IMPAIRED ABSORPTION AND METABOLISM OF ORAL LIGNOCAININE IN PATIENTS UNDERGOING LAPAROSCOPY


SUMMARY

Lignocaine hydrochloride (400 mg) was given orally to 12 patients prior to anaesthesia for laparoscopy. Serial blood samples were taken for estimation of plasma lignocaine concentrations. The results were compared with those obtained from 7 conscious healthy volunteers who took lignocaine alone. There was a marked delay in the rise of plasma concentrations of lignocaine in the anaesthetized patients indicating delayed absorption. In these patients the drug disappeared from the plasma much more slowly, suggesting impaired metabolism of lignocaine. This effect could not be attributed to halothane.

Very little is known of the effects of anaesthesia on the absorption, distribution and metabolism of drugs. If anaesthetic agents cause impairment of liver function, the effects of many lipid soluble drugs are likely to be exaggerated and prolonged since these compounds are usually inactivated by metabolism in the liver (Brodie, 1964; Prescott, 1972). Such effects could be of particular significance in view of the alleged hepatotoxicity of halogenated hydrocarbons such as halothane and chloroform.

In the course of an investigation into the use of oral lignocaine in the prophylaxis of ventricular arrhythmias occurring during laparoscopy, serial plasma concentrations of lignocaine were determined and found to differ considerably from those seen in normal conscious subjects. The results of these studies are presented below.

METHODS

Patients.

Twelve healthy patients aged between 22 and 39 years scheduled for laparoscopy and tubal diathermy volunteered for the study. Except for 5 patients on oral contraceptives, none of the patients was taking drugs regularly and none had clinical evidence of hepatic, cardiac, renal or gastrointestinal disease.

Procedure.

After an overnight fast each patient ingested 400 mg of lignocaine hydrochloride as tablets (equivalent to 346 mg lignocaine base) with 40 ml of water 0.5 to 2 hr before induction of anaesthesia. Venous blood was sampled at frequent intervals for 12 hr through an indwelling cannula.

Premedication consisted solely of atropine sulphate 0.6 mg given intramuscularly 1 hr preoperatively. Induction was carried out with thiopentone 400 mg intravenously. In 6 patients gallamine 60 mg was given and anaesthesia was maintained with halothane 2% and a mixture of nitrous oxide (3 l/min) and oxygen (1 l/min) in a semiclosed system incorporating a carbon dioxide absorber. Respiration was spontaneous throughout. The other 6 patients received gallamine 80 mg, halothane was omitted, and respiration was controlled using intermittent positive pressure.

The duration of anaesthesia varied from 8 to 15 min. Carbon dioxide insufflation was used for the laparoscopy and the duration of peritoneal inflation was 4–5 min. There were no operative complications. All patients were ambulant 3 hr after laparoscopy and were discharged home the following day.

Controls.

Control studies were carried out in 7 fasting unanaesthetized healthy volunteers (4 males, 3 females) aged between 22 and 37. They received oral lignocaine only as described above.

Plasma lignocaine.

Plasma was stored at −20°C until the time of analysis. Lignocaine was estimated in plasma using the specific gas-liquid chromatographic method of
Keenaghan (1968) as modified by Prescott and Nimmo (1971a). A Hewlett-Packard Model 402 gas-liquid chromatograph equipped with flame ionization detectors was used. The column was a glass U-tube, 4 ft long, 1/2 in. diameter, packed with 3% HI-EFF 8 BP on 80/100 mesh Gas Chrom Q. The nitrogen carrier gas flow was 60 ml/min and the oven was maintained at 210°C. The standard deviation of a single estimation of a sample containing 0.5 μg lignocaine/ml is approximately 4% in this laboratory.

RESULTS

There were no consistent differences between the mean plasma lignocaine concentrations in the two anaesthetized groups of patients and their data have therefore been pooled for comparison with the control subjects (table I).

Lignocaine absorption was much slower and the drug disappeared from the plasma more slowly in the patients than in the healthy volunteers (figs. 1 and 2). Thus the mean peak plasma lignocaine concentration occurred at 45 min in the healthy volunteers as compared with 3 hr in the patients. However, the mean of the individual peak plasma lignocaine concentrations were similar in volunteers and anaesthetized patients (table II). The estimated mean plasma lignocaine half-life was 1.3 hr in control subjects and 2.8 hr in the patients. After 9 hr the half-life was prolonged to 4.8 hr in the patients undergoing laparoscopy.

