Separation of cough and reflex bronchoconstriction by inhaled local anaesthetics

N.B. Choudry*, R.W. Fuller*, N. Anderson**, J-A. Karlsson***

Separation of cough and reflex bronchoconstriction by inhaled local anaesthetics. N.B. Choudry, R.W. Fuller, N. Anderson, J-A. Karlsson.
ABSTRACT: Cough and airway constriction are common features of respiratory diseases. Both can be caused by stimulation of airway nerves. We have studied the effects of airway anaesthesia on these reflexes, stimulated by inhaled capsaicin, in order to determine whether they are controlled by the same sensory nerves. Ten volunteers had capsaicin cough dose responses performed before and at 10 min after inhaling placebo (ascorbic acid in saline), and the topical anaesthetics lignocaine 40 mg, and dyclonine 8 and 4 mg. The effect of the drugs on respiratory resistance (Rrs), measured using a forced oscillation technique, was measured both before and after the inhalation of a dose of capsaicin which caused less than two coughs. Lignocaine (40 mg) and dyclonine (8 mg) caused significant reports of oral anaesthesia but only lignocaine reduced the cough response to inhaled capsaicin, increasing the log dose of capsaicin causing three or more coughs by 162%. None of the treatments altered basal Rrs or its increase after inhaled capsaicin. Thus, the cough and reflex bronchoconstriction caused by inhaled capsaicin have different sensitivities to inhaled local anaesthesia, suggesting that the effect may be mediated by different sensory pathways.
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Cough and wheezing due to bronchoconstriction are common symptoms of lung disease. Cough can also be an early manifestation of asthma [1, 2], pointing to an apparent relationship between cough and bronchoconstriction in obstructive airways disease.

Topically administered local anaesthetics (>200 mg of lignocaine) are used in bronchoscopy to block reflexes, including cough, produced by mechanical irritation of the larynx and tracheobronchial tree. Lignocaine has also been reported to suppress chronic cough in a few patients [3, 4]. The local anaesthetic bupivacaine inhibits citric acid induced cough and reflex bronchoconstriction in healthy subjects [5]. Despite the extensive use of local anaesthetics for endoscopy, very little is known about the sensitivity of airway reflexes to these drugs and whether different compounds separately affect different reflexes.

Local anaesthetics may have different effects on nerve conduction, depending upon the type and size of nerve fibres. The physicochemical properties of the anaesthetic may also depend on the lipophilicity of the anaesthetic drug and the surface membrane to which it is applied [6]. It can therefore be presumed that airway reflexes if conducted *via* different nerves or originating in different sites of the airway would be affected separately by local anaesthetics. Indeed, in animal studies [7–9] coughing is inhibited at lower doses of local anaesthetics than the Hering-Breuer reflex, which regulates the rate and depth of breathing [10]. Although afferent pathways in both reflexes are in the vagus nerves, cough is presumably mediated by nerves with endings close to the airway epithelium, affording easier access for the local anaesthetic than the nerves controlling the Hering-Breuer reflex, which originate within the smooth muscle [11].

The aim of the present study was to examine the effect of low doses of inhaled local anaesthetics on buccal anaesthesia, cough and reflex bronchoconstriction produced by nebulized capsaicin [12, 13] in healthy subjects. Lignocaine was compared to dyclonine (an ester-type local anaesthetic) which is reported to be about ten times more potent than lignocaine on the mucosal tissue [14].

Methods

Subjects

Ten healthy, nonsmoking volunteers (aged 23–34 yrs, 6 female) gave informed consent to take part in the study which had the approval of the local hospital Research

Ethics Committee. None of the subjects had a history of recent respiratory disease and none was taking any medication other than oral contraceptives.

Total respiratory resistance

Total respiratory resistance (Rrs) was measured using a forced oscillation technique [15]. The subject was seated, with cheeks and floor of the mouth supported by the palms of the hands, and breathed quietly on a mouthpiece connected to a screen pneumotachograph. A bias flow prevented changes in inspired O_2 and CO_2. Pseudo-random noise was applied at the mouth by means of a loudspeaker over the range 4–26 Hz for a 16 s period. Mouth pressure and flow across the pneumotachograph were recorded by two identical differential pressure transducers (Validyne PM 5%). Values for Rrs at 2 Hz intervals between 4–26 Hz were computed and represented the mean values for inspiration and expiration over the 16 s period of tidal breathing. Baseline measurements of Rrs were the mean of three consecutive 16 s periods of tidal breathing. To allow measurement of the airway constriction after inhaled capsaicin, the subjects inhaled a single breath of the highest concentration of capsaicin which caused fewer than two coughs (because coughing interferes with the measurement of Rrs); this dose was chosen from the baseline cough response on each day. The subject then immediately started to breathe on the mouthpiece and Rrs was measured over the next 16 s. The same dose of capsaicin was then used in the study for all subsequent measurements of the Rrs response to inhaled capsaicin.

