PLASMA LIGNOCAINE CONCENTRATIONS FOLLOWING ENDOTRACHEAL SPRAYING WITH AN AEROSOL

D. B. SCOTT, D. G. LITTLEWOOD, B. G. COVINO AND G. B. DRUMMOND

SUMMARY

Plasma concentrations of lignocaine were measured in three groups of anaesthetized patients following spraying of the trachea and larynx with a lignocaine 10% aerosol spray. Greater venous plasma concentrations occurred in patients who were paralysed with suxamethonium. A mean plasma concentration of 0.1 μg/ml of lignocaine resulted from each 10 mg of lignocaine used in spontaneously breathing patients, and 0.15 μg/ml in paralysed patients. In individual patients a concentration 50% in excess of the mean value may occur. The use of lignocaine 100 mg as a 10% aerosol spray can be considered safe.

The use of an endotracheal spray containing a local anaesthetic occurs commonly in anaesthesia. It allows the patient to tolerate the presence of an endotracheal tube at a lighter plane of anaesthesia than would be possible otherwise. In addition, during and after endotracheal intubation, it prevents reflex activity such as tachycardia, an increase in arterial pressure and, frequently, cardiac arrhythmia.

Lignocaine 4% is used most commonly, and this is applied in a variety of sprays. In recent years lignocaine 10% has been available as a freon-propelled aerosol spray. To avoid an overdose, the aerosol container has a metered valve and depression of its release button allows only 0.1 ml of solution (10 mg of lignocaine) to escape. In general, 10 such aliquots (100 mg) are sufficient to anaesthetize the trachea and larynx.

The plasma concentrations of lignocaine following aerosol spraying were studied in anaesthetized patients under varying conditions and at different doses. This study was conducted to determine whether lignocaine 10% delivered as a very fine spray results in a rapid absorption which might be potentially toxic.

METHOD

Three groups of patients were studied. All were adults under the age of 60 yr, about to undergo surgery under general anaesthesia with endotracheal intubation. Atropine 0.6 mg i.m. 1 h before operation was the only premedication.

Anaesthesia was induced with thiopentone 300-400 mg given i.v. In two groups this was accompanied by gallamine 60 mg. Under direct laryngoscopy the trachea was sprayed using lignocaine 5% (five patients) and 10% (six patients). In each case the spraying routine was the same: the spray nozzle was inserted into the trachea through the larynx and the release button was depressed seven times. The nozzle was then withdrawn from the larynx, which was itself sprayed using three more aliquots of drug. The total spraying time was about 15 s. Thus, the total dose was 50 mg when the 5% spray was used (35 mg to the trachea and 15 mg to the larynx), and 100 mg with the 10% solution (70 mg to the trachea and 30 mg to the larynx). An endotracheal tube was passed immediately after the spraying was complete and spontaneous respiration was present throughout surgery. Gallamine was employed to prevent excessive coughing and laryngeal spasm during the spraying.

Five patients received suxamethonium 100 mg after the injection of thiopentone, and were paralysed at the time of spraying. To alleviate muscle pain after surgery, which might be a result of suxamethonium, gallamine 20 mg was given 2 min before the thiopentone in this group. The procedures of spraying and intubation were the same as for the other groups. Lignocaine 10% was used, the total dose being 100 mg. Ventilation was controlled using intermittent positive pressure.

Venous blood was withdrawn before and 1, 2, 5, 10, 15, 20, 25 and 30 min after completion of the spraying. The plasma was separated and lignocaine concentrations were determined by gas chromatography. All concentration values stated apply to lignocaine base.

To establish that the aerosol discharged the same quantity of drug each time the release button was activated, the combined weight of 10 aliquots was...
TABLE I. Plasma concentrations of lignocaine following endotracheal spraying with an aerosol. The mean maximum concentrations represent the mean of the greatest concentrations measured in individual patients regardless of when this occurred.