Although mean plasma lignocaine concentrations were higher in healthy volunteers up to 2 hr, the

![Fig. 1. Mean plasma lignocaine concentrations after ingestion of 400 mg lignocaine hydrochloride in 12 laparoscopy patients and 7 unanaesthetized healthy volunteers.](image)

<table>
<thead>
<tr>
<th>Time after ingestion (hr)</th>
<th>0.25</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
<th>1.25</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With halothane</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0.06 ±0.03</td>
<td>0.12</td>
<td>0.19</td>
<td>0.18</td>
<td>0.22</td>
<td>0.23</td>
<td>0.28</td>
<td>0.6</td>
<td>0.39</td>
<td>0.21</td>
<td>0.095</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td><strong>Without halothane</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.054 ±0.05</td>
<td>0.16</td>
<td>0.083</td>
<td>0.22</td>
<td>0.24</td>
<td>0.24</td>
<td>0.28</td>
<td>0.24</td>
<td>0.24</td>
<td>0.28</td>
<td>0.24</td>
<td>0.28</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Number of observations are given in parentheses.

<table>
<thead>
<tr>
<th>Mean of individual peak concentrations</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td>0.67</td>
<td>0.51</td>
<td>0.52</td>
<td>0.31</td>
<td>0.18</td>
</tr>
<tr>
<td>±0.04</td>
<td>±0.1</td>
<td>±0.06</td>
<td>±0.03</td>
<td>±0.02</td>
<td>±0.01</td>
</tr>
<tr>
<td>Laparoscopy patients</td>
<td>0.55</td>
<td>0.14</td>
<td>0.20</td>
<td>0.29</td>
<td>0.47</td>
</tr>
<tr>
<td>±0.07</td>
<td>±0.03</td>
<td>±0.04</td>
<td>±0.05</td>
<td>±0.08</td>
<td>±0.03</td>
</tr>
<tr>
<td>P value</td>
<td>n.s.</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>n.s.</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

n.s. = not significant.
IMPAIRED ABSORPTION AND METABOLISM OF ORAL LIGNOCAINE

CONCENTRATIONS WERE MUCH HIGHER IN THE PATIENTS AT ALL TIMES AFTER 2 HR (TABLE II AND FIGS. 1 AND 2). FOR EXAMPLE, AT 6 HR THE MEAN PLASMA LIGNOCAINE CONCENTRATION IN LAPAROSCOPY PATIENTS WAS MORE THAN FIVE TIMES HIGHER THAN THAT IN HEALTHY VOLUNTEERS (TABLE II AND FIG. 2).

DISCUSSION

THE PLASMA CONCENTRATION OF LIGNOCAINE AT ANY GIVEN TIME IS DETERMINED BY THE RELATIVE RATES OF ABSORPTION, DISTRIBUTION AND ELIMINATION. THE PRESENT FINDINGS INDICATE THAT THE ABSORPTION AND ELIMINATION OF LIGNOCAINE ARE SIGNIFICANTLY DELAYED IN PATIENTS UNDERGOING LAPAROSCOPY. THE ABNORMALLY SLOW ABSORPTION IN THE PATIENTS COULD HAVE BEEN CAUSED BY DECREASED GASTROINTESTINAL MOTILITY, DELAYED GASTRIC EMPTYING (PRESCOTT AND Nimmo, 1971b) OR REDUCTION IN SPLANCHNIC BLOOD FLOW. THESE FACTORS MAY BE AFFECTED BY NERVOUS TENSION IN UNSEDATED PATIENTS PRIOR TO SURGERY. IN ADDITION WE HAVE SHOWN THAT ATROPINE ALONE SLOWS ABSORPTION OF ORAL LIGNOCAINE IN MAN—PRESUMABLY BY DELAYING GASTRIC EMPTYING (Adjepon-Yamoh, Prescott and Scott, unpublished). INSUFFLATION OF THE PERITONEUM WITH CARBON DIOXIDE DURING LAPAROSCOPY IS UNLIKELY TO HAVE HAD A MAJOR EFFECT SINCE ABSORPTION WAS DELAYED LONG AFTER THE END OF THE PROCEDURE. SINCE NEGLIGIBLE AMOUNTS OF LIGNOCAINE ARE EXCRETED UNCHANGED IN THE URINE, THE HIGHER PLASMA LIGNOCAINE CONCENTRATIONS AFTER 3 HR AND THE LONGER LIGNOCAINE HALF-LIFE IN THE PATIENTS CAN PROBABLY BE ATTRIBUTED TO DECREASED HEPATIC LIGNOCAINE METABOLISM.

