Acute effects of fentanyl on breathing pattern in anaesthetized subjects

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Background. The predominant effect of opioids on respiratory pattern during anaesthesia is an increase in the duration of expiration (an effect on ‘timing’), but there may also be changes in tidal volume (an effect on ‘drive’). Timing and drive are controlled by separate neuronal systems, but are infrequently considered individually. The effects of opioids on breathing are not well characterized clinically because changes in carbon dioxide and anaesthetic levels usually occur at the same time, and can obscure the effects of the opioid.

Methods. To study these effects in isolation, we established stable mild hypercapnia in female patients breathing spontaneously during sevoflurane anaesthesia, and then gave fentanyl 0.5 μg kg⁻¹ i.v. End-tidal carbon dioxide and sevoflurane concentrations were maintained constant, and the changes in timing of inspiration, expiration and tidal volume were measured.

Results. The duration of inspiration increased by 30%, and the duration of expiration increased by 95%. Tidal volume increased in proportion to inspiratory duration, and the pattern of flow during the breath was recognizably changed, with a reduction in the rate of increase of flow at the onset of inspiration.

Conclusions. Small doses of opioid given when anaesthesia and carbon dioxide are stable affect respiratory timing predominantly, but in addition changes in the pattern of motor output can be detected.

Br J Anaesth 2006; 96: 384–90

Keywords: analgesics opioid, fentanyl; ventilation, anaesthetics, effects of respiration; ventilation, analgesics, effects of respiration; ventilation, pattern

Accepted for publication: December 28, 2005

Opioids such as fentanyl are often given during anaesthesia to supplement the effects of general anaesthetic agents, particularly to reduce motor or sympathetic responses to surgical stimuli. In a spontaneously breathing patient, an obvious effect is respiratory depression, mediated particularly by a decrease in the frequency of breathing. In contrast, depression caused by other i.v. agents and by volatile anaesthetics results from a reduction in tidal volume. After giving opioids, the resultant hypoventilation has secondary effects on alveolar gas composition, which are an increase in carbon dioxide and a decrease in anaesthetic concentration. Such changes may influence and can offset the depression caused by the opioid. In clinical practice, the changes in breathing pattern caused by the opioid cannot be separated clearly from the changes resulting from alveolar hypoventilation such as hypercapnia and reduced anaesthetic concentration. In particular, although previous studies have shown that opioids have an immediate and significant effect on the timing of breathing, the changes in tidal volume are less evident, perhaps because of these secondary changes. However, when tidal volume changes do occur, the onset of these effects appears to be more rapid than those on timing, which develop more gradually. Another relevant factor is that tidal volume can be affected by the duration of inspiration. In conscious man, there is a linear relationship between these variables although in anaesthetized animals, with active Hering Breuer reflexes, the relationship is inverse. During anaesthesia, fentanyl can alter the time course of inspiratory flow, causing a biphasic pattern.
Recently, Lalley\textsuperscript{5} showed a clear difference between low doses of opioid, which had a specific effect on respiratory timing, and greater doses, which depressed neuronal excitability (i.e. also depressed respiratory ‘drive’ in addition to the effect on ‘timing’). The respiratory rhythm is probably generated in the pre-Bötzinger complex in the ventrolateral medulla.\textsuperscript{6} In this region, opioid injection reduces respiratory frequency,\textsuperscript{7} and lesions abolish the frequency changes caused by chemical stimuli, supporting the concept that drive and timing of ventilation are two distinct components with a neuroanatomical basis. We set out to study the effects of low doses of opioid on these features of breathing, in anesthetized subjects with stable carbon dioxide and anaesthetic concentrations. We aimed to determine the time course of the effects of an opioid on the volume and timing components of the breathing pattern, to see if these changes had separate time courses, and secondarily to consider the interaction that there might be between these components and possible effects on inspiratory flow pattern.

