Effect of i.v. lignocaine on the breathing of patients anaesthetized with propofol

N. W. GOODMAN AND N. STRATFORD

Summary
Local anaesthetics are ventilatory depressants, but previous investigators have not commented on the effects on ventilatory timing. There is concern about the possible ventilatory depression caused by systemic absorption of local anaesthetics injected extradurally. We have studied ASA grade I patients anaesthetized with a propofol infusion and breathing spontaneously; they were given in random order lignocaine 1.5 mg kg$^{-1}$ i.v. and an equivalent volume of 0.9% saline. Breathing, was analysed using respiratory inductance plethysmography in 30-s periods for 4 min after injection, each period scaled to the 30-s period preceding injection. Lignocaine reduced minute ventilation. The greatest mean reduction in the 4 min was to 85%, occurring 2.5–3 min after injection; the greatest individual reduction was to 60–65%, which occurred by 30–60 s. Lignocaine decreased tidal volume and ventilatory rate by prolonging expiratory time. Lignocaine had no effect on or promoted bimodality of expiratory time. End-tidal carbon dioxide increased by a mean of 0.1%; the largest individual change was 0.3%. This suggests that lignocaine may have reduced the metabolic rate, affecting ventilation indirectly, but we conclude that lignocaine in a normal extradural dose should not be an important ventilatory depressant. (Br. J. Anaesth. 1995; 75: 573–577)

Key words
Anaesthetics i.v., propofol. Anaesthetics, local, lignocaine. Ventilation, effects.

The effect of local anaesthetics on the control of ventilation is confusing and contradictory [1, 2]. Studies have been of direct i.v. injection or injection for regional anaesthesia, especially into the extradural space. Most reports are of effects on the ventilatory response to hypercapnia or hypoxia. It is tempting to be able to quote a precise ventilatory response in terms of litres per minute per kilopascal, and by how much this is altered by drugs, but the great variability of these responses, even within a group of normal subjects, makes any precision illusory [3, 4]. According to a review by Gal [2], an i.v. bolus of lignocaine decreases the slope of the carbon dioxide response but an infusion increases it; high thoracic extradural block decreases the slope, but lumbar extradural block increases it, and this is attributed to the systemic effects of lignocaine. However, spinal block, which causes less systemic absorption, increases the response and this was attributed to block of chest wall afferents, although they should also have been inhibited by high extradural block. Gal also reported that intercostal nerve blocks, causing the same degree of block and systemic lignocaine concentrations as those after extradural block, did not affect the response to carbon dioxide.

A change in response to carbon dioxide to less than 25% of normal is needed for there to be an increase in resting carbon dioxide of 1 kPa. The mean percentage change in ventilatory responses in the studies of the ventilatory effects of local anaesthetics is usually less than 40%, and some workers reported no change, for example Dohi, Takeshima and Naito [5].

The effect on resting ventilation is more useful to clinicians than seemingly exact measures of chemosensitivity [3, 4]. We investigated the effect with bolus injections of lignocaine in patients anaesthetized with propofol, which avoids the problem of measuring ventilatory responses in awake patients, a procedure that makes measurement even more variable.

In addition, Telivuo and Katz [6] published an incomplete observation on the effect of local anaesthetics [6]. They confirmed earlier reports of a reduced tidal volume, but made no comment on the effect on ventilatory rate. There was a clear decrease in rate in the two records published. In one, the pattern of breathing seemed to become bimodal after injection of lignocaine 3 mg kg$^{-1}$. We wondered if this was a specific effect of lignocaine which could be used to investigate bimodal breathing patterns [7].

Patients and methods
The study was approved by Southmead Medical Research Ethics Committee and patients were asked for written informed consent. We studied patients of ASA grade I, of slim build and judged clinically to

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have an easily managed airway under general anaesthesia for dental extractions. Specific exclusions included any previous reaction to local anaesthetics and any suggestion of epilepsy.