<table>
<thead>
<tr>
<th>Dose of lignocaine</th>
<th>Control</th>
<th>1 min</th>
<th>2 min</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>Mean max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) 50 mg (spontaneous breathing) (n = 5)</td>
<td>Mean</td>
<td>0</td>
<td>0.14</td>
<td>0.36</td>
<td>0.48</td>
<td>0.47</td>
<td>0.44</td>
<td>0.34</td>
<td>0.29</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0</td>
<td>0.11</td>
<td>0.24</td>
<td>0.25</td>
<td>0.29</td>
<td>0.22</td>
<td>0.13</td>
<td>0.11</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.05</td>
<td>0.11</td>
<td>0.11</td>
<td>0.13</td>
<td>0.10</td>
<td>0.10</td>
<td>0.06</td>
<td>0.05</td>
<td>0.07</td>
</tr>
<tr>
<td>(B) 100 mg (spontaneous breathing) (n = 6)</td>
<td>Mean</td>
<td>0.13</td>
<td>0.38</td>
<td>0.57</td>
<td>0.78</td>
<td>0.82</td>
<td>0.96</td>
<td>0.89</td>
<td>0.84</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.10</td>
<td>0.18</td>
<td>0.22</td>
<td>0.38</td>
<td>0.22</td>
<td>0.25</td>
<td>0.21</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
<td>0.04</td>
<td>0.07</td>
<td>0.09</td>
<td>0.15</td>
<td>0.09</td>
<td>0.10</td>
<td>0.09</td>
<td>0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>Comparison of A and B</td>
<td>t</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>2.82</td>
<td>4.90</td>
<td>5.59</td>
<td>5.11</td>
<td>2.97</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.02</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>(C) 100 mg (paralysed)</td>
<td>Mean</td>
<td>0.30</td>
<td>0.90</td>
<td>1.28</td>
<td>1.46</td>
<td>1.46</td>
<td>1.33</td>
<td>1.19</td>
<td>1.17</td>
<td>1.60</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>SD</td>
<td>0.22</td>
<td>0.41</td>
<td>0.35</td>
<td>0.43</td>
<td>0.33</td>
<td>0.33</td>
<td>0.16</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
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<td>0.18</td>
<td>0.16</td>
<td>0.19</td>
<td>0.19</td>
<td>0.15</td>
<td>0.07</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Comparison of B and C</td>
<td>t</td>
<td>n.s.</td>
<td>2.85</td>
<td>4.11</td>
<td>2.77</td>
<td>3.93</td>
<td>2.82</td>
<td>3.02</td>
<td>4.16</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&lt;0.02</td>
<td>&lt;0.005</td>
<td>&lt;0.025</td>
<td>&lt;0.005</td>
<td>&lt;0.02</td>
<td>&lt;0.02</td>
<td>&lt;0.005</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Statistical analysis was performed using Student's t test.

RESULTS

The plasma lignocaine concentrations are shown in table I and figure 1. Maximum concentrations were usually reached between 10 and 20 min after spraying, although it occurred occasionally at 5 min or was delayed until 30 min.

In the two groups who were breathing spontaneously, the mean maximum concentration of lignocaine was 0.55 \( \mu \text{g/ml} \) in those receiving 50 mg of the drug, and 1.03 \( \mu \text{g/ml} \) in those receiving 100 mg. This difference was statistically significant \((P<0.02)\), as were the differences between the mean plasma concentrations at 15, 20, 25 and 30 min after spraying. The highest concentration in any patient was 1.44 \( \mu \text{g/ml} \).

The patients who were paralysed had greater plasma concentrations of lignocaine than did those who breathed spontaneously. The mean maximum venous plasma concentration in this group was 1.60 \( \mu \text{g/ml} \), compared with 1.03 \( \mu \text{g/ml} \) in the non-paralysed patients. This difference was statistically significant \((P<0.02)\), as were the differences at all time intervals beyond 1 min.

Endotracheal spraying achieved its clinical purpose. There was no response to endotracheal intubation in the non-paralysed patients and good subsequent toleration of the tube in all patients in whom the 10% spray was used. A few patients reacted to the tube when the 5% aerosol was employed.

DISCUSSION

The absorption of local anaesthetic agents after spraying of the larynx and the trachea will vary greatly according to the site of application and the...
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general condition of the patient. Thus, drug deposited in the upper airway may be swallowed and gain access to the general circulation only after passage through the liver where the amide anaesthetics will be metabolized rapidly. More of the drug is likely to be coughed into the pharynx and swallowed in conscious patients. Telivuo (1965) found that plasma concentrations of prilocaine in conscious subjects were only 20–30% of those found in paralysed anaesthetized patients. A drug will be absorbed more rapidly in the more distal parts of the bronchial tree, since the surface available for absorption is increased. Finally, should any drug reach the alveoli, the absorption may approach the rapidity of that following an i.v. injection. Thus, it is easy to understand the difference between the plasma concentrations in the patients who breathed spontaneously and those who were paralysed. In the former case, some of the drug sprayed into the trachea will be exhaled into the upper airway, particularly if coughing occurs during spraying.

The plasma concentrations measured in this study indicate that, even under conditions most favourable to absorption, the instillation of lignocaine 100 mg into the trachea, using a 10% aerosol, is unlikely to cause overt toxicity. The greatest concentration of lignocaine measured in any patient was 2.16 µg/ml and all others were less than 2 µg/ml. Even in conscious subjects, signs of toxicity in the central nervous system are rare with values less than 4–5 µg/ml (Scott, 1975). Convulsions are rare at venous plasma concentrations less than lignocaine 10 µg/ml (Bromage and Robson, 1961). If the patient is anaesthetized the threshold values are greater.

However, account must be taken of an increase in the plasma lignocaine concentration of 2 µg/ml in patients who may concurrently have received lignocaine by another route.

