produced in a mixture of nitric oxide–nitrogen and oxygen. In this case the concentration of nitrogen dioxide immediately after the canister was as high as it would have been without the absorber in place, if the concentration of nitric oxide is taken as that measured after the absorber.

The rate at which nitric oxide is oxidized to nitrogen dioxide in the presence of oxygen has been studied in sealed chambers and follows the equation, 

\[ -d\text{NO}/dt = k\times[\text{NO}]^2 \times [O_2]. \]

However, nitric oxide is a free radical with an unpaired electron. Its reaction with other molecules is a complicated process and does not follow simple biochemical mechanisms.14 16 We have analysed the velocity of this reaction in a dynamic system for delivering inhaled nitric oxide and found that the reaction appears to take place in two steps following the equation:

\[ [\text{NO}] = 

k_a \times [\text{NO}] + k_b \times [\text{NO}]^2 \times [O_2] \times t \times [\text{NO}] \times [O_2]. \]

An initial fast reaction is followed by slow formation of nitrogen dioxide and this slow phase follows the kinetics described by the equation established in sealed chambers. Nitrogen dioxide formed by the initial, rapid reaction appears immediately after nitric oxide and oxygen come in contact with each other.1

Our study indicated that an initial fast reaction between nitric oxide and oxygen and consequently new formation of nitrogen dioxide also appeared immediately after nitrogen dioxide had been effectively scavenged by a filter. It seems unlikely that nitrogen dioxide could pass the absorber without being scavenged as nitrogen dioxide–nitrogen in the absence of active gases is effectively scavenged. In addition, nitrogen dioxide is almost completely absorbed when mixed with nitric oxide in any proportion in an oxygen-free mixture.11 Even the addition of two soda lime absorbers close to each other in series in the inspiratory limb did not reduce the concentration of nitrogen dioxide further, indicating that oxidation of nitric oxide takes place in a fast and then a slow reaction.17 These findings are consistent with the hypothesis that a rapid build-up of nitrogen dioxide occurs in the gas phase, despite earlier findings14 of a slow “time-dependent” reaction.

The level to which the concentration of nitrogen dioxide rises after having been scavenged by an absorber depends on the concentration of nitric oxide and oxygen after the absorber. We have shown that the initial formation of nitrogen dioxide is proportional to oxygen concentration and the square of nitric oxide concentration, and is not linearly related to time.3 The initial oxidation of nitric oxide is very rapid and most probably occurs in the deadspace between the grain particles of the filter material or in the deadspace at the end of the canister, or both. This oxidation of nitric oxide leads to decreased concentration of nitric oxide in the gas mixture. Squire, Kightley and Petros also suspected that the reduction

Table 1  Absorption of nitrogen dioxide (NO$_2$/N$_2$) by the three different filter materials

<table>
<thead>
<tr>
<th>Absorber</th>
<th>NO$_2$ without absorber (ppm)</th>
<th>NO$_2$ after absorber (ppm)</th>
<th>Absorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soda lime</td>
<td>9.93</td>
<td>0.56</td>
<td>94</td>
</tr>
<tr>
<td>noXon</td>
<td>10.18</td>
<td>0.17</td>
<td>98</td>
</tr>
<tr>
<td>Zeolite</td>
<td>10.20</td>
<td>0.13</td>
<td>99</td>
</tr>
</tbody>
</table>

Table 2  Transformation of nitrogen dioxide (NO/NO$_2$) to nitric oxide (NO) during passage through the three different filter materials

<table>
<thead>
<tr>
<th>Absorber</th>
<th>NO$_2$/NO without absorber (ppm)</th>
<th>NO$_2$/NO after absorber (ppm)</th>
<th>Transformation of NO$_2$ to NO(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soda lime</td>
<td>9.93/1.30</td>
<td>0.30</td>
<td>–10</td>
</tr>
<tr>
<td>noXon</td>
<td>10.18/1.10</td>
<td>2.80</td>
<td>+17</td>
</tr>
<tr>
<td>Zeolite</td>
<td>10.20/1.10</td>
<td>0.00</td>
<td>–11</td>
</tr>
</tbody>
</table>

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in concentration of nitric oxide with soda lime was caused by oxidation of nitric oxide to nitrogen dioxide in the absorber rather than true absorption. The rate of nitric oxide oxidation in the filter may depend on factors such as density, grain size and deadspace. A very rapid reaction between nitric oxide and oxygen explains why filter materials cause a decrease in nitric oxide concentration, new formation of nitrogen dioxide and return to an almost similar proportion between nitrogen dioxide and the delivered and inhaled nitric oxide levels immediately after the canister. This initial formation of nitrogen dioxide is impossible to eliminate by the use of scavengers.