We inserted two i.v. cannulae: one in the non-dominant arm for injection and infusion of propofol and one in the dominant arm for injection of test solution. All patients were anaesthetized with enough propofol to allow insertion of a laryngeal mask airway, and an infusion was started at 13 mg kg⁻¹ h⁻¹. The infusion was stepped down at 10-min intervals to 11 and then to 9 mg kg⁻¹ h⁻¹; the interval was prolonged if clinically a patient was judged to be lightly anaesthetized. Patients breathed 100 % oxygen. All patients were monitored by pulse oximetry and capnography. Tidal air was sampled via manometer tubing placed near the proximal end of the laryngeal mask. A cuff for non-invasive arterial pressure monitoring was placed, but because measurement inevitably disturbs breathing, we intended not to use it unless indicated clinically.

Two syringes were prepared by one investigator (N.W.G.): one syringe contained lignocaine 1.5 mg kg⁻¹ (Xylocaine, Astra Pharmaceuticals) and the other the same volume of saline. They were labelled A and B, determined simply by tossing a coin. The first injection was given at least 5 min after the infusion rate was changed to 9 mg kg⁻¹ h⁻¹, and the second at least 5 min later. Drugs were given by single rapid injection, flushed through immediately with saline 5 ml. The injections were made by the other investigator (N.S.) who, concealed from N.W.G., recorded the syringe letter. The codes were broken after the results had been analysed.

Breathing was recorded by respiratory inductance plethysmography (Respitrace AMI Model 150, Studley Data Systems). The Respitrace was calibrated [8] before induction of anaesthesia by multiple linear regression against a pneumotachograph, itself calibrated against a 1-litre syringe. The ventilatory variables were extracted and stored on computer (Acorn BBC B+) using a simple algorithm: each beginning of inspiration is taken as the time when the volume signal exceeds a threshold above the preceding minimum; each end of inspiration is when the volume signal exceeds a threshold below the preceding maximum. The tidal volume is the difference between the minimum and maximum volume signals. Tidal volume, inspiratory time, ventilatory cycle time and clock time are collected for each recorded breath. Inspiratory times are calculated as cycle time minus inspiratory time. The analogue-to-digital conversion rate (two channels, 10 ms per channel) is a maximal 50 Hz, but the effective accuracy of that section of program is 25 ms (40 Hz). These data were transferred from the BBC computer to a Macintosh II (FileMac v 1.2, BBC Basic v 3.2, Human-Computer Interface Ltd). This system has been used in previous studies (for example [7, 8]).

We examined tidal volume (VT), inspiratory time (TI), expiratory time (TE), total cycle time (Ttot) and minute ventilation (VE). Volumes were not corrected to BTPS. Each variable was averaged in nine 30-s periods, starting 30 s before injection and ending 4 min after. One-way repeated measures analysis of variance (ANOVA) (StatView SE + Graphics, Abacus Concepts) was applied to the absolute values of all variables except VT. P < 0.05 was taken as significant. The variables were also scaled, each to its baseline 30-s period (Microsoft Excel 3.0).

Results

All patients were studied on a morning operating list, so they had not eaten or drunk since midnight. No patient was taking any drug which might be expected to have an important respiratory effect. We did not keep records of whether or not women were taking the contraceptive pill. Partial results have been published from eight of these patients, commenting on the bimodality of their expiratory times [7].

We were unable to use data from four patients: one moved throughout, one sighed at the same time that an injection (lignocaine) was given, one study was abandoned because of time and in one study there was too much baseline noise in the plethysmographic trace. The 10 patients (eight women) studied were aged 19–35 yr, weighed 52–73 kg and were 1.55–1.83 m in height.

In two patients we judged anaesthesia clinically to be too light to reduce the infusion rate, and the test injections were given with the usual timing but while propofol was infused at 11 mg kg⁻¹ h⁻¹. In one of these patients ventilation was too irregular for measurement. Nitrous oxide (33 %) was added and breathing became regular. In five of 10 patients from whom we obtained analysable records, the first injection was lignocaine. The second test injections were made between 5 and 10.2 min after the first.

