Effect of oral L-arginine on airway hyperresponsiveness to histamine in asthma

H W F M de Gouw, M B Verbruggen, I M Twiss, P J Sterk

Abstract

Background—Nitric oxide (NO) may exert protective properties within the airways of asthmatic patients. It was postulated that airways obstruction in asthma may be associated with endogenous NO deficiency caused by limited availability of NO synthase substrate.

Methods—In a double blind, crossover study 14 asthmatic patients received pretreatment with oral L-arginine (50 mg/kg body weight) or placebo prior to histamine challenge. Histamine challenge was performed until a 50% fall in forced expiratory volume in one second (FEV1) occurred and the response was expressed as the provocative concentration causing a 20% fall in FEV1 (PC20) and as the dose–response slope (maximal % fall in FEV1/cumulative dose (µmol)).

Results—Pretreatment with L-arginine did not affect PC20 histamine (mean change: 0.7 (95% CI 0.6 to 0.9), p = 0.016).

Conclusions—Oral L-arginine does not influence airway hyperresponsiveness to histamine as reflected by PC20, although the dose–response slope is slightly reduced in patients with asthma. This indicates only marginal, clinically unimportant limitation of NO synthase substrate in asthma.

Keywords: nitric oxide; asthma; airway hyperresponsiveness

Evidence is accumulating that endogenous nitric oxide (NO) is involved in the pathophysiology of asthma. NO is formed by NO synthase (NOS) using L-arginine as a substrate. It has been shown that the level of NO in exhaled air is increased in subjects with asthma, and that it varies with disease severity. However, the functional role of NO in the pathophysiology of asthma is still unclear.

Recent studies on the modulation of endogenous NO production have revealed protective features of NO during episodes of airways obstruction. Increased airway hyperresponsive-
Table 1  Effect of pretreatment with placebo or L-arginine on FEV$_1$, exhaled NO levels, PC$_{20}$, and dose-response slope to histamine

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>L-arginine</th>
<th>Difference in changes between L-arginine and placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV$_1$ (% predicted)</strong></td>
<td>92.8 (85.8 to 99.9)</td>
<td>96.6 (87.9 to 105.4)</td>
<td>3.8% predicted (95% CI –3.8 to 7.4)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>95.1 (88.3 to 102.0)</td>
<td>95.3 (88.1 to 102.6)</td>
<td>–0.3% predicted (95% CI –2.4 to 7.4)</td>
</tr>
<tr>
<td><strong>30 min</strong></td>
<td>95.4 (85.8 to 101.5)</td>
<td>93.3 (85.3 to 101.5)</td>
<td>–2.0% predicted (95% CI –3.7 to 2.3)</td>
</tr>
<tr>
<td><strong>60 min</strong></td>
<td>95.2 (87.9 to 102.5)</td>
<td>94.0 (87.2 to 102.8)</td>
<td>–1.2% predicted (95% CI –2.9 to 0.5)</td>
</tr>
<tr>
<td><strong>Exhaled NO (ppb)</strong></td>
<td>17.4 (12.5 to 22.3)</td>
<td>19.9 (13.0 to 26.8)</td>
<td>13.6% predicted (95% CI –3.2 to 5.1)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>19.0 (13.9 to 24.2)</td>
<td>21.8 (14.8 to 28.7)</td>
<td>14.0% predicted (95% CI –0.1 to 5.1)</td>
</tr>
<tr>
<td><strong>30 min</strong></td>
<td>18.0 (14.0 to 22.0)</td>
<td>21.6 (14.6 to 28.5)</td>
<td>13.8% predicted (95% CI –0.1 to 5.1)</td>
</tr>
<tr>
<td><strong>90 min</strong></td>
<td>19.5 (15.5 to 23.5)</td>
<td>22.0 (15.3 to 28.5)</td>
<td>13.5% predicted (95% CI –0.1 to 5.1)</td>
</tr>
<tr>
<td><strong>DRS (% fall/µmol)</strong></td>
<td>0.41 (0.20 to 0.82)</td>
<td>0.46 (0.24 to 0.86)</td>
<td>13.8% predicted (95% CI –0.1 to 5.1)</td>
</tr>
</tbody>
</table>

FEV$_1$ = forced expiratory volume in one second; ppb = parts per billion; PC$_{20}$ = provocative concentration causing a 20% fall from baseline FEV$_1$; DRS = dose-response slope.