Dose cough response

Capsaicin (Sigma Chemical, Poole, UK) was dissolved in absolute alcohol to make a stock 10^{-2} M solution and further diluted with 0.9% saline to 1.9×10^{-5} to 2.5×10^{-3} for inhalation; 0.9% (w/v) saline was used as the control solution. Capsaicin dose cough responses (DCR) were performed by the subjects inhaling a single breath (0.02 ml particle size 3.5–4 μm) of saline or different doses of capsaicin (0.4–100 nmol) in 0.9% saline and 1% ethanol. The subject was unaware of the concentration of capsaicin in each inhalation. The doses were given from a compressed air nebulizer (Devilbis) controlled by a breath-activated dosimeter (P. K. Morgan). The number of coughs was recorded by means of a microphone connected to a fast running chart recorder (Mingograph; Simons, Elema AB, Sweden). The doses were given in a random order at one minute intervals until a dose that caused more than five coughs was reached. From the DCR the largest dose that caused less than two coughs was taken for the measurements of the Rrs response to inhaled capsaicin and the lowest dose that caused three or more coughs (D_3) was taken for analysis of the sensitivity of the cough response.
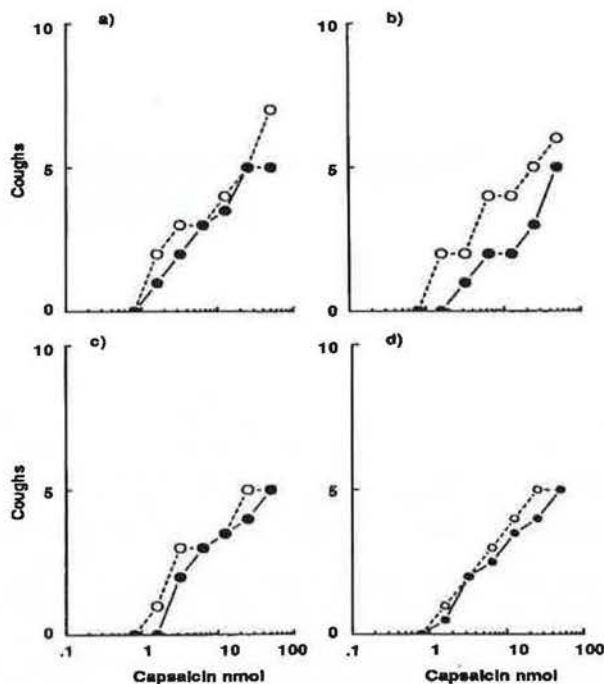

Fig. 1. – This shows the DCR capsaicin (a) before (open circles) and after (closed circles) placebo (ascorbic acid 4 mg), (b) lignocaine (40 mg), (c) dyclonine (4 mg) and (d) dyclonine (8 mg). DCR: dose cough response.

Protocol

Each subject attended the Clinical Laboratory at the same time of day on four separate occasions. Following baseline measurements of Rrs, a capsaicin DCR was performed. After a further baseline measurement of Rrs, the subject inhaled the highest dose of capsaicin that caused less than two coughs and Rrs was immediately measured. Treatment was then administered with subjects inhaling tidally *via* the same nebulizer as used in the cough challenge driven by compressed air at 8 $l \cdot min^{-1}$ until all of the drug was inhaled. The drugs were dissolved in 0.9% saline immediately before use and administered in a randomized, double-blind manner. The subjects inhaled 1 ml of solution containing 40 mg lignocaine, 4 mg and 8 mg dyclonine or 4 mg ascorbic acid (control solution having a pH similar to that of the solutions of the active drugs) on the different study days. Two minutes after inhalation, Rrs was again measured followed by the Rrs response to the doses of inhaled capsaicin which caused less than two coughs. At 10 min subjects were asked to report their level of oropharyngeal anaesthesia on a scale 0, 1 slight, 2 mild, 3 moderate and 4 complete anaesthesia. A second capsaicin DCR was then performed.

