I.v. lidocaine worsens histamine-induced bronchoconstriction in dogs

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We have assessed the effect of lidocaine (lignocaine) on histamine-induced bronchoconstriction by direct visualization with a superfine fibreoptic bronchoscope. Seven mongrel dogs were anaesthetized with pentobarbital (pentobarbitone) 30 mg kg\(^{-1}\) followed by 2 mg kg\(^{-1}\) h\(^{-1}\) and pancuronium 200 µg kg\(^{-1}\) h\(^{-1}\). The trachea was intubated with a tracheal tube containing a second lumen for insertion of a 2.2-mm fibreoptic bronchoscope. This allowed estimation of the bronchial cross-sectional area (BCA) of the third bronchial bifurcation of the right lung. We used NIH image, a public domain image processing and analysis program. Bronchoconstriction was produced with a bolus dose of histamine 10 µg kg\(^{-1}\) i.v. followed by continuous infusion of 500 µg kg\(^{-1}\) h\(^{-1}\). After 30 min the following i.v. doses of lidocaine were given: lidocaine 0 (saline), 0.01, 0.1, 1.0 and 10 mg kg\(^{-1}\) at 10-min intervals. BCA was assessed 90 s after each dose. Arterial blood sampling was performed for measurement of plasma catecholamines. Lidocaine 1.0 and 10 mg kg\(^{-1}\) significantly reduced histamine-decreased BCA from 69.7 (SEM 4.1)% to 59.8 (7.3)% and 34.3 (6.8)% respectively. Plasma concentrations of catecholamines decreased significantly after lidocaine 10 mg kg\(^{-1}\) i.v. In addition, there was a significant correlation between percentage decreases in plasma concentrations of epinephrine (adrenaline) and norepinephrine (noradrenaline) and reduction in %BCA (epinephrine–BCA, \(P<0.01, r=0.674\); norepinephrine–BCA, \(P<0.01, r=0.510\)). This study suggests that i.v. lidocaine may exacerbate histamine-induced bronchoconstriction by a sympatholytic effect. This may have therapeutic implications for patients with acute asthma or anaphylactic shock who may become dependent on circulating catecholamines.

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Lidocaine (lignocaine) has been reported to be effective in the treatment of bronchospasm during general anaesthesia.\(^1\) In addition, lidocaine is used commonly to blunt airway reflexes during tracheal intubation, extubation and suction, and bronchoscopy. Kai and colleagues\(^2\) reported that lidocaine has direct spasmolytic effects on airway smooth muscle by inhibition of Ca\(^{2+}\) influx and release of stored Ca\(^{2+}\).

We have recently developed a new direct visualization method to quantify bronchial calibre using a superfine fibreoptic bronchoscope. This direct method may be more specific than conventional measurements such as airway pressure, airway resistance or dynamic pulmonary compliance to assess airway calibre.\(^3\)–\(^8\) Using this method, we have evaluated the effects of i.v. lidocaine on histamine-induced bronchoconstriction in dogs.

Materials and methods

The study was approved by the Animal Care and Use Committee of the University of Hirosaki School of Medicine. Seven mongrel dogs (8–12 kg) were anaesthetized with pentobarbital (pentobarbitone) 30 mg kg\(^{-1}\) i.v. followed by continuous infusion of 2.0 mg kg\(^{-1}\) h\(^{-1}\). Neuromuscular block was produced with pancuronium 0.2 mg kg\(^{-1}\) h\(^{-1}\). The trachea was intubated with a tracheal tube (id 7.0 mm, Univent tube, Fuji System, Tokyo) containing a second lumen for insertion of a superfine fibreoptic bronchoscope.

The lungs were ventilated mechanically with oxygen using a volume controlled respirator (Servo 900C) and end-tidal carbon dioxide concentration was maintained at 4.0–4.5%. The femoral artery was cannulated to monitor arterial pressure and to sample arterial blood for measurement of plasma catecholamines by high-pressure liquid chromato-
graphy. Blood samples (6 ml) were centrifuged immediately at 3000 rpm for 10 min at –10°C to separate plasma which was then frozen at –70°C until assayed. The femoral vein was also cannulated to insert a pulmonary catheter (Swan-Ganz catheter, Baxter Health Co, Tokyo). A superfine fibreoptic bronchoscope (od 2.2 mm: AF type 22A, Olympus, Tokyo) was inserted through the second lumen of the tracheal tube so that the tip lay between the second and third bifurcation of the right bronchus in order to monitor continuously bronchial cross-sectional area at the third bifurcation.

