Breath interval as a measure of dynamic opioid effect

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We measured breath interval to characterize the time course of opioid effect in anaesthetized patients breathing spontaneously during knee replacement surgery with concurrent regional nerve blockade. Breath interval was recorded before and after a single dose of fentanyl 0.75 μg kg⁻¹ i.v. Breath interval was measured between the start of successive inspirations, identified by a decrease in carbon dioxide concentration, sampled at the laryngeal mask connection. Nineteen patients were admitted to the study, of whom nine were withdrawn (there was a recording failure for one patient, five patients had inadequate block and three were excessively depressed by the fentanyl). Using MKMODEL software, the mean (sd) dynamic elimination half-life and dynamic mean brain residence time of fentanyl were 15.3 (7.8) and 24.1 (8.1) min, respectively. The times to detection of change from baseline, and peak effect of fentanyl on breath interval were 0.9 (0.6) and 5.2 (1.4) min, respectively. Breath interval increased from 2.9 (1.0) s to a maximum of 9.0 (5.7) s. There were no differences between the time course of changes in breath interval and end-tidal carbon dioxide concentrations. End-tidal carbon dioxide concentrations increased from a baseline of 6.6 (0.9)% to a peak of 8.2 (0.8)%. Breath interval was a useful and reproducible method of monitoring the duration of opioid effect in anaesthetized patients breathing spontaneously when surgical stimulation was not affecting the CNS. The data provide information on the duration of action of fentanyl and could guide dosage.

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The pharmacokinetics of opioid drugs have been reported widely1 and are relatively straightforward to study by measuring opioid concentrations in serial blood samples after opioid administration. Although such studies provide useful information on the time course of opioid concentrations in the blood, they may not indicate the time course of the pharmacodynamic effects of opioids, because tolerance can develop.

Ideally, to study the duration of action of opioids in human subjects, relief of pain would be used to measure opioid effect. The pharmacodynamic features of the analgesic effect of opioid drugs have been described in animal models using analgesia as a variable. For example, stimulation of the tooth pulp of rabbits has provided information on the duration of analgesia in animals given fentanyl.2 Other methods used to measure analgesia in human subjects, such as verbal rating scales and visual analogue scales, are imprecise3 and not applicable to anaesthetized patients. The duration of opioid effect has been studied under anaesthesia4 by measuring time required for fentanyl supplements during neurolept anaesthesia, based on clinical observations.

In clinical practice, the analgesic effects of pure μ-opioid antagonists have never been separated from their depressant effects on the respiratory system. Although respiratory rate is a poor measure of respiratory function, it offers a method to study opioid effect using the reciprocal, the breath-to-breath interval. Respiratory rate is derived from the reciprocal of breath interval.

Breath interval data may provide information on the duration of action of fentanyl and a guide to dosing interval taken directly from a dynamic effect.

Methods

The study was approved by the Local Ethics Committee, and informed written consent was obtained the day before surgery. Nineteen patients were studied. All were admitted for elective total knee replacement surgery, an operation lasting 45–75 min. Patients were excluded from the study if their weight or any concurrent medical condition made it inappropriate to use the technique of spontaneous breathing through a laryngeal mask airway.

All patients received temazepam 10 mg orally 1 h before
surgery. Anaesthesia was induced using propofol 2–3 mg kg\(^{-1}\) i.v. A laryngeal mask airway was inserted into the pharynx and anaesthesia was maintained with isoflurane 0.8% and nitrous oxide 67% in oxygen.

Sciatic and three-in-one femoral nerve blocks were then performed using a nerve stimulator to guide needle placement. The femoral nerve, lateral cutaneous nerve of the thigh and obturator nerves were all blocked by injecting 0.375% bupivacaine 20 ml next to the femoral nerve. When a current of \(\leq 0.5\) mA produced a visible twitch in the quadriceps femoris muscle, pressure was applied just distal to the needle and the bupivcaine was injected. The sciatic nerve was blocked via an anterior approach with 0.375% 40 \(\mu\)g i.v. at time 0. Values before time 0 provide baseline. Breath interval did not return completely to baseline before surgery finished.

After insertion of nerve blocks, patients were transferred into theatre. Routine monitoring of the patient included sidestream analysis of the respiratory gases at the airway opening using a Capnomac Ultima (Datex, Helsinki, Finland). The analogue output of the carbon dioxide concentration was fed to an analogue–digital converter attached to a personal computer. A point on the downstroke of each carbon dioxide waveform was identified from analysis of the area under the curve. The time, in milliseconds, between each of these points was recorded as the breath interval. By digitizing the analogue output of the carbon dioxide monitor to derive the breath interval signal, no further influence on breathing was imposed beyond that used in routine clinical practice.

