EFFECT OF FENTANYL ON VENTILATORY RESISTANCES DURING BARBITURATE GENERAL ANAESTHESIA

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SUMMARY

Fentanyl has been shown to increase the overall resistance to inspiratory flow of the ventilatory system (Rmax). Rmax is the sum of the airway resistance (Raw) and of the non-Newtonian resistance (AR) which may result from the viscoelastic properties of the thoracic tissues, from inequalities of the regional time constants within the lung, or from both. A bronchoconstrictor challenge may increase the magnitude of variation in regional time constants. Thus, in order to describe the effect of fentanyl on the two components of Rmax, this study was performed, with the end-inflation occlusion method, during paralysis and mechanical ventilation in 10 normal men undergoing barbiturate anaesthesia for minor urological procedures. The patients were anaesthetised with methohexitone and paralysed with vecuronium. Before administration of fentanyl, AR accounted for 56% of Rmax. Fentanyl 5 μg kg⁻¹ elicited a significant increase in Rmax (+34.5%; P = 0.005) and a parallel increase in both Raw (+35.2%, P = 0.017) and AR (+33.5%, P = 0.005). The increase in Raw, but not in AR, was reversed by atropine, suggesting that the increase in these two components of Rmax was not linked. Thus fentanyl increased both components of Rmax, but the effects of fentanyl on Raw and AR seemed to depend on different mechanisms.

PATIENTS AND METHODS

After approval from the local Ethics Committee, we studied 10 men undergoing elective surgery for testicular biopsy under general anaesthesia (mean age 30 yr (range 26–34 yr) weights 69.7 (SD 5.9) kg). The exclusion criteria were clinical or radiological abnormality of the ventilatory system; heavy smoking; suspected (history of atopy) or overt (history of wheezes) bronchial hypersensitivity; treatment with a beta blocker [10].

Mechanical ventilation was performed with a Servo Ventilator 900 D (Siemens-Elema, Sweden). This ventilator produces a constant inflation flow (V̇i), and an accurate tidal volume (VT) [11, 12]. It allows end-expiratory and end-inspiratory airway occlusions [13]. The ventilatory circuit comprised short tubing (40 cm) without a humidifier, in order to reduce the compressible volume. Each disposable tracheal tube (internal diameter 8 mm) was fitted with a lateral port at its distal end ("Blue Line", ref. 100/196/080 Portex Great Britain), that allowed measurement of the tracheal pressure [14]. The pressure signal and the flow signal fed by the ventilator were recorded on a Gould TA 550 polygraph, at a paper speed of 15 mm s⁻¹.

Ventilatory mechanics were studied using the end-inspiratory occlusion method which has already been described.
achieve a standard volume history and the patient was connected to the ventilator. Six minutes later, above, the lungs were ventilated manually in order to was intubated with the orotracheal tube described subject during the duration of the study. The trachea surgical level of paralysis was observed in every stimulation of the adductor pollicis muscle. A muscular block was produced with vecuronium infusion of this drug (0.1 mg kg\(^{-1}\)). Neuro- and maintained with a continuous (SD 0.5) mg kg\(^{-1}\). During the constant inflation flow preceding occlusion (VT), an occlusion of about 6 s was performed at the ventilator valves (while pressing the "inspiratory hold" button) to detect any air leak. After airway occlusion, there was an abrupt decrease in tracheal pressure from a maximum pressure \(P_{\text{max}}\) to an inflection point \(P_i\), and a more gradual decay to a plateau pressure which is the elastic recoil pressure of the ventilatory system (\(P_{\text{el}}\)) [12]. Gas exchange during occlusion has a negligible effect on \(P_{\text{el}}\), which was measured after 3 s of the end-inspiratory occlusion. The initial decrease in pressure (\(P_{\text{max}} - P_i\)) reflects the resistive pressure attributable to the airway resistance (\(R_{\text{aw}}\)) during the constant inflation flow preceding occlusion (VT). Thus Raw equals (\(P_{\text{max}} - P_i\)) VT\(^{-1}\).

