Effects of thiopental on airway calibre in dogs: direct visualization method using a superfine fibreoptic bronchoscope

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Summary
Induction of anaesthesia with thiopental sometimes causes bronchospasm. Although the mechanism by which thiopental induces bronchospasm may involve cholinergic stimulation, direct spastic effect and histamine release, the spastic effects of thiopental have not been comprehensively defined. In this study, we have assessed the effect of thiopental on in vivo airway smooth muscle tone using direct visualization method with a superfine fibreoptic bronchoscope as previously reported. Twenty-one mongrel dogs were anaesthetized with pentobarbital (30 mg kg⁻¹) and paralysed with pancuronium (200 µg kg⁻¹ h⁻¹). The trachea was intubated with a tube that had a second lumen for insertion of the bronchoscope (od: 2.2 mm) to continuously measure bronchial cross-sectional area. The tip of the bronchoscope was placed between the second and third bronchial bifurcation of the right lung. The dogs were allocated to three groups of seven: group T, A+T, H+T. In group T, thiopental 0 (saline), 0.1,1.0 and 10 mg kg⁻¹ was given i.v. In group A+T, saline i.v., 5 min later atropine 0.1 mg kg⁻¹ i.v., and 5 min later thiopental 10 mg kg⁻¹ was administered. In group H+T, bronchoconstriction was produced with histamine 10 µg kg⁻¹ i.v. followed by infusion at 500 µg kg⁻¹ h⁻¹. Thirty minutes later, thiopental 0, 1.0 and 10 mg kg⁻¹ were given. Arterial blood sampling was performed for measurement of plasma catecholamines and histamine. In group T, thiopental significantly reduced bronchial cross-sectional area (maximally by 28.7 (5.6% at T, thiopental significantly reduced bronchial smooth muscles in dogs.

Key words: anaesthetics i.v., thiopental; complications, bronchospasm; histamine; measurement techniques, fibreoptic bronchoscope

Induction doses of thiopental do not abolish airway reflexes and hence tracheal intubation sometimes causes bronchospasm.¹ Baker and colleagues reported that induction doses of thiopental produced a significant decrease in the angle formed by the vocal cords. In addition they observed complete glottic closure in four of 14 patients. As the entire motor innervation to the laryngeal muscles is supplied by two branches of the vagus nerve: the superior and recurrent laryngeal nerves,¹ the reduction in angle between the vocal cords including laryngospasm may be caused by vagal stimulation by thiopental. Thiopental related allergic reactions may be partially because of bronchospasm, as thiopental causes histamine release from leucocytes.⁴ Several in vitro studies⁷ have also shown direct spastic effects of thiopental on tracheal smooth muscle. The use of thiopental in asthmatic patients is controversial. Shnider and Papper² reported that thiopental in itself did not cause bronchospasm in asthmatic patients, while Pizov and colleagues¹⁰ described that both asthmatic and non-asthmatic patients receiving thiobarbiturates had a greater incidence of wheezing (45%, 13%, respectively) than did asthmatic and non-asthmatic patients receiving propofol (0%, 3%, respectively).

We have recently developed a new direct method for quantification of bronchial calibre using a superfine fibreoptic bronchoscope, and have shown that this direct method may be more specific than conventional measurements such as airway pressure, airway resistance or dynamic pulmonary compliance.¹¹⁻¹⁵ In the present study, we have used this method to evaluate the in vivo effects of thiopental on bronchial smooth muscles in dogs.

Methods
Our study design was approved by Animal Care and Use Committee of the University of Hirosaki School of Medicine. Twenty-one mongrel dogs (8–12 kg) were anaesthetized with pentobarbital 30 mg kg⁻¹ i.v. and paralysed with pancuronium at 200 µg kg⁻¹ h⁻¹. The tracheas were intubated with tubes (id: 7.0 mm, Univent tube, Fuji System, Tokyo) that have a second lumen for the insertion of a superfine fibreoptic bronchoscope. The lungs were mechanically ventilated.
using a volume-controlled respirator (Servo 900C) with oxygen and the end-tidal carbon dioxide maintained at 4.0–4.5%. The femoral artery was cannulated to monitor arterial pressure and to obtain arterial blood samples. The femoral vein was also cannulated to insert a Swan-Ganz catheter (Baxter Health Co., Tokyo) via its sheath to avoid potentiation of histamine-induced bronchospasm by flushing histamine from the dead space of a single i.v. catheter.