**Methods**

With approval from the local Ethics Committee and written consent of the patients, we recruited ASA I and II female patients about to have day care orthopaedic or gynaecological surgery. We did not consider patients with current respiratory or cardiac disorders, those taking medication which could interact with fentanyl, those who were to have a local anaesthetic procedure during the surgery, and those in whom fentanyl would not have been given during the anaesthetic. We did not recruit patients who were very anxious or had a poor command of English. We recorded the weight, age and height of each patient.

On arrival in the anaesthetic room, a noninvasive blood pressure monitor, finger probe pulse oximeter and standard ECG leads were attached. Propofol 50 mg i.v. was given via a cannula placed in a vein on the back of the hand, followed by induction of anaesthesia by inhalation of oxygen and incremental increases in sevoflurane vapour, up to 8%. This is the routine method used in these patients. A laryngeal mask airway was inserted, and anaesthesia maintained with sevoflurane and oxygen. The standard breathing circuit was then replaced by a non-rebreathing valve (Hans Rudolph 2700, Kansas City, MO, USA), connected to a T-piece breathing system. This allowed carbon dioxide to be added to the inspired gas, and the exhaled gas could be scavenged, with minimal changes in gas pressure in the tubing system (Fig. 1). The respiratory flow generated by the patient was measured by detecting the pressure difference across an airway bacterial filter, using a differential transducer (Furness FC40, Bexhill, Sussex, UK). The filter therefore acted as a pneumotachograph. Over the relevant flow range, the pressure/flow characteristics were highly linear. The pressure signal was captured using an analogue to digital converter and commercial software (CED1004 and Spike 2, both from Cambridge Electronic Design, Cambridge, UK). Gas was sampled from a second airway filter, placed on the patient side of the first, for analysis for carbon dioxide and sevoflurane concentration (Datex AS5, Datex Ohmeda Ltd, Hatfield, Hertfordshire, UK). At the end of each day, we recorded the pressures associated with calibration values of 0 and 15 litre min\textsuperscript{-1} flow through the filter.

![Diagram](image-url)
The breathing system was supplied with oxygen and sevoflurane vapour from the anaesthetic machine, at 15 litre min\(^{-1}\). A controlled flow of carbon dioxide was metered into the fresh gas using a precision needle valve and a low reading rotameter. The flow of carbon dioxide was adjusted so that the patient’s end-tidal carbon dioxide value, obtained during stable breathing, was increased by \(\sim 1\) kPa. When ventilation and end-tidal carbon dioxide and sevoflurane concentrations had been steady for 8 min, a recording of respiratory flow was started, and end-tidal carbon dioxide and sevoflurane concentrations recorded at the end of each minute. Two minutes later, fentanyl 0.5 μg kg\(^{-1}\) in 5 ml saline was given i.v., followed immediately by saline 0.9% 5 ml. The respiratory flow recording was continued and end-tidal carbon dioxide and sevoflurane concentrations noted at the end of each minute for a further 5 min after giving fentanyl. During this time, the added carbon dioxide and sevoflurane vapour concentration were adjusted as necessary to keep the end-tidal concentrations stable.

We used a custom-written program to process the flow data, and calculate the duration of inspiration \((T_I)\), expiration \((T_E)\), tidal volume \((V_T)\) and the mean inspiratory flow \((V_T/T_I)\) for each breath.

In each patient record, we inspected the 2 min period of control breathing, immediately before drug administration, for a stable breathing pattern. If either the tidal volume or breath timing showed a significant linear trend \((P<0.05)\) over this time, we rejected the patient data for subsequent analysis. In each subject we then sampled 10 breaths at four separate intervals, the first immediately before fentanyl administration and the other three centred at 90, 150 and 240 s after administration. These times were chosen to allow an adequate separation and no overlap of the 10-breath blocks. Values are reported as median and interquartile range. Statistical analysis was by Friedman’s analysis of variance for repeated measures. \(P<0.05\) was considered significant. We used GraphPad-Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com) for statistical analysis.

