EFFECT OF FENTANYL ON VENTILATORY RESISTANCES DURING BARBITURATE GENERAL ANAESTHESIA

R. COHENDY, J. Y. LEFRANT, M. LARACINE, T. REBIERE AND J. J. ELEDJAM

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 (ΔR) 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 anaesthetized with methohexitone and paralysed with vecuronium. Before administration of fentanyl, ΔR 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 ΔR (+33.5%, P = 0.005). The increase in Raw, but not in ΔR, 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 ΔR seemed to depend on different mechanisms. (Br. J. Anaesth. 1992: 69: 595-598)

KEY WORDS


Fentanyl increases ventilatory impedance in man. The drug induces truncal muscular rigidity [1] and bronchoconstriction [2] and it increases the overall resistance to inspiratory flow of the ventilatory system (Rmax) [3]. This resistance is the sum of two distinct resistances [4]: airway resistance (Raw) and non-Newtonian resistance (ΔR) which varies with the ventilatory pattern [5]. ΔR may result from either or both of two distinct phenomena [6, 7]—viscoelasticity of the thoracopulmonary tissues or inhomogeneity of regional time constants within the lungs; the latter is considered to be negligible in the normal subject. However, a bronchoconstrictor challenge may induce or aggravate this phenomenon [8].

The aim of this study was to describe the effects of fentanyl on Rmax and on its two components, ΔR and Raw, in anaesthetized, paralysed man undergoing mechanical ventilation. For this purpose we used the end-inflation occlusion method [7]. The study was completed with the description of the effect of fentanyl on the elastic properties of the ventilatory system: static elastance (Est) and dynamic elastance (Edyn). Moreover, as atropine decreases Rmax during general anaesthesia in man [9], its effects on the fentanyl-induced modifications of the ventilatory mechanics were also described.

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 (ΔV), and an accurate tidal volume (TV) [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 port was connected to a pressure transducer (model SK 220 cm H2O, EFFE, Le Pré St Gervais, France) and a linear amplifier (MRC 4411, LEIM, Aix en Provence, France). 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
achieved a standard volume history and the patient was connected to the ventilator. Six minutes later, was intubated with the orotracheal tube described in the first group of occlusions were recorded ($T_0$). The trachea was given and a second group of occlusions ($T_1$) was recorded 6 min later. A second dose of fentanyl 1.75 (0.3) µg 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: $R_{\text{max}}$ ($P=0.005$), $\text{Raw}$ ($P=0.017$) and $\Delta R$ ($P=0.005$) (table I). The increase in $\text{Raw}$ paralleled the increase in $\Delta R$, because the contribution of AR to $R_{\text{max}}$ remained stable: 56% at $T_0$ and 56.8% at $T_2$. While $\text{Est}$ remained stable during the whole study, $\text{Edyn}$ increased slightly (+6.4%) ($P=0.005$) with fentanyl (table II).

When atropine was added to fentanyl, $\text{Raw}$ 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 $T_0$ ($P=0.14$) 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 $\text{Rmax}$ at $T_2$ was significant compared with those at $T_1$ ($P=0.005$) and $T_0$ ($P=0.04$). $\text{Edyn}$ remained stable between $T_1$ and $T_2$ ($P=0.64$) (table II).

DISCUSSION

We have found that, in anaesthetized, paralysed patients undergoing mechanical ventilation, fentanyl increased all the measured resistances. There was a

<table>
<thead>
<tr>
<th>Resistance (cm H$_2$O litre$^{-1}$ s)</th>
<th>$T_0$</th>
<th>$T_1$</th>
<th>$T_2$</th>
<th>$P_f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{\text{max}}$</td>
<td>3.62 (0.87)</td>
<td>4.87 (1.2)</td>
<td>3.95 (0.99)</td>
<td>0.0002</td>
</tr>
<tr>
<td>$\text{Raw}$</td>
<td>1.59 (0.47)</td>
<td>2.15 (0.8)</td>
<td>1.40 (0.55)</td>
<td>0.02</td>
</tr>
<tr>
<td>$\Delta R$</td>
<td>2.03 (0.56)</td>
<td>2.71 (0.5)</td>
<td>2.54 (0.59)</td>
<td>0.0002</td>
</tr>
<tr>
<td>$\Delta R/R_{\text{max}}$ (%)</td>
<td>56 (0.076)</td>
<td>56.8 (0.075)</td>
<td>64.9 (0.071)</td>
<td>0.02</td>
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<thead>
<tr>
<th>Elastance (cm H$_2$O litre$^{-1}$)</th>
<th>$T_0$</th>
<th>$T_1$</th>
<th>$T_2$</th>
<th>$P_f$</th>
</tr>
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<tbody>
<tr>
<td>$\text{Edyn}$</td>
<td>14.30 (2.6)</td>
<td>15.21 (2.67)</td>
<td>15.07 (2.63)</td>
<td>0.0001</td>
</tr>
<tr>
<td>$\text{Est}$</td>
<td>12.27 (2.36)</td>
<td>12.50 (2.41)</td>
<td>12.53 (2.41)</td>
<td>0.18</td>
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Table I. Overall resistance of the ventilatory system ($R_{\text{max}}$), arterial resistance ($\text{Raw}$), non-Newtonian resistance (AR) and baseline values). A first dose of fentanyl 4.9 (0.4) µg 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) µg 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.

Table II. Dynamic elastance ($\text{Edyn}$) and static elastance ($\text{Est}$) of the ventilatory system (mean (SD)) at baseline ($T_0$), 6 min after fentanyl 5 µg kg$^{-1}$ ($T_1$) and 6 min after fentanyl 1.75 µg kg$^{-1}$ ($T_2$).
parallel increase in $R_{\text{Raw}}$ and $\Delta R$, their respective contribution to $R_{\text{max}}$ remaining stable. When atropine was given, $R_{\text{Raw}}$ decreased and returned to the control value, while the contribution of $\Delta R$ to $R_{\text{max}}$ increased.

We have used the end-inspiratory occlusion method [7]; this allows separation of airway resistance ($R_{\text{Raw}}$) 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 $R_{\text{max}}$ and $R_{\text{Raw}}$. 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 µg 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 $R_{\text{max}}$, $R_{\text{Raw}}$, $\Delta R$ and $\text{Est}$ were in the range of values calculated from the data of D'Angelo and colleagues [5], who studied adult subjects anaesthetized with enflurane and nitrous oxide and paralysed with pancuronium. In our study, with fentanyl, $R_{\text{max}}$ and its two components, $R_{\text{Raw}}$ and $\Delta R$, increased. An increase in $R_{\text{max}}$ with a similar dose of fentanyl during thiopentone anaesthesia was described by Cigarini and colleagues [3]: In their study, such an increase in $R_{\text{max}}$ with fentanyl did not occur during anaesthesia with propofol. However, these authors did not partition $R_{\text{max}}$. The initial component of $R_{\text{max}}$ is $R_{\text{Raw}}$. 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 $\text{Est}$ 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 $R_{\text{Raw}}$ resulted from bronchoconstriction and not a reduction in lung volume.

Moreover, the increase in the initial pressure change after occlusion after a bronchoconstrictive challenge reflects an effective increase in $R_{\text{Raw}}$, despite introduction of significant mechanical heterogeneities in the lung, as shown by Ludwig and colleagues [24]. Because $R_{\text{Raw}}$ 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 $R_{\text{max}}$ 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 $\text{Est}$ 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