* p<0.05.
† Data are geometric mean (95% confidence interval).
‡ Difference in changes from baseline values in FEV$_1$ and exhaled NO between L-arginine and placebo pretreatment.

Results

All subjects completed the study. The data are presented in Table 1. Baseline FEV$_1$ and exhaled NO did not differ between the two study days (mean difference 3.8% predicted (95% CI –0.9 to 8.5) and 2.5 ppb (95% CI –2.4 to 7.4), respectively; p>0.05). There was a slight but significant improvement in FEV$_1$ following placebo (p = 0.03) but no significant change in FEV$_1$ occurred following pretreatment with L-arginine (p = 0.45; table 1). However, the pre-histamine baseline FEV$_1$ was not significantly different between the two study days (mean difference –1.3% predicted (95% CI –4.0 to 1.4), p = 0.3). There was no significant change in exhaled NO levels after L-arginine or placebo (p>0.1; table 1) nor were blood pressure and heart rate significantly affected (p>0.4).

Supplementation with L-arginine did not significantly affect airway sensitivity to histamine, determined by PC$_{20}$ compared with placebo (mean change in doubling dose: 0.18 (95% CI –0.36 to 0.71), p = 0.5). However, there was a slight but significant reduction in airway reactivity as determined by the dose-response slope following pretreatment with L-arginine compared with placebo (mean change 0.7 (95% CI 0.6 to –0.9), p = 0.016).

Discussion

These results show that oral L-arginine does not affect airway hyperresponsiveness to inhaled histamine in patients with asthma, although a slight reduction in airway reactivity (as indicated by the dose-response slope) was seen. These findings suggest only marginal limitation of NOS substrate in asthmatic subjects in vivo and therefore argue against a clinically relevant deficiency of endogenous NO in asthma.

This is the first study of the effects of L-arginine supplementation on airway hyperresponsiveness in patients with asthma. Previous animal studies have demonstrated the ability of L-arginine to reverse the enhanced bronchoconstriction to non-sensitising stimuli following inhibition of NO synthesis and to reduce contractility to histamine in vitro. In addition, they provided indirect evidence for an association between endogenous NO deficiency and the increase in airway sensitivity and reactivity following either respiratory virus infection or allergen exposure in guinea pigs. Our results do not confirm these findings, although a slight improvement in airway reactivity occurred following supplementation with oral L-arginine.

It is unlikely that our results can be explained by measurement errors since they were obtained using validated methodology for challenge testing and measurement of exhaled NO. The dose and timing of L-arginine pretreatment were based on a previous report which showed increased levels in exhaled NO two hours after ingestion of 50 mg/kg L-arginine in asthmatic subjects. In this study, however, we were not able to detect an increase in exhaled NO. Since our patients did not have an L-arginine deficient or weighted diet, we cannot exclude the possibility that these subjects had little or no NOS substrate limitation. Finally, since high concentrations of L-arginine have been shown to act as a non-competitive antagonist of the contractile response to bronchoconstrictor stimuli in vitro, we cannot exclude the contribution of the anti-histamine effects of L-arginine to the present findings.

Besides having immunomodulatory and cytotoxic properties, NO is known to exert protective effects within the airways. This “relaxant” effect is likely to be derived from constitutive NOS activity (cNOS), of which neuronal NOS (nNOS) in inhibitory non-adrenergic non-cholinergic (iNANC) nerves seems to predominate. It has been suggested that a deficiency of endogenous “relaxant” NO is one of the underlying mechanisms for increased response to bronchoconstrictor stimuli in asthma. This may be explained either by a reduction in NOS activity or/and reduced local availability of the NOS substrate. Asthma has been associated with increased exhaled NO levels, of which the major part seems to derive from local inducible NOS (iNOS) activity. The relatively high NO levels produced by iNOS may subsequently attenuate cNOS activity, thereby potentially reducing its relaxant effects.

Since L-arginine is metabolised not only by NOS, but also by arginase, increased arginine levels and/or activity may limit L-arginine availability. Indeed, both NO and arginase activity may be increased during inflammation. More importantly, at reduced L-arginine levels, arginine...
nase activity is favoured over NO synthesis. However, at present there is no evidence of increased arginase levels and/or activity in asthma. Finally, Chakder and colleagues reported that continuous iNANC activation in smooth muscle strips caused significant decreases in levels of L-arginine. It can be speculated that in asthma the iNANC system may be perpetually activated, thereby exhausting its own bronchodilator features. It remains to be elucidated whether these in vitro findings can be extrapolated to the human situation.

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