This explains the findings in the original report by Pickett and colleagues who found that soda lime reduced concentrations of nitrogen dioxide at the expense of similar reductions in inhaled concentrations of nitric oxide. In a subsequent study by Ishibe and colleagues, nitrogen dioxide was completely absorbed by soda lime and it was concluded that soda lime is useful for nitrogen dioxide absorption during nitric oxide inhalation therapy. Ishibe and co-workers stated that Pickett’s results from the original study had been corrected in subsequent experiments by using electrochemical fuel cells and vertical instead of horizontal placement of the canister. We believe that the results of all three reports are correct, but because nitrogen dioxide was added to the test gas mixtures in the study by Ishibe and colleagues and in the second study by Pickett and colleagues, the readers are misled to believe that the absorbers are very effective during inhalation of nitric oxide. According to our findings, almost all nitric dioxide was probably scavenged by the absorbers but as nitric oxide and oxygen concentrations in the experimental gas mixtures were low, little nitrogen dioxide was formed. With an artificially high concentration of nitrogen dioxide before the absorber, it seemed as if the absorber was very effective. In such a test system the author can freely change the effect of the absorber by varying the concentration of the added nitrogen dioxide and the concentrations of nitric oxide and oxygen in the gas mixture. Similarly, a high gas flow decreases the formation of nitrogen dioxide and also affects the results if nitrogen dioxide is added to the gas mixture. In the original report by Pickett and colleagues, spontaneously formed nitrogen dioxide was scavenged and subsequently re-formed. They concluded correctly that there was no role for a nitrogen dioxide scavenger in their system.

That the effectiveness of a nitrogen dioxide scavenger is dependent on the concentration of nitric oxide in a system with a fixed concentration of nitrogen dioxide was shown by Foubert and colleagues who found that the percentage absorption of nitrogen dioxide decreased with increasing concentration of nitric oxide.

Soda lime fails to absorb nitric oxide if the system is free of oxygen and, water. Squire, Kightley and Petros found it difficult to scavenge nitric oxide and discovered that the most effective method was to first oxidize nitric oxide to nitrogen dioxide. Continuous oxidation of nitric oxide with oxygen may explain depletion of nitric oxide when soda lime is used in a circle system. If nitrogen dioxide is added to a gas mixture containing nitric oxide but without oxygen and is passed through a soda lime canister, an equimolecular amount of nitric oxide is depleted, but no new nitrogen dioxide can be detected after the absorber. Foubert and colleagues showed that the concentration of nitric oxide decreases with increasing concentration of nitrogen dioxide. This finding indicates that nitric oxide, in addition to oxidation by oxygen, may be oxidized by a non-volatile product formed by the reaction between nitrogen dioxide and soda lime or a volatile product that is immediately consumed by the reaction, with inactivation of nitric oxide. This nitrogen dioxide-dependent depletion of nitric oxide was not apparent in the noXon material where, on the contrary, nitrogen dioxide seemed to be transformed to nitric oxide.

The noXon material was the only scavenger that reduced nitrogen dioxide to values less than without scavenger. One reason could be that it has the ability to transform nitrogen dioxide to nitric oxide. However, in a gas mixture of nitric oxide, oxygen and the nitrogen dioxide produced by the, the final effect was a decrease in nitric oxide concentration, and therefore noXon cannot be defined as a nitrogen dioxide-selective scavenger as Gilly, Krebs and Nowotny suggested. Their nitric oxide, oxygen and nitrogen dioxide mixtures were also prepared with a nitrogen dioxide concentration greater than would have appeared spontaneously, and accordingly they found that the efficacy of the scavenger improved with higher concentrations of nitrogen dioxide.

Zeolite absorbed nitrogen dioxide most effectively, but it also effectively decreased nitric oxide concentrations. The proportion of nitrogen dioxide to delivered nitric oxide after the canister was similar to the theoretical values we calculated. However, as the concentrations of nitric oxide and nitrogen dioxide decreased to below the set concentrations of nitric oxide, the value as a scavenger, defined as nitrogen dioxide concentrations at comparable concentrations of nitric oxide delivered with and without zeolite, could not be assessed directly. A zeolite consists of uniformly sized compartments in which gas molecules can be trapped if the diameter corresponds to the compartment in the zeolite. The density of the absorbed gas could be higher than the density of gas in the liquid phase. This implies that the pressure of each single gas molecule is very high. Hence, if two nitric oxide molecules and one oxygen molecule fit in one compartment, we have very rapid formation of nitrogen dioxide (or the dimer N₂O₅), and this newly formed nitrogen dioxide is also effectively depleted.

Soda lime was of no use as it increased the concentration of nitrogen dioxide relative to the concentration of nitric oxide, probably as a result of increased oxidation in the deadspace of the canister containing the filter material.

In summary, our tests showed that there is a limited role for nitrogen dioxide scavengers in this delivery system. Zeolite decreased concentrations of nitrogen dioxide and nitric oxide substantially. Of the two other nitrogen dioxide scavengers, noXon was the only one that reduced nitrogen dioxide to concentrations less than those without a filter.

References

1. Rasmussen TR, Kniaergaard SK, Tarp U, Pedersen OF. Delayed effects of NO₂ exposure on alveolar permeability and