**Results**

We studied 18 patients, but rejected 8 because stable ventilation was not present in the control period. The remaining 10 subjects had a mean (range) age of 40 (30–60) yr, a mean (sd) height of 161 (4) cm and weight 71 (16) kg. The mean end-tidal carbon dioxide value before drug administration was 6.95 kPa and the sevoflurane concentration was 2.55%.

After drug administration, these values were kept within acceptable limits by manual control of the inspired gas composition (Fig. 2). Throughout the studies, there were no adverse effects, and no episodes of decrease in pulse oximeter values.

After fentanyl administration, the duration of inspiration increased progressively from 0.83 (0.14) to 1.08 (0.33) s, and the duration of expiration from 1.52 (0.63) to 2.97 (2.68) s, at 240 s after administration. Both these changes were significant \((P<0.0001)\). Tidal volume increased significantly, from 387 (280) to 435 (170) ml \((P<0.001)\), but the mean inspiratory flow rate did not change. Figure 3 shows these individual values and the changes are summarized by the spirogram in Figure 4.

To assess possible changes in the pattern of inspiratory muscle activity, representative inspiratory flow patterns were taken from the control period and from the last period of measurement (centred at 240 s after fentanyl) and these are shown in Figure 5. The patterns all showed the same feature: the rate of increase in flow rate was less after fentanyl administration. There was no evidence of a biphasic flow pattern.

**Discussion**

We found a prompt effect of fentanyl on the timing of breathing cycle components. In contrast, the changes in tidal volume were small and in fact tidal volume increased. In contrast to previous findings, the effects on tidal volume did not seem to occur sooner than the changes in breath timing and although the inspiratory flow pattern was changed, it did not become biphasic.\(^1\)
Several technical aspects of the study require consideration. We chose to study a single sex of subject because there appear to be differences between sexes in responses to opioids, and gynaecological patients were available for this study. We had to use end-tidal carbon dioxide as a measure of stable brain carbon dioxide partial pressure and there are limitations to this assumption if gas exchange is impaired. However, ethical constraints made this the only possible strategy. It is possible that the propofol dose used had some effect on respiration but this is our clinical routine, the dose used was small, it was given some time before the study started, and would have a common effect in all the patients.

After i.v. administration, the rate of onset of the respiratory effects of fentanyl will depend upon several factors. Fentanyl is taken up in the lungs by both active and passive processes. This slows the transit of fentanyl through the lung. In sheep, the lung has an apparent volume of distribution of 1.2 litre kg\(^{-1}\) body weight. During an infusion of fentanyl, the difference between pulmonary artery and aortic concentrations rapidly decreases, so the effect of the lung is to delay slightly the transfer to the systemic circulation. We aimed to deliver the agent rapidly and reliably into the central venous system by giving the dose in a large volume and flushing the vein after administration.

Cerebral uptake of fentanyl is affected by both active uptake and extrusion. A recent study in sheep suggested that fentanyl equilibration in the brain was 50% complete after 10 min, and the authors suggested that this was consistent with studies where the EEG was used as a measure of cerebral effect.

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**Fig 3** Effects of fentanyl 0.5 μg kg\(^{-1}\) on breathing pattern. The values of duration of inspiration (T\(_I\)), expiration (T\(_E\)) and tidal volume (V\(_T\)) increased significantly (all \(P<0.01\), Friedman test).

**Fig 4** Summary spirogram of the effects of fentanyl on the breathing pattern.
However, in the present study, the onset of respiratory effects was noticeable 90 s after injection and was prominent after 4 min. Similar observations have been made by previous authors.\textsuperscript{11,12} This contrasts with previous studies of the EEG effect, where a delay between plasma concentration and brain effect was noticeable, for both fentanyl and sufentanil, and a time constant for the effect compartment was calculated to be more than 6 min. The same workers did find a much shorter time for equilibration with alfentanil.\textsuperscript{11} The differences in onset of these effects could be that although fentanyl combines rapidly with opioid receptors, subsequent EEG changes could take some time to develop. Subjective effects are often reported over the same timescale as the respiratory effects we report here: EEG changes although objective may be a sluggish surrogate for these effects. Alternatively, the perfusion of the medulla may be greater than the cortex so that wash in and the onset of respiratory action is more rapid. This could also explain the more prompt onset of respiratory effects, compared with other measures of anaesthesia, during induction of anaesthesia with volatile and i.v. agents.\textsuperscript{13} Study of the effects for more than 4 min would have been of considerable interest: for example to note the decline of effects with redistribution. However, it would have been difficult to maintain a steady state, and operational constraints limited the time available for the study.

