2 Brasfield D, Hicks G, Soong SJ, Tiller RE. The chest roentgenogram in cystic fibrosis: a new scoring system. *Pediatrics* 1979;**63**:24–9.
3 Pierce RJ, Brown DJ, Holmes M, Cumming G, Denison DM. The estimation of lung volume from chest radiographs using shape information. *Thorax* 1979;**34**:726–34.
4 Pierce RJ, Brown DJ, Denison DM. Radiographic, scintigraphic and gas-dilution estimates of individual lung and lobar volume. *Thorax* 1980;**35**:773–80.
5 Bush A, Denison DM. Use of different magnification factors to calculate radiological lung volumes. *Thorax* 1986;**41**: 158–9.
6 Denison DM, du Bois R, Sawicka E. Pictures in the mind. *Br J Dis Chest* 1983;77:35–50.

Thorax 1994;49:1166–1168

Effects of inhaled lignocaine and adrenaline on capsaicin-induced cough in humans

L Hansson, B Midgren, J-A Karlsson

Abstract

***Background* – The hypothesis that adrenaline can augment and/or prolong the antitussive effect of nebulised lignocaine was examined.**

***Methods* – The effect of inhaled lignocaine alone (20 mg) and in combination with adrenaline (400 µg) was studied on capsaicin-induced cough in 10 healthy subjects.**

***Results* – Cough was significantly reduced between five and 25 minutes by lignocaine. Adrenaline alone had no inhibitory effect and it neither augmented nor prolonged the antitussive effect of lignocaine. The subjective anaesthesia by lignocaine was short lasting (less than 15 minutes) and not altered by adrenaline, suggesting different sensory mechanisms for anaesthesia and cough suppression. Plasma concentrations of lignocaine were low (<30 ng/ml), not altered by adrenaline, and did not correlate with the local anaesthetic or the antitussive effect.**

***Conclusions* – Lignocaine acts locally in the oropharynx and airways and adrenaline does not alter the effect or absorption of nebulised lignocaine on the human respiratory mucosa.**

(*Thorax* 1994;**49**:1166–1168)

Department of Lung Medicine, University Hospital, S-221 85 Lund, Sweden
L Hansson
B Midgren

Discovery Biology, Rhône-Poulenc Rorer Ltd, London, UK
J A Karlsson

Reprint requests to:
Dr L Hansson.

Received 29 November 1993
Returned to authors
20 April 1994
Revised version received
27 June 1994
Accepted for publication
19 July 1994

Lignocaine inhibits experimental cough in humans in a dose-dependent manner[1] and inhalation of a large dose of lignocaine has been reported to be an effective treatment in patients with severe persistent cough.[2,3] Unfortunately, lignocaine has a short duration of action. Phenylephrine reduces blood flow in the tracheobronchial mucosa and adrenaline increases vascular resistance in the nasal mucosa[4] in the dog. We therefore determined whether α-adrenoreceptor stimulation would potentiate the effects of inhaled lignocaine. The aim was to examine the antitussive effect and the oropharyngeal numbness of inhaled lignocaine and adrenaline on capsaicin-induced cough in healthy human subjects. In addition, plasma levels of lignocaine were measured to determine the degree of systemic absorption.

Methods

Ten non-smoking healthy subjects (five women) of mean age 27 (range 18–33 years) took part in the study. They gave their written informed consent and the study was approved by the University Hospital medical ethics committee, Lund. Capsaicin (Sigma) was dissolved in ethanol and diluted with 0·9% NaCl to 0·4 µmol/l, 2 µmol/l, 10 µmol/l, and 50 µmol/l.

Capsaicin was inhaled by tidal breathing from a nebuliser (BIRD Asmastick, output 0·5 ml/min and mass median diameter 3 µm) filled with 2 ml of solution.[1] A microphone and tape recorder were used to register the sounds of breathing and cough. The number of coughs was counted from the tape recordings. Blood samples were drawn from an arm vein into heparinised tubes. All blood samples were centrifuged and plasma was then separated and stored at −25°C until analysed by gas chromatography (Astra Alab, Södertälje, Sweden).