A NUMBER OF FACTORS MIGHT ALTER LIVER FUNCTION AND THUS CONTRIBUTE TO THE REDUCED HEPATIC METABOLISM OF LIGNOCAINE. HEPATIC BLOOD FLOW CAN BE A MAJOR DETERMINANT OF THE DISPOSITION OF METABOLIZED DRUGS (Whitsett, Dayton and McNay, 1971) AND Shackman, Graber and Melrose (1953) FOUND A 30% DECREASE IN HEPATIC BLOOD FLOW AND DECREASED HEPATIC AND SPLANCHNIC OXYGEN CONSUMPTION IN ANAESTHETIZED SUBJECTS. FURTHERMORE, LIVER METABOLISM IS IMPAIRED BY HYPOXIA AND THIS MIGHT ALSO RENDER THE LIVER MORE SUSCEPTIBLE TO POTENTIALLY HEPATOTOXIC AGENTS. THERE IS NO SIGNIFICANT CHANGE IN CARDIAC OUTPUT DURING LAPAROSCOPY (Marshall et al., 1972), BUT THE HEPATIC CLEARANCE OF LIGNOCAINE COULD BE REDUCED THROUGH REGIONAL HAEMODYNAMIC CHANGES ASSOCIATED WITH INCREASED INTRA-ABDOMINAL PRESSURE.

Hypercarbia is another possible contributory factor. Morris and Feldman (1963) found that the postoperative retention of bromsulphthalein (BSP) was increased by hypercarbia during halothane anaes-
thiesis. Retention of carbon dioxide undoubtedly occurred in the laparoscopy patients since the mean $P_{CO_2}$ rose from 43.2 to 60.8 mm Hg in other patients undergoing the same procedure (Scott and Julian, 1972).

Because the plasma lignocaine concentrations were similar in the two groups of patients, hepatotoxicity due to halothane can probably be excluded as a cause of the prolonged lignocaine half-life. Alternatively, it could be postulated that nitrous oxide and halothane are equally toxic to the liver.

Thiopentone, halothane and lignocaine are metabolized by hepatic drug metabolizing enzymes and the drug with the greatest affinity for the enzymes would be metabolized in preference to those with lower affinity. Acute administration of some microsomal inducing agents can cause an initial inhibition of drug metabolism (Kato, Chiesara and Vassanelli, 1964). Thiopentone could perhaps interfere with lignocaine metabolism by this mechanism.

The changes observed in the present study occurred after short periods of anaesthesia in patients with no complicating pathology. The ability of the liver to metabolize different drugs during longer periods of anaesthesia is not known, but Karlin and Kutt (1970) described diphenhydantoin intoxication in an epileptic patient after halothane anaesthesia. For reasons which are obscure, these workers attributed this effect to impaired diphenhydantoin metabolism due to halothane hepatotoxicity.

Delayed gastrointestinal absorption following anaesthesia is of little consequence, but impaired hepatic drug metabolism could be very important clinically.

ACKNOWLEDGEMENTS

We wish to thank Professor R. J. Kellar, Dr P. R. Myerscough and Dr D. T. Baird for allowing us to study patients under their care. This work was supported by grants from the World Health Organization and the Scottish Hospitals Endowment Research Trust.

REFERENCES


ABSORPTION ET METABOLISME ALTERES DE LIGNOCAINE PAR VOIE ORALE CHEZ DES PATIENTS SUBISSANT UNE LAPAROSCOPIE

SOMMAIRE

400 mg d'hydrochluroz ont été administrés par voie orale à douze patients avant l'anesthésie pour laparoscopy. Des échantillons sanguins ont été prélèvés en série pour estimer les concentrations plasmatiques de lignocaine. Les résultats obtenus ont été comparés avec ceux obtenus chez sept volontaires sains conscients, recevant lignocaine seule. Il y eut un retard marqué de l'augmentation des concentrations plasmatiques de lignocaine chez les patients anesthésiés, indiquant une absorption retardée. Le médicament s'élimina beaucoup plus lentement du plasma chez ces patients, suggérant un métabolisme altéré de lignocaine. Cet effet n'a pas pu être attribué à l'halothane.