Similarly, overall resistance, Rmax, was calculated as \(R_{\text{max}} = (P_{\text{max}} - P_i) VT\)\(^{-1}\); additional resistance (\(\Delta R\)) = \(R_{\text{max}} - R_{\text{aw}}\); static elastance (\(E_{\text{st}}\)) = \(P_{\text{el}} VT\)\(^{-1}\) [12]; dynamic elastance (\(E_{\text{dy}}\)) = \(P_{\text{max}} VT\)\(^{-1}\). The possibility of an intrinsic PEEP (PEEPi) was excluded by an end-expiratory occlusion performed at the ventilator valves (while pressing the "expiratory hold" button). It would have been necessary to take account of any PEEPi in calculating resistance and elastance, but it was never seen in our patients. In order to avoid absorption atelectasis, the lungs were ventilated with 30% oxygen in nitrogen [16].

At each experimental time, at least one end-expiratory occlusion followed by at least three end-inspiratory occlusions were performed. All the occlusions were separated by five tidal breaths. As the ventilatory mechanics are frequency-, flow- and volume-dependent [5], all the subjects underwent ventilation of the lungs with the same pattern: frequency 15 b.p.m., \(V_T\) = 0.6 litre, inspiratory time (\(T_I\)) 1 s, expiratory time (\(T_E\)) 3 s.

The study was performed in the operating theatre, before the beginning of the surgical procedure. Midazolam 5 mg i.m. was given as a premedication. Anaesthesia was induced with methohexitone 2.85 (SD 0.5) mg kg\(^{-1}\) and maintained with a continuous infusion of this drug (0.1 mg kg\(^{-1}\) min\(^{-1}\)). Neur- muscular block was produced with vecuronium 0.15 mg kg\(^{-1}\) and monitored with train-of-four stimulation of the adductor pollicis muscle. A surgical level of paralysis was observed in every subject during the duration of the study. The trachea was intubated with the orotracheal tube described above, the lungs were ventilated manually in order to achieve a standard volume history and the patient was connected to the ventilator. Six minutes later, the first group of occlusions were recorded (\(T_0\): baseline values). A first dose of fentanyl 4.9 (0.4) \(\mu\)g kg\(^{-1}\) was given and a second group of occlusions (\(T_1\)) was recorded 6 min later. A second dose of fentanyl 1.75 (0.3) \(\mu\)g kg\(^{-1}\) was given together with atropine 1 mg. The last group of occlusions (\(T_2\)) was performed 6 min later. The duration of the study did not exceed 25 min and recovery was always uneventful.

**Statistical analysis**

Data are given as mean (SD). Means were compared with a non-parametric Friedman test and Wilcoxon signed-rank tests. \(P < 0.05\) was considered to be significant.

**RESULTS**

After administration of fentanyl, all the measured resistances increased significantly: \(R_{\text{max}}\) (\(P = 0.005\)), \(R_{\text{aw}}\) (\(P = 0.017\)) and \(\Delta R\) (\(P = 0.005\)) (table I). The increase in Raw paralleled the increase in \(\Delta R\), because the contribution of \(\Delta R\) to \(R_{\text{max}}\) remained stable: 56% at \(T_0\) and 56.8% at \(T_1\) (\(P = 0.87\)). While \(E_{\text{st}}\) remained stable during the whole study, \(E_{\text{dy}}\) increased slightly (+6.4%) (\(P = 0.005\)) with fentanyl (table II).

When atropine was added to fentanyl, Raw decreased significantly (\(P = 0.007\)) and returned to its control value (\(P = 0.17\)). However, \(\Delta R\) at \(T_2\) remained stable compared with its value at \(T_1\) (\(P = 0.14\)) but was significantly greater than at \(T_0\) (\(P = 0.012\)); its contribution to \(R_{\text{max}}\) increased significantly (\(P = 0.028\)) between \(T_1\) and \(T_2\) and was significantly greater at \(T_2\) than at \(T_0\) (\(P = 0.01\)). The decrease in \(R_{\text{max}}\) at \(T_2\) was significant compared with those at \(T_1\) (\(P = 0.005\)) and \(T_0\) (\(P = 0.04\)). \(E_{\text{dy}}\) remained stable between \(T_1\) and \(T_2\) (\(P = 0.64\)) (table I).

**DISCUSSION**

We have found that, in anaesthetized, paralysed patients undergoing mechanical ventilation, fentanyl increased all the measured resistances. There was a
parallel increase in Raw and \( \Delta R \), their respective contribution to Rmax remaining stable. When atropine was given, Raw decreased and returned to the control value, while the contribution of \( \Delta R \) to Rmax increased.