The image of the third bifurcation was printed using a video printer (VY -170, Hitachi, Tokyo) during the end-expiratory pause. The printed image was scanned into a Macintosh computer (Power Macintosh 7100/80 AV, Apple Computer Inc, CA, USA; Scan-Jet IIc, Hewlett Packard Co, CO, USA) to measure bronchial cross-sectional area. We used the NIH Image program, which is a public domain image processing and analysis program (Wayne Rasband, US National Institutes of Health, available from the Internet by anonymous ftp from zippy.nimh.nih.gov or on floppy disk from NTIS, 5285 Port Royal Road, Springfield, VA 22161, part number PB93-504868). This image processing was performed by an investigator who was blinded to the study. The bronchial cross-sectional area measurement was performed at baseline before induction of bronchoconstriction by bolus injection of histamine 10 µg kg⁻¹ followed by a continuous infusion of 500 µg kg⁻¹ h⁻¹. This was given into the pulmonary arterial cannula until the end of the experiment. Systolic arterial pressure was maintained greater than 80 mm Hg with fluid (lactate Ringer’s solution 30–70 ml kg⁻¹). After 30 min the following i.v. doses were given at 10-min intervals: lidocaine 0 (saline), 0.01, 0.1, 1.0 and 10 mg kg⁻¹. Bronchial cross-sectional area was measured 90 s after each lidocaine dose. Bronchial cross-sectional area was expressed as percentage of basal bronchial cross-sectional area.

**Statistical analysis**

All data are expressed as mean (SEM). The relationship between percentage reduction in plasma concentrations of catecholamines and BCA by lidocaine (% reduction = (plasma catecholamines or BCA at 90 s after lidocaine i.v./ plasma catecholamines or BCA at 90 s after saline i.v.)×100) was examined by Pearson’s correlation coefficient and a least squares linear regression line was fitted using GraphPad Prism 1.03. Data were analysed with a paired t test or repeated measures analysis of variance followed by Fisher’s protected least significant difference test using Stat View II on Macintosh computer. P<0.05 was considered significant.

**Results**

There were no significant differences in %BCA and plasma catecholamine concentrations between 30 min after the start of histamine infusion and 90 s after administration of saline i.v. (%BCA 69.7 (4.1) vs 70.2 (5.0); epinephrine (adrenaline) 1.96 (0.61) vs 2.05 (0.63) ng ml⁻¹; norepinephrine (noradrenaline) 378 (91) vs 384 (100) pg ml⁻¹, respectively).

Doses greater than lidocaine 1.0 mg kg⁻¹ significantly reduced BCA (Fig. 1). Plasma concentrations of epinephrine and norepinephrine also decreased after lidocaine 10 mg kg⁻¹ i.v. (Fig. 2). Moreover, there was a significant correlation between percentage reduction in plasma catecholamine concentrations and histamine-decreased BCA by lidocaine (Fig. 3).

**Discussion**

We have demonstrated that i.v. lidocaine worsened histamine-induced bronchoconstriction accompanied by reductions in plasma catecholamines. We have confirmed that %BCA is stable, at least from 30 to 90 min after the start of histamine infusion. Therefore, reduction in %BCA may not be a result of a cumulative effect of histamine,
lidocone may inhibit only reflex bronchospasm caused by tracheal intubation, extubation or suction.

In our study, histamine was used as a bronchoconstrictor. Histamine release from mast cells accounts in part for allergic responses such as asthma and anaphylactic shock, and hence our model will reflect some of these clinical conditions.

In summary, we have shown that i.v. lidocaine may worsen histamine-induced bronchoconstriction by a sympatholytic effect. This may have therapeutic implications for patients with acute asthma or anaphylactic shock.

References