Approximately 25 min passed between insertion of the peripheral nerve blocks and the start of surgery. This allowed the nerve blocks to achieve their maximal effect before painful surgical stimuli. During this time we measured baseline breath intervals.

After the start of surgery, a further 5 min were used to confirm that surgery was not associated with any alteration in baseline breath interval. Fentanyl 0.75 \(\mu\)g kg\(^{-1}\) was then given as a single rapid i.v. injection while each successive breath interval was logged to personal computer.

Patients were withdrawn from the study if their respiratory rate decreased to <6 b.p.m. or if their end-tidal carbon dioxide concentration exceeded 9%.

**Analysis**

Data obtained throughout the operation were plotted as breath interval against time. A representative example from one patient is given in Figure 1. Fentanyl was injected at time 0. Data points describe a curve resembling curves for blood or plasma concentrations obtained after absorption and elimination of a single dose of drug. We took data points after the peak to represent the elimination phase of opioid from the effect site.

Pharmacokinetic analysis was not attempted. Breath interval provides no value for change in mass of drug; so clearance and volume of distribution cannot be calculated. MKMODEL\(^5\) was used as a convenient means of calculating the rate constant as breath intervals decrease from a maximum back to baseline. It was configured to extrapolate curves to baseline, by dividing the last data point by the elimination rate constant, \(k\), and thus to calculate the area under the curve and its first moment to infinity. The slope of the regression line through the latter two-thirds of the natural logarithm of breath intervals from peak to baseline gave \(k\). The dynamic elimination half-life (\(t_{1/2}\)) of the opioid effect was calculated from \(t_{1/2} = \ln(2)/k\). The mean residence time (MRT)\(^6\) of fentanyl in the effect site was also calculated from the ratio of the area under the first moment curve to the area under the curve. Both areas under the curve were extrapolated to zero.

Mean and SD are used to describe group values of \(k\), \(t_{1/2}\) and MRT. Times to onset and peak effect of breath interval and end-tidal carbon dioxide concentration were compared by analysis of variance. Statistical significance was accepted when \(P<0.05\).

**Results**

Nineteen patients were recruited for study. Nine patients were withdrawn from analysis. In one patient, computer logging failed. In three patients, breathing slowed to <6 b.p.m. or end-tidal carbon dioxide concentration increased to >9%, requiring ventilation to be assisted transiently. Five patients had more than usual pain after surgery; they had irregularities in their breath interval curves (Fig. 2) and were considered to have inadequate nerve blocks. The mean (range) age, mean (SD) weight and height of the remaining 10 patients were 61 (27–84) yr, 71 (10) kg and 168 (9) cm.

There were seven male patients. Patients received fentanyl 53 (9) \(\mu\)g i.v., equivalent to fentanyl 0.74 (0.12) \(\mu\)g kg\(^{-1}\). The time between induction of anaesthesia and injection of fentanyl was 31 (14) min.

A plot of successive breath intervals against time resembled a plot of blood concentration after absorption of a drug. In such curves, there is a lag before values change from baseline, then values increase rapidly to a maximum and decrease more slowly back to baseline (Fig. 1, Table 1). The time taken for breath interval to increase from
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Discussion

Breath interval was a reproducible method of measuring dynamic opioid effect. We calculated the dynamic MRT and dynamic elimination half-life of fentanyl. Coefficients of variation of these values in the group of 10 patients were 51 and 34%, respectively. These results correspond closely with those from previous reports. This method of measuring the duration of opioid effect is easy to perform, non-invasive and does not require the measurement of relief from pain. Analgesic effects of pure µ-opioids in clinical practice have never been separated from respiratory effects; so the time course of changes in breath interval are likely to correspond with changes in analgesic effect.

We calculated the dynamic MRT of fentanyl from the oral absorption model. Although given as a rapid i.v. injection the effect on breath interval is not immediate. This is analogous to the changes in blood concentration seen after oral, subcutaneous or i.m. injection where initial absorption must occur. Fentanyl was injected rapidly into a peripheral vein. Circulation to the heart, temporary sequestration in the lung and time taken for uptake from cerebral circulation to the effect site in the brain could delay the onset of effect. However, even with these delays, peak effects were obtained at 8 and 9 min for end-tidal carbon dioxide concentration and breath interval, respectively.

In pharmacokinetic models, MRT equates to the mean duration of the presence of a drug within the body. In our dynamic model, we consider MRT to be the mean duration of drug effect. Breath interval was used as a signal of drug effect. The time to onset of drug effect and time to peak effect were the same for breath interval and end-tidal carbon dioxide concentration. Changes to both occurred in phase, suggesting that they indicate the same drug effect, rather than one responding to a change in the other.