Tidal volume increased after saline and decreased after lignocaine (table 1, fig. 1). Cycle time did not change after saline but increased after lignocaine. The prolongation resulted from increased expiratory time; inspiratory time did not change.

Scaled results from individual patients are shown in fig. 2. In no subject did tidal volume decrease after saline; there was a small and steady upward drift. After lignocaine, tidal volumes in all subjects increased in the 30 s-period that started as the injection was given, but then decreased in most subjects. The largest decrease in tidal volume was to about 65 % of baseline. There was no trend in cycle time after saline, and generally an increase (i.e. decreased ventilatory rate) after lignocaine. The greatest individual reduction in minute ventilation was to 60–65 %, which had occurred by 30–60 s; the greatest mean reduction in the 4 min was to 85 %, occurring 2.5–3 min after injection. After saline in this same period, mean minute ventilation was 108 % of baseline.

The peak effect of lignocaine occurred during our measurement period, although the total effect outlasted it. Mean end-tidal carbon dioxide concentration was 5.6 % (range 4.6–7.5 %) before saline and 5.7 % (4.7–7.6 %) before lignocaine. There was no change after saline and a mean increase of 0.1 % after lignocaine. The largest increase in end-tidal carbon dioxide after lignocaine was 0.3 % in one patient.

Seven of the 14 patients had bimodal expiratory
times. Four of these were patients not reported previously [7]. There was no evidence that lignocaine either affected or promoted bimodality.

**Discussion**

Lignocaine reduced ventilation. End-tidal carbon dioxide concentration, which is an index of ventilatory depression [3], did not increase as much as expected for the measured changes in expired minute ventilation. This may be because lignocaine reduced the metabolic rate, because we were not measuring true alveolar ventilation or because end-tidal measurement was not of alveolar air when the tidal volume decreased. We cannot comment on metabolic rate or alveolar ventilation. End-tidal measurement did not increase later when tidal volume returned to baseline values, which would be expected if, for a period, end-tidal air was not alveolar air.

Tidal volume for the 30-s period that started with injection of lignocaine was usually greater than baseline but this was an effect of time: tidal volume increased in most patients over the measurement period, and this is shown by the increase after saline injection. This was probably because of drift in background ventilatory depression produced by propofol, whether of pharmacokinetic or pharmacodynamic origin. We did not recalibrate the Respirtrace and therefore we cannot rule out that some of this background change in ventilation was caused by changing calibration.

We decided by simple coin tossing which solution to inject first. In retrospect, although coin tossing is a valid method of randomization, we were lucky that, for the 10 patients who gave results, five first injections were saline and five lignocaine. With unequal numbers we would have had to take account of any carry-over effect in the ANOVA, although a balanced design would guarantee only equal numbers given one injection first, not necessarily equal numbers to analyse.

Telivuo and Katz [6] reported that local anaesthetics decrease tidal volume. Our findings confirmed this and, what was obvious in their figures but unremarked on, that a decreased ventilatory rate was produced by lignocaine. There was no effect on inspiratory time, and thus by inference mean inspiratory flow was decreased; expiratory time was prolonged. This, especially the effect on expiratory time, makes lignocaine more similar in its depressant effect on ventilatory control to opioids than to general anaesthetics, which generally increase ventilatory rate. Telivuo and Katz [6] studied anaesthetized patients recovering from neuromuscular block. They concluded that lignocaine depressed ventilation by a central action, not by an effect on neuromuscular transmission. They gave lignocaine 3 mg kg⁻¹ (they tested bupivacaine, mepivacaine and prilocaine), and the effect was a mean decrease in tidal volume of about 40 %, lasting 2–9 min. They suggested that ventilation be monitored for a few minutes if lignocaine is given to treat postoperative arrhythmia.

