In vivo assessment of droperidol-induced bronchial relaxation in dogs using a superfine fibreoptic bronchoscope

N. OTOMO, K. HIROTA, T. SATO, Y. HASHIMOTO AND H. ISHIHARA

Summary

Droperidol has been reported to cause bronchodilatation but its mechanism(s) of action is unknown. We have evaluated the spasmolytic effect of droperidol on histamine- and serotonin (5-HT)-induced bronchoconstriction in dogs. Bronchial cross-sectional area was assessed with a superfine fibreoptic bronchoscope. Twenty-eight mongrel dogs were allocated randomly to one of two groups (histamine and 5-HT) to receive either histamine or 5-HT to induce bronchoconstriction. Changes in bronchial cross-sectional area were presented as percentage of basal bronchial cross-sectional area. Continuous i.v. infusion of histamine 500 μg kg⁻¹ h⁻¹ or 5-HT 500 μg kg⁻¹ h⁻¹ decreased percentage bronchial cross-sectional area by 46.4 (14.3) % or 68.9 (13.7) %, respectively. In both groups, droperidol reversed bronchoconstriction in a dose-dependent manner. In the histamine but not in the 5-HT group, plasma adrenaline and noradrenaline concentrations increased significantly after i.v. droperidol. In addition, propranolol antagonized droperidol-induced relaxation in the histamine but not in the 5-HT group. Our data indicate that the spasmolytic effect of droperidol on canine airway was caused, at least in part, by catecholamine release and 5-HT receptor antagonism. (Br. J. Anaesth. 1997; 78: 579–582).

Key words


Materials and methods

After approval of our Animal Experiment Committee, 28 mongrel dogs, weighing 8–12 kg, were anaesthetized with pentobarbitone 30 mg kg⁻¹ i.v. and paralysed with pancuronium 200 μg kg⁻¹ h⁻¹ i.v. The trachea was intubated using a tracheal tube (internal diameter 7.0 mm; Fuji system, Tokyo, Japan) with an additional small lumen for insertion of a superfine fibreoptic bronchoscope with an outer diameter of 2.2 mm (OES Angiofiberscope AF type 22A, Olympus, Tokyo, Japan) to monitor continuously bronchial cross-sectional area. The tip of the fibrescope was located between the second and third bifurcation of the right lung. Fibreoptic image of bronchial cross-sectional area was printed via a videoprinter (Videoprinter VY-170, Hitachi, Tokyo, Japan) and measured with an NIH image program which is well established and widely used (written by Wayne Rashand at the US National Institutes of Health and available from the Internet by anonymous ftp from zippy. nih. govt. or on floppy disk from NTIS, 5285 Port Royal Rd., Springfield, VA 22161, part number PB93–504868). Changes in bronchial cross-sectional area were represented as percentage of basal bronchial cross-sectional area (assessed before bronchoconstrictor infusion). The lungs were ventilated with an animal ventilator (AR-300, Acoma, Tokyo, Japan) and end-tidal carbon dioxide was maintained continuously at 4.5–5.0% before induction of bronchoconstriction. Systemic arterial pressure was monitored continuously via a femoral arterial cannula which was also used for blood sampling. A pulmonary artery catheter was inserted via the femoral vein to administer drugs and superfine fibreoptic bronchoscope with increased sensitivity compared with measures of airway resistance, dynamic pulmonary compliance and airway pressure. After this study, we have assessed in vivo the spasmolytic effects of droperidol on histamine- and 5-HT-induced bronchoconstriction in dogs by measuring airway calibre using a fibreoptic bronchoscope.

