Topical analgesia of the upper airway with lignocaine

Absorption and its relationship to toxic and anti-arrhythmic levels

D. F. MORRELL, W. A. CHAPPELL, I. W. C. WHITE

Summary

After routine topical application of lignocaine to the upper airway before passage of an endotracheal tube during general anaesthesia, plasma lignocaine levels were assayed in 20 artificially ventilated and 21 spontaneously ventilating patients. Systemic absorption was found to be rapid but very variable. Mean peak levels were attained 15 minutes after spraying and were well below the convulsive threshold for anaesthetized patients, while reputedly anti-arrhythmic levels were achieved by 5 minutes and maintained until 40 minutes. Levels in the ventilated group were significantly higher 20 minutes after administration.

Lignocaine administration

The topical lignocaine was applied using a modified Macintosh spray (Fig. 1). This modification was carried out locally, the object being to do away with the nozzle tip which has been known to come loose and be propelled down the trachea. The unit consists of two co-axial polyethylene tubes — the outer being connected to a pressure bulb in the centre, a plastic reservoir of 4 ml capacity at one end and a pinched outer tip. Bulb pressure therefore forces fluid up the inner tube and causes nebulization at the distal end.

Patients and methods

Forty-one adults, rated grade I on the American Society of Anaesthesiologists scale, who were scheduled for elective orthopaedic procedures on the lower limbs were studied. After informed consent had been obtained the patients were arbitrarily assigned to one of two groups, namely: group A — in whom ventilation during anaesthesia would be controlled by intermittent positive pressure (IPPV); and group B — in whom ventilation during anaesthesia would be spontaneous.

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Lignocaine assay

Lignocaine was extracted from plasma and assayed by gas liquid chromatography. A Pye Unicam GCV chromatograph equipped with 2,1 m long glass columns (outer diameter 6 mm, inner diameter 4 mm) packed with 5% OV 101 and dual flame ionization detectors was used. A 5-point calibration curve was constructed for each patient on his own (blank) plasma using standard solutions and cyclizine as an internal standard. Plasma concentrations were then estimated from peak height ratios. The coefficient of correlation for the calibration curve was consistently better than 0.998 and the coefficient of deviation less than 5% on replicate samples. The two principal metabolites of lignocaine, mono-ethyl glycine xylidide and glycine xylidide, were found not to interfere with the lignocaine peaks, but no attempt was made to measure their concentration.

### Results

The groups were evenly matched for age, weight and sex.

Mean plasma levels of lignocaine at the 5-minute intervals are shown in Table II and Fig. 2. Plasma lignocaine levels in group A were higher than those in group B, but statistical significance was achieved at 20 minutes only \((P < 0.05)\). The highest mean levels occurred at 15 minutes in both groups. The highest individual level at any time was 6.4 mg/ml in group A and 4.8 mg/ml in group B. Levels greater than 5 mg/ml were achieved in 2 patients only, both of whom were in group A.

### Discussion

Controversy exists as to the efficacy of topical analgesics in suppression of cardiovascular and respiratory responses to laryngoscopy and intubation. Many clinicians are convinced that the technique reduces these untoward effects and practise it routinely before intubation.

Previously reported studies on the uptake of lignocaine are remarkable for the variation in the method of spraying, dose and apparatus used. The numbers involved in these studies are often small, the duration of sampling is often too short and venous plasma levels are given when tissue distribution is incomplete (when arterial levels will be higher). In addition, lignocaine is rapidly metabolized and unless the assay technique has excluded the presence of metabolites from the chromatographic peak in question, the quoted drug levels may be spurious. We chose to examine the technique as practised at this institution using arterial plasma concentrations, which can be regarded as representing the concentrations being presented to the target organs in question, viz. the heart and brain.

We examine three aspects of the results obtained, viz. (i) absorption; (ii) central nervous system (CNS) toxicity; and (iii) anti-arrhythmic effects.

### Absorption

Rate and degree of absorption are theoretically affected by droplet size, site of deposition and mucosal conditions. We attempted to standardize droplet size by using the same spray on all patients. As regards site of deposition, it has been reported

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**Table II. Dosage and Lignocaine Concentrations in Ventilated (Group A) and Spontaneously Ventilating (Group B) Patients at Sampling Times after Spraying of the Upper Airway**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
<th>25 min</th>
<th>30 min</th>
<th>35 min</th>
<th>40 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2.4</td>
<td>1.81</td>
<td>2.59</td>
<td>2.96</td>
<td>2.90</td>
<td>2.44</td>
<td>2.04</td>
<td>1.81</td>
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<tr>
<td>SEM</td>
<td>0.31</td>
<td>0.19</td>
<td>0.25</td>
<td>0.28</td>
<td>0.25</td>
<td>0.19</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>Group B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2.3</td>
<td>1.46</td>
<td>2.03</td>
<td>2.25</td>
<td>2.20</td>
<td>1.96</td>
<td>1.83</td>
<td>1.59</td>
</tr>
<tr>
<td>SEM</td>
<td>0.4</td>
<td>0.18</td>
<td>0.25</td>
<td>0.24</td>
<td>0.21</td>
<td>0.20</td>
<td>0.15</td>
<td>0.15</td>
</tr>
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</table>