More recently, anaesthetists have been concerned about possible ventilatory depression caused by local anaesthetics given extradurally. We did not measure systemic lignocaine concentration, but the peak concentration and the rate of development of peak concentration, and thus effect, of our i.v. dose

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**Table 1** Mean (range) ventilatory variables (VT = tidal volume; T = ventilatory cycle time; I = inspiratory time; E = expiratory time; V = minute ventilation) recorded from 10 patients anaesthetized with propofol infusion. Baseline values are mean over the 30 s before injection of saline (sal) or lignocaine (lig). F and P values from one-way repeated measures analysis of variance (ANOVA) applied to nine 30-s periods, baseline being the first

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>ANOVA</th>
<th>Direction</th>
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<tbody>
<tr>
<td>VT (ml)</td>
<td>326 (188–492)</td>
<td>5.67 &lt; 0.0001 Increase</td>
<td></td>
</tr>
<tr>
<td>VT (ml)</td>
<td>332 (194–499)</td>
<td>7.88 &lt; 0.0001 Decrease</td>
<td></td>
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<tr>
<td>T (s)</td>
<td>3.95 (2.64–5.60)</td>
<td>1.11 0.37</td>
<td></td>
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<tr>
<td>T (s)</td>
<td>3.85 (2.60–5.26)</td>
<td>4.70 &lt; 0.0001 Increase</td>
<td></td>
</tr>
<tr>
<td>I (s)</td>
<td>1.33 (1.11–1.80)</td>
<td>1.33 0.25</td>
<td></td>
</tr>
<tr>
<td>I (s)</td>
<td>1.32 (1.15–1.74)</td>
<td>0.75 0.65</td>
<td></td>
</tr>
<tr>
<td>E (s)</td>
<td>2.62 (1.53–3.85)</td>
<td>1.10 0.37</td>
<td></td>
</tr>
<tr>
<td>E (s)</td>
<td>2.53 (1.44–3.64)</td>
<td>6.48 &lt; 0.0001 Increase</td>
<td></td>
</tr>
<tr>
<td>E (l/min)</td>
<td>5.09 (2.68–8.92)</td>
<td>— — Increase</td>
<td></td>
</tr>
<tr>
<td>E (l/min)</td>
<td>5.40 (2.59–9.59)</td>
<td>— — Decrease</td>
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(1.5 mg kg\(^{-1}\)) should be greater (Gross and co-workers [9] measured it as 9 µg ml\(^{-1}\)) than any extradural dose (for which Gal [2] gives “about 3 µg ml\(^{-1}\)”) unless mistakenly injected into a vein. The ventilatory effect of lignocaine in our study, which caused no clinical concern to us, was superimposed on the already depressed ventilation of anaesthetized patients. Most of the reported work, and most of the worries about the effects of extradural analgesia on ventilation, are in patients who are not anaesthetized, who are either sedated or fully awake. We think that conflicting and confusing findings emanate from studies of the ventilatory effects of local anaesthetics because the effects are small, and the responses variable. We do not believe that extradural local anaesthesia is a clinically important central ventilatory depressant.

Steinbrook [10] commented that regional anaesthesia occasionally causes dyspnoea despite good inspiratory effort, and anaesthetists commonly give opioids extradurally. Both of these factors are more important risks to ventilation than the systemic effects of lignocaine, and although bupivacaine is the more usual extradural drug in the UK, bupivacaine 0.75 mg kg\(^{-1}\) i.v. had less effect on ventilation than lignocaine 3 mg kg\(^{-1}\) [6].

Investigators in this field often try to explain why their results differ from those of other similar studies. We believe it likely that these differences require no more explanation than wide variability in what are usually small studies. Nonetheless, although the systemic effects of local anaesthetics on ventilation are not clinically important, they differ from the effects of general anaesthetics, even though infusions of local anaesthetics are popular with some anaesthetists either as full general anaesthetics or to reduce the requirements for general anaesthetic agents. Their mode of action, in reducing tidal volume and prolonging expiratory time, is similar to that of opioids, although we do not suggest this is an action at any opioid receptor; it is more likely because of their action as stabilizers of excitable membranes.

We saw no evidence that lignocaine had any effect on bimodality of ventilatory timing [7]. This does not prove that it had no effect, but the apparent triggering of bimodality seen but unremarked on in previous work [6] may have been coincidental.

References
6. Telivuo L, Katz RL. The effects of modern intravenous local