Draperidol is an effective agent for the treatment of status asthmaticus. The bronchodilating effect of droperidol may be mediated via α₁-adrenoceptor block, catecholamine release and serotonin (5-HT) receptor antagonism. Gentil and colleagues demonstrated that droperidol prevented 5-HT but not histamine-induced bronchospasm in guinea pigs. In contrast, we have reported previously that droperidol inhibits tracheal contraction induced by both 5-HT and histamine. Gentil and colleagues evaluated bronchospasm by measuring respiratory conductance, a classical indirect measure with low sensitivity and reliability. We have developed a direct method to quantify bronchial calibre using a superfine fibreoptic bronchoscope with increased sensitivity compared with measures of airway resistance, dynamic pulmonary compliance and airway pressure. In this study, we have assessed in vivo the spasmolytic effects of droperidol on histamine- and 5-HT-induced bronchoconstriction in dogs by measuring airway calibre using a fibreoptic bronchoscope.

NORIAKI OTOMO, MD, KAZUYOSHI HIROTA, MD, TETSUJI SATO, MD, YOSHI HASHIMOTO, MD, HIRONORI ISHIHARA, MD, Departments of Anaesthesiology, University of Hirosaki, School of Medicine, Hirosaki 036, Japan. Accepted for publication: January 10, 1997.

Correspondence to K. H.
to infuse lactate Ringer’s solution 4 ml kg\(^{-1}\) h\(^{-1}\). Dogs were allocated randomly to one of two groups; 14 dogs received histamine to induce bronchoconstriction (histamine group) and the remaining 14 dogs received 5-HT (5-HT group).

**HISTAMINE GROUPS**

Bronchoconstriction was induced with a bolus dose of histamine 10 \(\mu\)g kg\(^{-1}\) i.v. followed by an infusion of 500 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) via the pulmonary artery catheter. Systolic arterial pressure was maintained greater than 80 mm Hg with infusion of fluid 50 ml kg\(^{-1}\) and with continuous infusion of phenylephrine 0.5–2.0 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) at a rate dependent on systolic arterial pressure and which could not significantly affect histamine-induced bronchoconstriction. Thirty minutes later, when stable bronchoconstriction was achieved, droperidol was given i.v. Seven of the 14 dogs were given each dose of droperidol: 0 (saline), 0.01, 0.1 and 1.0 mg kg\(^{-1}\) i.v. (histamine–droperidol group), and the remaining seven dogs were given droperidol 0 and 1.0 mg kg\(^{-1}\) followed by 100 \(\mu\)g kg\(^{-1}\) of propranolol (histamine–droperidol–propranolol group). In both groups, bronchial cross-sectional area was assessed before and 30 min after the start of histamine infusion and 5 min after administration of each dose of droperidol and propranolol. At least 15 min elapsed between administration of each dose. Arterial blood was obtained simultaneously with bronchial cross-sectional area assessments for measurement of plasma concentrations of adrenaline and noradrenaline in the histamine–droperidol group. Log-dose–response curves were constructed using DeltaGraph Pro. (DeltaPoint, Inc. 1992). Plasma adrenaline and noradrenaline concentrations were measured by gas chromatography–mass spectrometry.

**5-HT GROUPS**

In the 5-HT groups, bronchoconstriction was induced with a bolus of 5-HT 10 \(\mu\)g kg\(^{-1}\) i.v. followed by an infusion of 500 \(\mu\)g kg\(^{-1}\) h\(^{-1}\). Seven dogs were included in the 5-HT–droperidol group and the remaining seven dogs in the 5-HT–droperidol–propranolol group. The remainder of the study was as described for the histamine groups.

**ANALYSIS OF DATA**

All data are expressed as mean (SD). Statistical analyses were by repeated-measures ANOVA followed by Fisher’s protected least significant difference test for the histamine and 5-HT–droperidol groups, and by Scheffe’s F test for the histamine and 5-HT–droperidol–propranolol groups. \(P<0.05\) was considered significant.

**Results**

**HISTAMINE GROUP**

In the histamine–droperidol group, histamine decreased percentage bronchial cross-sectional area by 46.4 (14.3) % (fig. 1A). Droperidol produced a dose-dependent increase in percentage bronchial cross-sectional area (i.e. bronchodilatation) with an \(ED_{50}\) of 0.157 (0.108) mg kg\(^{-1}\); 1.0 mg kg\(^{-1}\) produced full reversal of histamine-induced bronchoconstriction. Plasma adrenaline and noradrenaline concentrations also increased significantly in a dose-dependent manner (fig. 2). In the histamine–droperidol–propranolol group, histamine decreased percentage bronchial cross-sectional area by 35.7 (14.0) % which was reversed by droperidol (percentage bronchial cross-sectional area 98.4 (15.1) %). Propranolol 100 \(\mu\)g kg\(^{-1}\) fully reversed the increase in bronchial cross-sectional area induced by droperidol (fig. 1B).