VERMINDERTE ABSORPTION UND STOFFWECHSEL NACH ORALER AUFNAHME VON LIGNOCAIN BEI PATIENTEN IM ZUSAMMENHANG MIT LAPARASKOPIE

ZUSAMMENFASSUNG

ALTERACION EN LA ABSORCION Y METABOLISMO DE LIGNOCAINA POR VIA ORAL EN PACIENTES SOMETIDOS A LAPAROSCOPIA

RESUMEN
Se administró 400 mg de lignocaina por vía oral a doce pacientes antes de la anestesia para laparoscopia. Fueron tomadas muestras seriadas de sangre para la determinación de las concentraciones de lignocaina en el plasma. Estos resultados fueron comparados con los obtenidos en siete voluntarios sanos despiertos que tomaron solamente la lignocaina. Hubo un acusado retraso en la elevación de las concentraciones en el plasma de la lignocaina en los pacientes anestesiados, lo cual indica un retraso en la absorción. En estos pacientes el medicamento desapareció del plasma con mucha mayor lentitud, sugiriendo una alteración en el metabolismo de la lignocaina. Este efecto no pudo ser atribuido al halotano.

BOOK REVIEWS


There could not be a better time for the publication of a readily available source of authoritative information on the problems of sterilizing anaesthetic instruments to avoid cross-infection. Anaesthetists in general, are dirty workers. They are sustained in their bad habits by the uncertainty of the extent of the danger of cross-infection that arises from their unclean habits. No one will deny that a clean endotracheal tube to be passed into the trachea of a patient should not be put on to a table top that is soiled with mucopurulent muck from the previous patient's throat. Or that a foul mask and breathing tube is abhorrent. This book, in a systematic and scholarly fashion, chides us gently but firmly for being guilty of these and many other equally undesirable practices. It sets out both the socially objectionable if perhaps relatively harmless practices, and those which carry proven risks of cross-infection. The authors discuss in considerable detail and with excellent documentation the various methods of cleansing and sterilizing anaesthetic instruments and apparatus. The Editor has the double advantage of receiving his anaesthetic training in Britain and of continuing his career in the United States. Perhaps the former is responsible for the unusually clear style of writing throughout and for the welcome international scope of the very comprehensive reference lists; the latter for perceiving the problems so clearly. His eleven authors consist of six anaesthetists, three microbiologists and two others with special knowledge of this field. British readers will welcome the contributions from Professors Blowers of Northwick Park, and Sykes of Hammersmith, but the whole book is of a very high standard. The views and recommendations of this group of eminent authors are likely to be acceptable to anaesthetists, microbiologists, surgeons and hospital authorities on both sides of the Atlantic. The value of this important book is in inverse ratio to its size and it is warmly recommended.

W. W. Mushin


It is a relief to see that something so basic to anaesthesia as the care of the airway is not only still being taught vigorously and correctly, but that modern textbooks reiterating what is at the very heart of clinical anaesthesia are still being written. This book is the work of a group of seven "practising anaesthesiologists" and one e.n.t. surgeon, all from Ontario, Canada. It brings the clinical subject of airway control up to date in the context of modern anaesthetic knowledge and practice. The relevant anatomical and physiological features of the pharynx and larynx are discussed from a clinical standpoint in the first section. Then follow essays on various problems concerned with the anaesthetic management of adults and children with airway problems, particularly when these occur in the intensive care unit. Three of the eight chapters deal with the peculiar problems of tracheostomy, one of them being written from a surgical point of view. This is a useful book in the Clinics series, which will be read with profit by every young anaesthetist (and by some older ones too). The style of writing is attractive, the illustrations clear and helpful, the references relevant and not too many, and the text is well illuminated with case reports so that the reader is in no doubt about the fundamental importance and overriding priority which must be given to the maintenance of a clear airway.

W. W. Mushin