Data analysis

Capsaicin DCR are shown graphically as the median number of coughs at each dose of capsaicin inhaled for the group of ten subjects. The results in the text for Rrs

Table 1. – Ten healthy subjects inhaled placebo (ascorbic acid 4 mg), lignocaine 40 mg or dyclonine 4 and 8 mg from a nebulizer. The median (range) anaesthesia score, geometric mean (95% CI) dose of capsaicin causing three more coughs (D_3), mean±95% CI Rrs before and after treatment and the mean±95% CI capsaicin induced percentage increase in Rrs before and after treatment are shown

Treatment	Anaesthesia	D_3		Baseline Rrs $cmH_2O \cdot l^{-1} \cdot s$		% increase Rrs after capsaicin	
		Pre	Post	Pre	Post	Pre	Post
Placebo	0 (0–3)	4.5(3.4–5.9)	7.8(4.8–12.5)	1.7±0.2	1.8±0.2	25±7	20±4
Lignocaine 40 mg	3(1–4)*	4.8(3.5–6.6)	12.6(7.8–20.4)*	1.9±0.3	2.2±0.3	22±6	18±4
Dyclonine 4 mg	1(0–2)	5.9(4.1–8.4)	8.9(5.1–15.7)	1.8±0.3	1.9±0.3	24±4	18±8
Dyclonine 8 mg	2.5(1–4)*	4.0(2.9–5.1)	6.8(3.0–12.0)	1.9±0.4	2.1±0.3	23±6	24±7

*: $p < 0.05$, compared to post placebo; Rrs: respiratory resistance; CI: confidence intervals.

are the mean (95% confidence intervals), for the D_3 the geometric mean (95% confidence intervals), and for anaesthesia score median (range). Analysis of Rrs and D_3 was by multiple analysis of variance and for the anaesthesia score and D_3 was by Friedman's analysis of ranks.

Results

In agreement with the previous studies with inhaled capsaicin, DCR could be constructed by giving the doses in random order with no evidence of tachyphylaxis (fig. 1). Inhaled capsaicin, in doses that cause fewer than two coughs, consistently caused an increase in Rrs at all frequencies in the first 16 s with a mean increase of 23.4±1.5% in 40 pre-drug studies recorded at 6 Hz. There was no difference between the anaesthesia score for lignocaine (40 mg) and dyclonine (8 mg) and both were significantly ($p < 0.01$) higher than placebo or dyclonine (4 mg) (table 1). Only lignocaine (40 mg) significantly ($p < 0.05$) shifted the capsaicin DCR to the right (fig. 1). There was no difference in the concentration of capsaicin causing three or more coughs (D_3) before and after inhalation of dyclonine 4 and 8 mg and placebo (ascorbic acid, 4 mg) (table 1). Lignocaine (40 mg), on the other hand, produced a 2.6 fold increase in D_3 ($p < 0.05$) (table 1). None of the treatments affected either the baseline or the increase in Rrs induced by inhaling a dose of capsaicin which caused <2 coughs (table 1).

Discussion

Cough and the increase in airways resistance produced by inhaling capsaicin were reproducible in the present study, with no evidence of tachyphylaxis. This is in accordance with previous studies [16] and makes it a suitable method for the evaluation of antitussive and antibronchoconstrictor agents.

In the present study, nebulized local anaesthetics caused moderate anaesthesia of the oropharynx, which could be sensed for up to 15 min and was dose-dependent (table 1). Lignocaine (40 mg) suppressed the cough response to capsaicin significantly shifting the log DCR to the right by 162%, a greater change than that found in previous studies in normal humans using nebulized citric acid. CROSS et al. [5], for example, found that citric acid induced cough was abolished by 10 min inhalation of a strong aerosol of the potent local anaesthetic bupivacaine (50 mg·ml⁻¹, yielding peak plasma concentrations of about 1 μg·ml⁻¹). However, it cannot be excluded that cough induced by capsaicin is more sensitive to lignocaine than that induced by citric acid. Another explanation is that lignocaine is a more potent antitussive than bupivacaine.

The shift produced by this dose of nebulized lignocaine appears to be quite modest. However, a larger dose would probably have produced a larger degree of inhibition and, moreover, the presently used method (DCR) may show smaller changes than, for example, repeat 1 min inhalations of capsaicin [17]. Interestingly, the effect of inhaled lignocaine in the present study is of the same magnitude as that of systemic administration of a large dose of opiates [16]. These data demonstrate that low dose anaesthesia could be used to reduce the sensitivity of the cough reflex. This reduction would be sufficient to return the abnormal sensitivity of the reflex to normal in patients in whom this is associated with cough [18].

The capsaicin-induced transient increase in respiratory resistance is inhibited by an anticholinergic drug, indicating that it is a vagal cholinergic reflex [13]. In contrast to the cough response, lignocaine was without effect on the increase in respiratory resistance. With the exception of the study by CROSS et al. [5], in which a citric acid induced bronchial obstruction in one subject was attenuated by inhaled lignocaine, most studies have shown no topical effect of administered local anaesthetics on reflex bronchoconstriction in man [18–20]. Bronchoconstriction is mediated by rapidly adapting