A measurement at each breath was sought to provide data to characterize the rapid onset of effect and recovery of a single i.v. dose of fentanyl in clinical anaesthetic practice. Arterial blood sampling for gas analysis would not have been rapid enough. The ventilatory response to inhaled carbon dioxide is similarly intermittent. The ratio of tidal volume to breath interval measured in minutes would give a value for minute volume at each breath and take account of depth and frequency of ventilation. Tidal volume could have been measured at each breath, but i.v. fentanyl did not influence tidal volume in anaesthetized patients with spinal analgesia undergoing lower body surface surgery. Inspiratory flow was reduced while duration of expiration was increased. End-tidal carbon dioxide concentration is dependent on carbon dioxide production and lung mechanics, and is affected by sampling site, the mode of ventilation, anaesthetic circuit and gas flow, limiting its usefulness as a physiological signal in these study conditions. Breath interval was measured from the carbon dioxide trace because it was easily identified, but it could equally

Table 1. Rate constant of elimination, mean residence time and elimination half-life for breath interval after fentanyl 0.75 µg kg⁻¹ i.v.; breath interval and end-tidal carbon dioxide concentrations after fentanyl, together with times from i.v. fentanyl to change from baseline and from i.v. fentanyl to peak values (mean (SD), n = 10)

<table>
<thead>
<tr>
<th></th>
<th>Breath interval</th>
<th>Carbon dioxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate constant of elimination (min⁻¹)</td>
<td>0.057 (0.030)</td>
<td></td>
</tr>
<tr>
<td>Dynamic elimination half-life (min)</td>
<td>15.3 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Mean residence time (min)</td>
<td>24.1 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Time (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>from fentanyl i.v. until change from baseline</td>
<td>0.9 (0.6)</td>
<td>1.3 (1.0)</td>
</tr>
<tr>
<td>from fentanyl i.v. to peak effect</td>
<td>5.2 (1.4)</td>
<td>6.7 (1.0)</td>
</tr>
<tr>
<td>Baseline value</td>
<td>2.9 (1.0) s</td>
<td>6.6 (0.9)%</td>
</tr>
<tr>
<td>Peak value</td>
<td>9.0 (5.7) s</td>
<td>8.3 (0.8)%</td>
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Fig 2 Serial measurements of breath interval before and after fentanyl 75 µg i.v. at time 0. Ineffective femoral three-in-one and sciatic nerve blocks prevented stable baseline breath intervals before i.v. fentanyl. Surgical stimuli affected breath interval during the elimination phase. Data from this patient are not included in analysis of f1 or MRT.

Fig 3 Serial measurements of breath interval(s) (lower trace) and end-tidal carbon dioxide concentration (%) (upper trace) after i.v. fentanyl at time 0.

baseline to maximum was the same as that for carbon dioxide (Table 1). The two variables appeared to change simultaneously. Correlation coefficients for the 10 patients between measurements of breath interval and end-tidal carbon dioxide concentrations were 68.6 (23.3)% . When breath interval increased there appeared to be a greater variation in successive breath intervals towards the peak value. No such changes were evident in the end-tidal carbon dioxide plot (Fig. 3).
well be measured from chest dimensions or change in direction of flow at airway opening. After a single painful surgical stimulus, breath interval is transiently increased. In the presence of effective nerve blocks, breath interval after i.v. fentanyl showed a smooth transition from baseline to peak, then back to baseline (Fig. 1). With ineffective nerve blocks the breath interval plot became erratic (Fig. 2) and data were impossible to analyse in the manner described. Spinal or epidural anaesthesia could be used more effectively to interrupt transmission of a painful surgical stimulus to the central nervous system. Axial blockade was not available because of its association with increased urine retention: we wanted to avoid catheterization and the consequent risk of bacteraemia.

Anaesthesia was maintained using a volatile anaesthetic agent and a nitrous oxide mixture in oxygen. Both drugs affect the respiratory rate. A change in ventilation caused by fentanyl will affect the uptake and alveolar concentrations of these agents and could affect respiratory timing. However, patients breathed through a laryngeal mask connected to a circle anaesthetic system into which a fresh gas flow delivered nitrous oxide 67% and isoflurane 0.8% in oxygen. Standardizing the concentrations of anaesthetic agents delivered was more practical than attempting to adjust the isoflurane concentration in the fresh gas to achieve a steady-state end-tidal isoflurane concentration.

In summary, breath interval gave a method of calculating the time course of opioid effects. The dynamic opioid half-life obtained can guide the timing of a second dose of opioid in anaesthetized patients, when afferent surgical stimuli are blocked.

References