**IMAGING AND ANALYSIS OF AIRWAY**

We inserted a superfine fibreoptic bronchoscope (od 2.2 mm: AF type 22A, Olympus, Tokyo) through the second lumen of the tracheal tube placing the tip between the second and third bronchial bifurcation of the right bronchus in order to continuously monitor bronchial cross-sectional area at the third bifurcation. The image at the third bifurcation was printed out with a videoprinter (VY-170, Hitachi, Tokyo) after expiration and before inspiration. The printed image was imported into a Macintosh computer (Power Macintosh 7100/80 AV, Apple Computer Inc., California) using a scanner (Scan-Jet 4c, Hewlett Packard Co, Colorado) to measure the bronchial cross-sectional area with the NIH Image program, which is a public domain image processing and analysis program (Wayne Rasband, US National Institutes of Health, available from Internet by anonymous ftp from zippy.nimh.nih.gov or on floppy disk from NTIS, 5285 Port Royal RD., Springfield, VA 22161, part number PB93–504868).

![Figure 1](image-url)  
*Figure 1* Effect of thiopental on basal bronchial cross-sectional area with (g) and without atropine (Atrop) pretreatment (a). Pre: before thiopental or saline i.v., Thiop: thiopental, *P<0.05, **P<0.01 compared with Pre. All values are expressed as mean (SEM).
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PROCEDURE 1: EFFECT OF THIOPENTAL ON THE BASAL AIRWAY TONE

Fourteen dogs were allocated to two groups: thiopental administration group (group T, n=7) and atropine-thiopental administration group (group A+T, n=7). One hour after the placement of a superfine fibreoptic bronchoscope, the experiment was started. This reduces the effect of pentobarbital induction as pentobarbital in itself decreases bronchial cross-sectional area. However, dogs remained anaesthetized until the following procedure started (confirmed by electroencephalography in another 7 dogs).

In group T, after the basal bronchial cross-sectional area was measured, each thiopental dose: 0 (saline), 0.1, 1.0, 10 mg kg⁻¹ was given in this order at 5-min intervals. The bronchial cross-sectional area was measured at 0.5, 1, 2, 3, 4 and 5 min after each thiopental dose i.v.

In group A+T, saline was given to confirm that the bronchoscope was well-fixed without any significant changes in bronchial cross-sectional area, 5 min later atropine 0.1 mg kg⁻¹ was given i.v. and then 5 min later thiopental 10 mg kg⁻¹ was administered. The bronchial cross-sectional area was measured at 0 and 5 min after atropine i.v. and 0.5, 1, 2, 3, 4 and 5 min after thiopental i.v.

PROCEDURE 2: EFFECTS OF THIOPENTAL ON HISTAMINE-INDUCED BRONCHOCONSTRICTION

Seven dogs were studied. The basal bronchial cross-sectional area measurement was performed before the induction of bronchoconstriction by continuous infusion of histamine at 500 μg kg⁻¹ h⁻¹ following a bolus injection of 10 μg kg⁻¹ via pulmonary arterial catheter until the end of the experiment. Systolic arterial pressure was maintained above 80 mm Hg with fluid (lactate Ringer’s solution: 50 ml kg⁻¹) and with continuous phenylephrine infusion at 0.5–2.0 μg kg⁻¹ min⁻¹, the rate of which was dependent on systolic arterial pressure. Thirty minutes after the start of histamine infusion, thiopental: 0 (saline), 1.0, 10 mg kg⁻¹ was given in this order at 5-min intervals. The bronchial cross-sectional area was measured at 0.5, 1, 2, 3, 4 and 5 min after each thiopental dose i.v. The bronchial cross-sectional area is presented as % of basal bronchial cross-sectional area.

PLASMA CATECHOLAMINES AND HISTAMINE ASSAY

Blood samples (6 ml) were taken through the arterial cannula at 1 and 5 min after each dose of thiopental i.v. and were immediately centrifuged at 3000 rpm for 10 min at −10 °C to separate plasma which was then frozen at −70 °C until assayed. The plasma concentrations of epinephrine and norepinephrine were determined by gas chromatography mass spectrometry in all groups. The coefficient of variation of the assay was 8.4% for epinephrine and 11.3% for norepinephrine. Plasma histamine concentrations in group T were measured by radioimmunoassay. The minimal detection limit was 0.2 nmol litre⁻¹ and the intra- and inter-assay coefficient of variations were 7.2% and 7.8%, respectively. The antiserum showed no significant cross-reactivity with L-histidine, methyl-histamine, imidazole or methyl-imidazole.

STATISTICAL ANALYSIS

All data were expressed as mean (SEM). Data were analysed statistically using repeated measures analysis of variance followed by Fisher’s protected least significant difference test using Stat View 2.0 for Macintosh. A P<0.05 was considered significant.

Results

PROCEDURE 1

Thiopental (>1.0 mg kg⁻¹) significantly reduced bronchial cross-sectional area, which spontaneously returned to the baseline within 3 min (group T, fig. 1A). With the exception of norepinephrine at 1 min after thiopental 10 mg kg⁻¹ i.v., plasma concentrations of epinephrine, norepinephrine and histamine did not change significantly after thiopental i.v. (table 1). In group A+T, atropine significantly increased bronchial cross-sectional area, and this preadministration blocked thiopental-induced decrease in the bronchial cross-sectional area (fig. 1B). Moreover, thiopental significantly increased atropine-pretreated bronchial cross-sectional area (fig. 1B).