* \( P < 0.05 \)

**Table III. Peak Lignocaine Levels**

<table>
<thead>
<tr>
<th>Time to peak (min)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
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<tbody>
<tr>
<td>Mean</td>
<td>20.8</td>
<td>18.4</td>
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<tr>
<td>SEM</td>
<td>1.95</td>
<td>1.41</td>
</tr>
<tr>
<td>Range</td>
<td>5-40</td>
<td>10-40</td>
</tr>
</tbody>
</table>

**Table IV. Peak Lignocaine Levels**

<table>
<thead>
<tr>
<th>Peak level (µg/ml)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.10</td>
<td>2.50</td>
</tr>
<tr>
<td>SEM</td>
<td>0.29</td>
<td>0.26</td>
</tr>
<tr>
<td>Range</td>
<td>1.3-6.4</td>
<td>0.7-4.8</td>
</tr>
</tbody>
</table>

There was no correlation either between the dose administered in mg/kg and the peak level or the time taken to reach peak level.

No untoward clinical effects or remarkable deviations from normal acid-base status were noted in any group or patients.
that IPPV results in more peripheral spread of droplets in the respiratory tree after spraying, with consequent greater absorption and systemic blood levels.\textsuperscript{1,8,9} Our study confirmed this finding in that levels were higher in group A than in group B. Anticholinergics might also enhance absorption by altering mucosal conditions, and it is therefore relevant that in contradistinction to other studies\textsuperscript{7,12} only 5 of our patients (12%) received an anticholinergic in their premedication. There was no significant difference between the time concentration curves of these patients and the rest.

In our patients absorption was rapid but very variable. If the time concentration curve for each patient was examined individually, a maximum level could be found at every sampling time over the 40-minute period. The rate of absorption in this study was not as rapid as that following intravenous administration when the plasma level is at a maximum within 2 minutes of injection and as might occur if absorption was from terminal airways. Uptake rather resembles that following epidural or intramuscular injection when maximum levels occur at 15-20 minutes. This indicates that a large proportion of the administered drug is deposited in the upper airway.

CNS Toxicity

Toxicity to amide-linked local anaesthetic agents (of which lignocaine is an example) is dose-related, 'idiosyncratic' and 'allergic' reactions to the preservative-free drug being rare. The reported convulsive threshold for lignocaine is in the range of 6-9 µg/ml in the unanaesthetized,\textsuperscript{11} and over 10 µg/ml\textsuperscript{12} in the anaesthetized subject. The highest recorded level in this study was 645 µg/ml and only 1 other patient achieved a level greater than 5 µg/ml. The routine used is therefore 'safe' as regards CNS toxicity in this class of patient.

Anti-arrhythmic effects

Serious cardiac arrhythmias have been shown to occur during laryngoscopy and intubation in up to 40% of cases\textsuperscript{13-16} and topical analgesia given before these procedures will diminish but not preclude the incidence.\textsuperscript{17,18} This protection is afforded by both depression of the afferent reflex arc and by direct myocardial effects following systemic absorption. Topical analgesia is established in 1-2 minutes after administration,\textsuperscript{19} but is less effective in protecting against reflexes initiated during laryngoscopy by stretching of oropharyngeal and neck structures.

Systemic levels of lignocaine between 1 and 2 µg/ml are generally considered to be partially effective, and those between 2 and 5 µg/ml usually effective in preventing ventricular arrhythmias.\textsuperscript{20,22} Our observations indicate that protection due to systemic absorption can be expected between 5 and 40 minutes after spraying, with maximal effect at 15 minutes. Variability in absorption is such that 27% of our patients did not achieve levels of 2 µg/ml at any stage and thus received only partial protection.

Conclusion

Topical analgesia of the upper airway with lignocaine before laryngoscopy and intubation under general anaesthesia results in rapid but variable systemic absorption of the drug. The plasma levels recorded are not in the range associated with CNS toxicity and are high enough to provide direct myocardial protection against ventricular arrhythmias. Neither this systemic protection nor protection afforded by local mucosal anaesthesia per se are operative against initial laryngoscopy or if intubation is executed within 1 - 2 minutes of spraying.

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References