Aerosol sprays deliver smaller droplets than most of the sprays in common use. Therefore, it is possible that the drug may be sprayed more distally in the bronchial tree. However, comparison with other published data does not reveal plasma concentrations significantly higher than those observed in the present investigation. Curran, Hamilton and Taylor (1975), using three times the dose used in the present study (3 ml of a 10% solution) sprayed entirely into the trachea of paralysed patients, found a mean maximum concentration of 5.6 µg/ml using the Forrester spray.

In the United States a disposable spray is available for tracheal anaesthesia which contains 5 ml of a 4% solution of lignocaine (200 mg). This delivers a coarse spray. Chu and others (1975) found plasma concentrations as great as 3.54 µg/ml after giving the total dose of 200 mg. Viegas and Stoelting (1975), using the same spray but a smaller dose (2 mg/kg), found a mean maximum plasma concentration of 1.7 µg/ml. Allowing for variations in dose and in technique, these results appear to be similar to those reported in this paper. Pelton and others (1970), using a lignocaine 10% aerosol spray in children, found similar plasma concentrations.

It is concluded that the spraying of lignocaine 100 mg into the tracheo-bronchial tree using a 10% aerosol spray is a safe and effective way of achieving local anaesthesia of the larynx and trachea, provided the total dosage is controlled carefully. As only 10 mg of lignocaine is delivered each time the release button is activated, overdose is unlikely unless excessive activations are employed. Ten milligrams of a lignocaine endotracheal aerosol produces a plasma concentration of approximately 0.1 µg/ml in spontaneously breathing patients and 0.15 µg/ml in paralysed patients. We doubt if more than 100 mg is necessary in anaesthetized patients.

ACKNOWLEDGEMENTS

We are grateful to Professor M. G. Kerr and his colleagues for allowing us to study their patients. All the estimations of plasma lignocaine concentrations were kindly performed by G. T. Tucker, Ph.D., of the Department of Therapeutics, University of Sheffield. We also acknowledge the technical assistance of P. F. Covino and B. M. Covino.

REFERENCES


CONCENTRATIONS DE LIGNOCAINE DANS LE PLASMA APRES VAPORISATION ENDOTRACHEALE AVEC UN AEROSOL

RESUME
Les concentrations de lignocaine dans le plasma ont été mesurées sur trois groupes de patients anesthésiés après vaporisation de la trachée et du larynx avec un aérosol contenant 10% de lignocaine. On a constaté des concentrations plus grandes de plasma veineux sur les patients qui avaient été paralysés par le suxaméthonium. Une concentration moyenne de 0,1 µg/ml de lignocaine dans le plasma s’est produite après chaque 10 mg de lignocaine utilisés sur les patients respirant spontanément et de 0,15 µg/ml sur les patients paralysés. Il peut se produire sur certains patients des concentrations supérieures de 50% à la valeur moyenne. L’emploi de 100 mg de lignocaine en vaporisations aérosols à 10% peut être considéré comme ne représentant aucun danger.

PLASMA-LIGNOCAINKONZENTRATIONEN NACH ENDOTRACHEALER BESPRÜHUNG MIT EINEM AEROSOL

ZUSAMMENFASSUNG
Die Plasmakonzentrationen von Lignocain wurden bei drei Gruppen narkotisierter Patienten gemessen, nachdem Trachea und Larynx mit einer 10%igen Lignoicainlösung besprüht worden waren. Höhere venöse Plasmakonzentrationen ergaben sich bei den Patienten, die durch Suxamethonium gelähm werden. Eine mittlere Plasmakonzentration von 0,1 µg/ml Lignocain ergab sich bei jeweils 10 mg Lignocain bei spontan atmenden Patienten und bei 0,15 µg/ml bei durch Narkose gelähmten Patienten. Bei individuellen Patienten kann sich eine Konzentration von mehr als dem Mittelwert ergeben. Die Verwendung von 100 mg Lignocain in Form einer 10%igen Aerosol- Sprühlösung kann als ungefährlich angesehen werden.

CONCENTRACIONES PLASMATICAS DE LIGNOCAINA TRAS ROCIAIÓN ENDOTRAQUEAL CON UN AEROSOL

SUMARIO
Se midieron las concentraciones de lignocaina en el plasma de tres grupos de pacientes anestesiados tras la rociación de la tráquea y laringe con un aerosolizador de lignocaina al 10%. En los pacientes inmovilizados mediante suxametonio se produjeron mayores concentraciones en el plasma venoso. Una concentración plasmática media de 0,1 µg/ml de lignocaina fue producida por cada 10 mg de lignocaina usada en pacientes con respiración espontánea, y 0,15 µg en los pacientes paralizados. En los pacientes individuales pudiera producirse una concentración del 50% en exceso del valor medio. El uso de lignocaina 100 mg como rociada en aerosol al 10% puede ser considerado inocuo.