The information from this study in human subjects cannot be related easily to other experimental studies of opioids and respiration. Since the discovery of endogenous ligands for opioid receptors, knowledge concerning the respiratory effects of opioids has increased greatly.\textsuperscript{14} Recent experimental studies have used a wide variety of preparations, some of which are ‘reduced’ such as isolated medulla or brain slices, or are of neonatal or juvenile animals.\textsuperscript{15–17} How results from such preparations can be related to breathing in intact adults is unclear. Although respiratory neurones are richly supplied with opioid receptors, such receptors are also widespread throughout the brainstem and opioid actions at different sites may well have different effects.\textsuperscript{18,19}

In cats, either anaesthetized with pentobarbital or decerebrate, low systemic doses of fentanyl increased the duration of expiration, although the rate of increase in activity of premotor neurones was also reduced. Direct application of an opioid peptide to inspiratory neurones had similar effects.\textsuperscript{5} In addition to showing that the effects in anaesthetized animals were much like those in decerebrate preparations, this study added to previous observations that the primary effects of low dose opioids, commonly used clinically, appear to be on central networks that control timing. With greater doses, effects on other mechanisms such as chemosensory pathways may also occur and this may reduce drive. These different effects could for example explain why...
it is that only large doses of opioid appear to reduce the response of ventilation to carbon dioxide. Other studies in intact anaesthetized animals show that after damage to the pre-Bötzinger complex, widely considered to be vital in the generation of rhythmic breathing, responses to chemical stimuli are impaired because respiratory frequency does not increase, whereas tidal volume responses are unaltered.20 A study that combined histochemistry and physiological recordings showed that ventral respiratory neurones have wide but variable responsiveness to opioids.21 Although many believe that the pre-Bötzinger complex is a crucial site of action of opioids in the expression of their respiratory effects,2 the exact cellular mechanisms remain in question. Other transmitters, potential interactions of other agents with opioids and even alternative neuronal networks make the physiology and pharmacology of the topic unpredictable.

Considering the possible interaction of inhaled volatile anaesthetics and opioids, it is of interest that both opioids22 and halothane23 can disturb the duration of expiration in a quantal fashion, as if the central oscillator responsible were ‘missing’ a cycle. However, the slowing we noted in the present study showed only a continuous effect, with no evidence of quantal timing.

Because opioids in larger doses can affect the motor output of the respiratory centre, and activate expiratory muscles,24 it is possible that the increased tidal volume that we observed could have been partly from expiratory muscle action. Part of the inspired volume could be the result of relaxation of the expiratory muscles. However, in these circumstances a biphasic pattern of inspiratory flow would be likely. Initial flow would be caused by the release of the abdominal expiratory effect at the onset of inspiration followed by a progressive increase in flow generated by the diaphragm. This was not found, although there was a clear reduction in the rate of increase of inspiratory flow, suggesting that the profile of activation of the respiratory motoneurones was affected by these small doses of opioid. Nevertheless, the increased duration of inspiration was sufficient, in most patients, to allow the tidal volume to increase, suggesting that the relationship between inspiratory duration and tidal volume (Fig. 6) in our patients was the same as noted in conscious man.25

In conclusion, we have shown that small doses of opioid have a discernable primary effect on respiratory timing. Consequently, investigation of agents that offset these actions may be of value in mitigating some of the depression caused by opioids.

Acknowledgements
The authors acknowledge support by a bench fee for undergraduate honours projects, Edinburgh University School of Medicine and Veterinary Medicine.

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