The antitussive effects of nebulised lignocaine (20 mg), adrenaline (400 µg), lignocaine in combination with adrenaline (20 mg + 400 µg), and vehicle (saline) were studied on four separate study days. Treatments were administered in a randomised, double blind manner. Increasing concentrations of capsaicin (0·4–50 µmol/l) were inhaled until a response of at least 10 coughs per minute was reached, and the concentration was then repeated and the mean response of the two challenges used as a baseline value. On each study day the chosen concentration was repeated. Capsaicin challenges were repeated five, 15, 25, 45, and 60 minutes after treatment with the study drug. Subjects were asked to subjectively assess the level of oropharyngeal anaesthesia according to a five point scale immediately before each capsaicin challenge. Blood samples for determination of plasma levels of lignocaine were drawn before and 10, 20, 30, 45, and 60 minutes after lignocaine inhalation. Kruskal–Wallis test was used at each

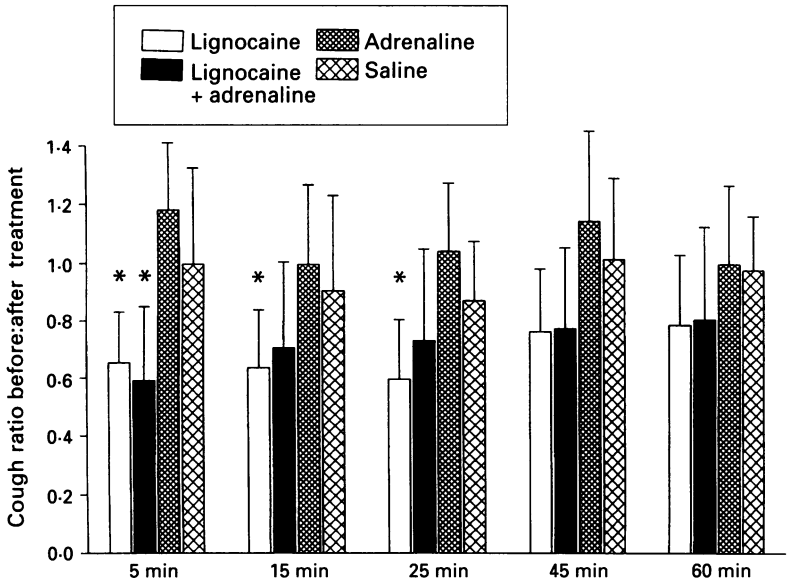

*Figure 1 Ratio of capsaicin-induced coughs before:after treatment with lignocaine (20 mg) alone, a combination of adrenaline (400 μg) and lignocaine (20 mg), adrenaline (400 μg) alone, and placebo at different time points after treatment. Mean data are shown and error bars indicate 95% CI. *p < 0·05 compared with placebo, Wilcoxon's test.*

time interval and Wilcoxon's test was used to compare statistically the number of coughs and the subjective oropharyngeal anaesthesia between the treatment periods. Analysis of variance was used to compare plasma concentrations of lignocaine.

Results

Capsaicin caused a highly reproducible cough response (fig 1, saline pretreatment). Inhaled lignocaine produced a mean 35% inhibition at five minutes (confidence interval (CI) 14% to 55%, $p < 0·05$) and was still significant after 15 and 25 minutes. The combination of lignocaine and adrenaline produced the same degree of inhibition (41%, CI 11% to 71%, $p < 0·05$) as lignocaine alone at five minutes and it was not statistically significant at 15 and 25 minutes. There were no differences between lignocaine and the combination at any time. Adrenaline and vehicle were both without effect. The subjective feeling of anaesthesia produced by aerosols containing lignocaine was most intense at five minutes and lasted less than 15 minutes. The mean scores (95% CI) at five minutes were 2·1 (1·6 to 2·5) ($p < 0·05$) for lignocaine and 1·7 (1·1 to 2·3) ($p < 0·05$) for the combination, 0·2 (−0·2 to 0·6) for adrenaline alone, and 0·1 (−0·1 to 0·3) for vehicle (fig 2). There were no differences between the two active treatments (fig 2). Plasma levels of lignocaine after 20 minutes were 19 ng/ml (range 10–30 ng/ml) for lignocaine alone and 18 ng/ml (range 10–20 ng/ml) for the combination and remained stable over 60 minutes ($p > 0·05$).

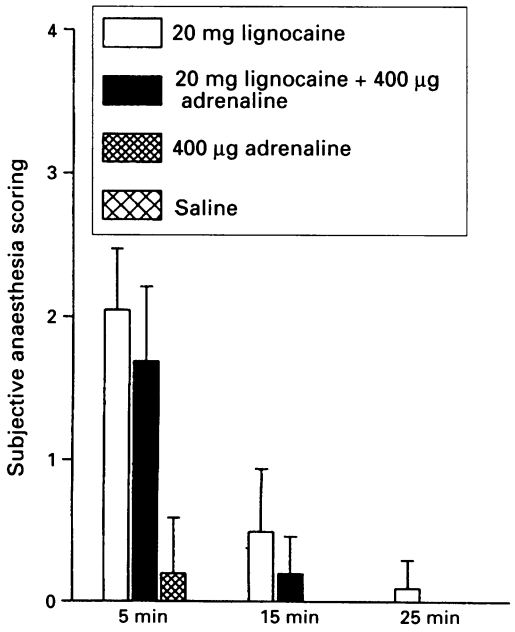

Figure 2 Subjective oropharyngeal anaesthesia according to a five point scale: 0 = no anaesthesia, 1 = noticeable anaesthesia, 2 = slight anaesthesia, 3 = moderate anaesthesia, 4 = severe anaesthesia. Mean + 95% CI (n = 10) data are shown.