stretch receptors and c-fibres, whereas rapidly adapting stretch receptors are believed to constitute the afferent pathway in the cough reflex [11]. A role for afferent c-fibres in cough also seems possible [11, 19]. Although it is not clear in man which fibres are stimulated by inhaled capsaicin, animal studies suggest that it is a rather selective stimulant of c-fibre endings [21]. Cough can be induced in the absence of bronchoconstriction and *vice versa*, and the two reflexes have a separate sensitivity to drugs and, therefore, different afferent nerves are believed to mediate these reflexes. It seems probable that capsaicin may activate a number of different pathways. Alternatively, it could be argued that the two reflexes occur from different levels of stimulation of the same sensory nerves. However, the present findings that lignocaine inhibits only one of the components support the view that different groups of sensory nerves are involved. These data are in accordance with the observations of SHEPPARD *et al.* [19] that lignocaine inhibits cough but not bronchoconstriction produced by inhaled distilled water in asthmatics. Interestingly, the water induced bronchial obstruction, but not cough, is sensitive to cromoglycate [19, 22]. Together with the observation that the two reflexes can be induced separately by, for example, inhaled aqueous solutions of different ionic composition and osmolarity [23, 24] it seems likely that these reflexes have separate afferent neural pathways.

Aerosolized local anaesthetics are rapidly absorbed from the airways to yield substantial plasma concentrations [25, 26]. The possibility exists, therefore, that the antitussive effect of lignocaine was due to an interaction of absorbed drug with peripheral or central nervous pathways in the cough reflex. However, to attenuate the cough reflex, plasma levels of >3 $\mu g \cdot ml^{-1}$ of intravenous lignocaine [27] have to be achieved. Antitussive doses of inhaled lignocaine 20–80 mg, as used in this study, according to MIDGEON *et al.* [17] would produce low plasma levels of lignocaine. It is, therefore, likely that lignocaine acted locally in the airways to inhibit conduction in the afferent neurones mediating cough. Unexpectedly, neither dose of dyclonine had an effect on the cough response or the change in respiratory resistance produced by capsaicin. Earlier human studies of anaesthesia of the mucosa of the tongue have suggested dyclonine to be 5–10 times more potent than lignocaine [14] and in the present study a similar degree of oropharyngeal anaesthesia was observed by 8 mg dyclonine and 40 mg lignocaine. This observation also rules out the possibility of a chemical inactivation of dyclonine in the nebulizer. The most likely explanation for the different effects on cough is a difference in the rate of penetration of the two local anaesthetics through the airway mucosa to the sensory nerve endings in the airway responsible for cough, although other factors such as the local metabolism and clearance of the anaesthetics from their site of action cannot be excluded.

From the present study it can be concluded that cough and reflex bronchoconstriction have a separate sensitivity to inhaled local anaesthetics. Thus, separate afferent pathways are likely to be involved.

Furthermore, different types of local anaesthetics differentially affect these two airway reflexes despite producing the same sensation of oropharyngeal anaesthesia. Selective inhibition of airway reflexes can thus be achieved by using inhaled local anaesthetics.

This also implies that selecting local anaesthetics as putative antitussives has to be based upon experiments involving tussive challenge, rather than based on the potency as anaesthetics in other sites.

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Distinction de la toux et du réflexe de bronchoconstriction par l'inhalation d' anesthésiques locaux. N.B. Choudry, R.W. Fuller, N. Anderson, J-A. Karlsson.

RÉSUMÉ: La toux et la constriction des voies aériennes sont des traits fréquents dans les maladies respiratoires. Les deux peuvent être provoqués par la stimulation des nerfs des voies aériennes. Nous avons étudié les effets de l'anesthésie des voies aériennes sur ces réflexes, stimulés par l'inhalation de capsaïcin, afin de déterminer s'ils étaient contrôles par les mêmes nerfs sensitifs. 10 volontaires ont été soumis à une étude dose-réponse de la toux par capsaïcin, avant et Dix minutes après l'inhalation de placebo (acide ascorbique dans la solution saline isotonique), et d'anesthésiques topiques (lignocaïne 40 mg, dyclonine 8 et 4 mg). L'effet des médicaments sur la résistance respiratoire (Rrs), mesurée par la technique d'oscillation forcée, a été étudié avant et après l'inhalation d'une dose de capsaïcin qui causait moins de 2 secousses de toux. La lignocaïne (40 mg) et la dyclonine (8 mg) ont provoqué toutes deux une anesthésie buccale, mais seule la lignocaïne a réduit la réponse tussigène à l'inhalation de capsaïcin, en augmentant de 162% la dose log de capsaïcin, provoquant 3 secousses de toux ou davantage. Aucun des traitements n'a modifié la Rrs basale ou son augmentation après inhalation de capsaïcin. Donc, les réflexes de toux et les réflexes de bronchoconstriction causés par l'inhalation de capsaïcin ont une sensibilité différente à l'égard de l'anesthésie locale par inhalation, ce qui suggère que cet effet pourrait être médie par des voies sensitives différentes.

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