5-HT decreased percentage bronchial cross-sectional area by 77.1 (13.0) % in the 5-HT–droperidol group and by 68.9 (13.7) % in the 5-HT–droperidol–propranolol group. Droperidol...
Droperidol-induced bronchial relaxation in dogs

581

1.0 mg kg\(^{-1}\) reversed 5-HT-induced decrease in bronchial cross-sectional area in both the 5-HT–droperidol (fig. 1A) and the 5-HT–droperidol–propranolol groups (fig. 1B). However, there were no significant changes in plasma adrenaline and noradrenaline concentrations, which were significantly lower than those in the histamine–droperidol group (fig. 2). Propranolol had no effect on droperidol-induced bronchodilatation (fig. 1B). The ED\(_{50}\) for droperidol reversal of 5-HT-induced bronchoconstriction was 0.013 (0.011) mg kg\(^{-1}\).

Droperidol was significantly more potent at reversing 5-HT than histamine-induced constriction (\(P<0.01\)).

Discussion

We have reported previously that droperidol inhibits histamine- and 5-HT-induced contraction of guinea pig tracheal smooth muscle in vitro.\(^6\) Our study has confirmed that droperidol was capable of producing bronchodilatation in bronchospastic states induced by histamine or 5-HT in vivo. The mechanism of droperidol-induced relaxation may be via \(\alpha\)-adrenoceptor block,\(^1\) \(\beta\)-adrenergic stimulation by catecholamine release\(^2,3\) and 5-HT receptor antagonism.\(^4,6\) However, our previous in vitro study\(^6\) indicated that prazosine (\(\alpha\)-blocker) did not alter either 5-HT-induced tracheal contraction or the relaxant effect of droperidol. None the less, \(\alpha\)-adrenoceptor block cannot be excluded as the \(\alpha\)-adrenoceptor is involved in the mechanism of asthma.\(^12,13\) Droperidol has been reported to induce catecholamine release.\(^2,3\) In our study, the histamine groups indicated that droperidol produced a spasmylic effect accompanied by catecholamine release and that propranolol completely antagonized droperidol-induced relaxation. Therefore, it is likely that catecholamine release is involved indirectly in droperidol-mediated relaxation. In contrast, in the 5-HT groups, droperidol-induced relaxation of 5-HT-induced bronchoconstriction was not caused by catecholamine release. Relaxation may be produced by a direct 5-HT receptor blocking action of droperidol. In agreement with our previous in vitro study\(^6\), in this study we found that the ED\(_{50}\) of droperidol against 5-HT was one order of magnitude more potent than against histamine. These findings suggest that 5-HT-induced bronchoconstriction is more specifically antagonized by droperidol than histamine.

Gentil and colleagues found that droperidol prevented 5-HT- but not histamine-induced constriction but this was assessed indirectly using respiratory conductance.\(^4\) However, Brown and colleagues\(^7,8\) reported that indirect assessment of airway calibre by airway resistance and pulmonary compliance may be a less reliable assessment of bronchodilatation compared with direct vision using high resolution computed tomography. We have also found that our direct vision method using a superfine fibreoptic bronchoscope was more sensitive than indirect measures.\(^10\)

Acknowledgement

We thank Emeritus Professor J. W. R. McIntyre (Department of Anaesthesiology, University of Alberta at Edmonton, Canada) and Dr D. G. Lambert (University Department of Anaesthesia, Leicester Royal Infirmary, UK) for their valuable comments. Supported in part by grant-in-aid for scientific research (No. 08771170) from the Minister of Education, Science and Culture in Japan.

References