Discussion

This study showed that lignocaine in a dose of 20 mg significantly reduced capsaicin-induced coughing. The duration of action of a local anaesthetic when infiltrated is prolonged by adrenaline, which is likely to be due to vasoconstriction at the site of injection. A low dose of lignocaine was used in this study to allow the detection of an interaction with adrenaline. However, adrenaline neither enhanced nor significantly prolonged the antitussive effect. The tracheobronchial mucosa has an extensive subepithelial vascular plexus and our data suggest that this dose of adrenaline, although rather high, was not able to significantly reduce mucosal blood flow or that other mechanisms determine the duration of action of lignocaine.

Recent studies have shown that reflex bronchoconstriction and cough are dissociated and mediated through different sensory pathways, and the absence of an antitussive effect of inhaled adrenaline in a bronchodilator dose supports the contention that the cough reflex in healthy subjects is independent of airway tone.

The duration of topical anaesthesia was short, but the antitussive effect was still significant 25 minutes after inhalation. The antitussive effect and the subjective anaesthesia seem to be mediated via different sensory mechanisms. Capsaicin-sensitive sensory neurones in the human respiratory tract are located superficially in the airway mucosa and we have recently shown that intrapulmonary nerve endings may be even more sensitive to capsaicin than those in the larynx.[5] The antitussive effect is most likely to be exerted by the local anaesthetic deposited within the tracheobronchial tree, whereas the subjective symptoms are due to anaesthesia of the oropharynx and larynx.

The maximum plasma concentration after inhalation of 20 mg of lignocaine was less than 20 ng/ml, which is about 1/50 of that attained after inhalation of 400 mg with an ultrasonic nebuliser before bronchoscopy.[6] This suggests

that the antitussive effect is due to anaesthesia of the sensory nerves locally in the airway rather than to inhibition of impulse conduction in large conducting nerves or to suppression of a putative "cough centre" in the central nervous system. Further support for this view comes from a study which showed that a high plasma concentration (>3000 ng/ml) was necessary to inhibit the cough reflex after intravenous administration.[7]

The present study has shown that capsaicin-induced cough can be reduced by inhaled lignocaine through an action locally in the tracheobronchial tree. Inhibition of the cough reflex was significantly more pronounced than the subjective sensation of oropharyngeal anaesthesia, suggesting the involvement of separate sensory mechanisms. Adrenaline had no antitussive effect and did not alter the response to inhaled lignocaine, indicating that the combined use of these two agents on the respiratory mucosa offers no advantage over lignocaine alone.

This study was supported by grants from the Swedish Heart and Lung Foundation and Astra-Draco AB, Lund, Sweden. The authors would like to thank Mr Göran Randwall and Mrs Carin Rolf for technical assistance.

1 Midgren B, Hansson L, Karlsson J-A, Simonsson BG, Persson CGA. Capsaicin-induced cough in humans. *Am Rev Respir Dis* 1992;**146**:347–51.
2 Howard P, Cayton RM, Brennan SR, Anderson PB. Lignocaine aerosol and persistent cough. *Br J Dis Chest* 1977; 71:19–24.
3 Sanders RV, Kirkpatrick MB. Prolonged suppression of cough after inhalation of lidocaine in a patient with sarcoid. *JAMA* 1984;**252**:2456–7.
4 Laitinen LA, Robinson NP, Laitinen A, Widdicombe JG. Relationship between tracheal mucosal thickness and vascular resistance in dogs. *J Appl Physiol* 1986;**61**:2186–93.
5 Hansson L, Wollmer P, Dahlbäck M, Karlsson J-A. Regional sensitivity of human airways to capsaicin-induced cough. *Am Rev Respir Dis* 1992;**145**:1191–5.
6 Gove RI, Wiggins J, Stableforth DE. A study of the use of ultrasonically nebulized lignocaine for local anaesthesia during fibreoptic bronchoscopy. *Br J Dis Chest* 1985;**79**: 49–59.
7 Yukioka H, Yoshimoto N, Nishimura K, Fujimori M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation. *Anesth Analg* 1985;**64**:1189–92.