PROCEDURE 2

Histamine decreased the bronchial cross-sectional area by 34.1% (2.6%) of basal bronchial cross-sectional area. The bronchial cross-sectional area decreased transiently but significantly after thiopental 10 mg kg⁻¹ (fig. 2). Plasma catecholamines did not change (table 2).

Discussion

The present study demonstrates that thiopental transiently but significantly increased basal bronchial smooth muscle tone, which was completely inhibited by atropine pretreatment. Several reports2,30 suggest that thiopental may increase upper airway reflex sensitivity to produce laryngospasm. This finding supports the notion that thiopental increases vaga tone to produce bronchospasm.

<table>
<thead>
<tr>
<th></th>
<th>T 0.1 mg kg⁻¹</th>
<th>T 1.0 mg kg⁻¹</th>
<th>T 10 mg kg⁻¹</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>1 min</td>
<td>5 min</td>
</tr>
<tr>
<td>Norepinephrine (μg ml⁻¹)</td>
<td>121 (27)</td>
<td>158 (31)</td>
<td>136 (32)</td>
</tr>
<tr>
<td>Epinephrine (μg ml⁻¹)</td>
<td>159 (15)</td>
<td>129 (13)</td>
<td>127 (23)</td>
</tr>
<tr>
<td>Histamine (nmol litre⁻¹)</td>
<td>1.7 (0.2)</td>
<td>1.6 (0.2)</td>
<td>1.6 (0.2)</td>
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</tbody>
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Table 1 Changes in plasma catecholamine and histamine concentrations 1 and 5 min following thiopental (T) i.v., mean (SEM). **P<0.01 compared with before thiopental
In vitro studies indicate that thiobarbiturates, but not oxybarbiturates, directly produce airway smooth muscle contraction which may result from the production of thromboxane A$_2$. However, our previous report showed that pentobarbital, an oxybarbiturate, increased bronchial smooth muscle tone. Moreover, the present study shows that thiopental-induced bronchospasm was completely blocked by atropine. Therefore, the production of thromboxane A$_2$ by thiopental may not be the primarily cause of bronchospasm in vivo.

Hirshman and colleagues reported that thiopental caused anaphylactic shock which may be because of histamine release from leucocytes. They also showed that thiopental induces histamine release in human skin mast cells. In addition, Lorenz and colleagues found increases in plasma histamine concentrations after i.v. administration of thiopental even in normal subjects. These findings suggest that histamine release may be involved in the mechanism of thiopental-induced bronchospasm. However, in the present study, as the plasma concentration of histamine did not change after i.v. thiopental, histamine release may not contribute to bronchospasm.

As thiopental inhibits sympathetic neural outflow, it may cause bronchospasm. However, in the present study, plasma level of catecholamines were not altered by thiopental i.v. with and without histamine infusion that increased plasma catecholamine concentration. Therefore, it is unlikely that sympatholytic effect of thiopental caused the bronchospasm in the present study.

In the present study, after atropine administration, thiopental unexpectedly produced a relaxant effect. Yamakage and colleagues reported that thiopental inhibits voltage sensitive Ca$^{2+}$ channels in porcine tracheal smooth muscle cells. It has been suggested that block of Ca$^{2+}$ channels causes airway relaxation. Taken together, the relaxant effect of thiopental following vagal denervation might be because of inhibition of Ca$^{2+}$ influx.

In conclusion, the present study indicates that thiopental should be used carefully in patients with hyper-reactive airway as thiopental produced and worsened bronchospasm via vagal stimulation, and that atropine might protect from thiopental-induced bronchospasm.

| Table 2 | Changes in plasma catecholamine concentrations 1 and 5 min after thiopental (T) i.v. in presence of histamine (H) infusion at 500 µg kg$^{-1}$ h$^{-1}$, mean (SEM). H30: 30 min after the start of histamine infusion |
|---------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|         | H30    | Saline  | T 1.0 mg kg$^{-1}$ | T 10 mg kg$^{-1}$ |
| Norepinephrine (pg ml$^{-1}$) | 237 (91) | 202 (57) | 321 (122) | 306 (140) |
| Epinephrine (ng ml$^{-1}$)     | 3.78 (1.53) | 3.16 (1.18) | 7.82 (5.91) | 4.84 (2.64) |
|                                 | 453 (296) | 293 (137) | 7.38 (6.37) | 16.5 (15.9) |

Figure 2 Effect of thiopental on histamine (H)-induced bronchoconstriction assessed by changes in bronchial cross-sectional area. Pre: before start of H infusion. H30:30 min after the start of H infusion, *P<0.05 compared with H30. All values are expressed as mean (SEM).
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