We have used the end-inspiratory occlusion method [7]; this allows separation of airway resistance (Raw) from the non-Newtonian, peripheral resistance (\( \Delta R \)). As \( \Delta R \) varies with the ventilatory pattern [5], we maintained the same pattern in all patients, to allow comparison of resistances. The tracheal pressure was measured within the airway, in order to avoid subtraction of the tracheal tube resistance from the resistance values [14]. Any occlusion has a finite time, and allows a residual flow [17]. The volume resulting from this residual flow can be estimated as 2.5% of \( V_T \), according to the calculations of Kochi and colleagues [18], who have studied ventilatory mechanics in cats with the same occlusion method and a very similar ventilator (Servo Ventilator 900 C). This leads to underestimation of the initial pressure change and thus of the values of Rmax and Raw. However, each subject acted as his own control and this allowed at least a qualitative comparison.

General anaesthesia and paralysis were obtained with methohexitone and vecuronium, respectively. It could be argued that these drugs might have modified bronchial size and reactivity. However, neither of these drugs induces measurable liberation of histamine [19,20], and vecuronium does not interact with the muscarinic receptor of the bronchial autonomic innervation [20]. Moreover, because fentanyl does not induce detectable liberation of histamine in plasma [21] or the tissues [22], we can postulate that the changes in resistance observed during the study were probably caused by the direct effect of fentanyl.

A second dose of fentanyl was given before the \( T_2 \) measurements in order to avoid an excessive decrease in plasma concentration of fentanyl. After a loading dose, there is a second distribution of fentanyl, with a half-life (\( T_1/2 \)) of 10–30 min, but with a wide variability in individual pharmacokinetics [23]. A second dose (1.75 \( \mu g \) \( kg^{-1} \)), is then able to maintain a relatively great plasma concentration of the drug [23]. Thus the effect of fentanyl on resistances would not be declining with time, and the observed values at \( T_2 \) could be attributed to the antagonism by atropine of the effect of fentanyl.

The baseline values of Rmax, Raw, \( \Delta R \) and Est were in the range of values calculated from the data of D'Angelo and colleagues [5], who studied adult subjects anæsthetized with enflurane and nitrous oxide and paralysed with pancuronium. In our study, with fentanyl, Rmax and its two components, Raw and \( \Delta R \), increased. An increase in Rmax with a similar dose of fentanyl during thiopentone anaesthesia was described by Cigarini and colleagues [3]: In their study, such an increase in Rmax with fentanyl did not occur during anaesthesia with propofol. However, these authors did not partition Rmax. The initial component of Rmax is Raw. The increase in our study could have been caused by a reduction in FRC which is observed commonly after induction of general anaesthesia [1]. In fact, the observed stability of Est suggests that such a change was negligible during the short duration of our study. Moreover, D’Angelo and colleagues [5] have shown that \( \Delta R \) varies in the same direction as lung volume. In our study, \( \Delta R \) increased with fentanyl. Thus the increase in Raw resulted from bronchoconstriction and not a reduction in lung volume. Moreover, the increase in the initial pressure change after occlusion after a bronchoconstrictor challenge reflects an effective increase in Raw, despite introduction of significant mechanical heterogeneities in the lung, as shown by Ludwig and colleagues [24]. Because Raw decreased with atropine, which blocks all muscarinic responses within the bronchial tree with equal efficacy [25], it is suggested that the observed effect of fentanyl on the bronchial muscle was vagally induced.

The second component of Rmax is the additional resistance, \( \Delta R \), that may result from the viscoelastic properties of the respiratory system, variation in regional time constants, or both. As Est remained stable, the increase in \( \Delta R \) was probably not caused by variation in lung volume. Moreover, in spite of the bronchodilatation induced by atropine, \( \Delta R \) did not change. This suggests that the bronchoconstrictor effect of fentanyl did not induce significant variations in regional time constants that could have explained the increase in \( \Delta R \) observed at \( T_1 \). Consequently, it can be argued that fentanyl acts directly on pulmonary viscoelastic properties [26]. An effect of thoracic and abdominal muscles is excluded, because of the presence of neuromuscular block. Thus fentanyl increased peripheral resistance, possibly through an effect on peribronchial contractile structures [27]. These structures are independent of the parasympathetic system and are insensitive to atropine because there are few muscarinic receptors in terminal bronchioles [23].

REFERENCES