pressure, impeding the accumulation of air in the venous system. Most importantly, however, is early recognition of air embolism to allow for rapid and effective treatment and to minimize postoperative sequelae.

REFERENCES


Effect and Interaction of pH and Lidocaine on Epinephrine Absorption

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To achieve optimal local hemostasis in patients undergoing surgery, a dilute solution of epinephrine is often injected. We previously demonstrated that lidocaine added to an epinephrine solution accelerates the transfer of epinephrine to the blood in patients undergoing craniotomy. Sosis et al. suggested that the pH of the solution might have been responsible for the variation in epinephrine uptake attributed to lidocaine, because the pH of commercially available lidocaine with epinephrine is made acidic to achieve stability of the added epinephrine. Therefore, in this study, we investigated the effect of the pH of the solution on the absorption of locally injected epinephrine into the blood stream.

MATERIALS AND METHODS

After obtaining approval of the committee for the protection of human subjects and informed consent, we studied 40 (18 males and 22 females) ASA I and II adult

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patients who were scheduled for elective craniotomy. Halothane 4% in oxygen was inhaled via a semiclosed
system for 10 min, and orotracheal intubation was per-
formed without using a muscle relaxant. The patients
were ventilated mechanically to keep the \( \text{PaCO}_2 \) at
30–35 mmHg. During the 30 min usually required for
positioning and preoperative preparation, anesthesia
was maintained with 2–2.5% halothane in 100% oxygen
or 1–1.5% halothane mixed with 50% nitrogen oxide in
oxygen, so that the systolic arterial pressure was main-
tained at 90–110 mmHg. Intermittent analysis of arte-
rrial blood gases and continuous monitoring of \( \text{P}_\text{aCO}_2 \)
were made. The ECG and the arterial pressure waves
from an indwelling catheter were continuously dis-
played on an oscilloscope and simultaneously recorded
with a thermostyloscope recorder.

The patients were divided into five groups, and the
following five different solutions containing 1:200,000
epinephrine were prepared for cutaneous injection: 1)
LE 4.9 (\( \text{pH} = 4.9 \)): a commercially available 1:100,000
epinephrine with 1% lidocaine solution diluted with a
normal saline solution of an equal volume, giving a
1:200,000 epinephrine in 0.5% lidocaine solution; 2)
LE 6.4 (\( \text{pH} = 6.4 \)): 1:200,000 epinephrine added to a
commercially available 0.5% lidocaine solution; 3) LE
7.6 (\( \text{pH} = 7.6 \)): a mixture of a commercially available
2% lidocaine solution, a 160 mMol NaHCO\(_3\) solution,
and epinephrine, giving a 1:200,000 epinephrine in
0.5% lidocaine solution; 4) E 6.1 (\( \text{pH} = 6.1 \)): 1:200,000
epinephrine in a normal saline solution; and 5) E 7.6
(\( \text{pH} = 7.6 \)): 1:200,000 epinephrine in a mixture of a
normal saline solution and a 150 mMol NaHCO\(_3\) solu-
tion. These solutions were prepared immediately be-
fore use.

After the patients were positioned for surgery, one of
the five epinephrine solutions was injected at 0.5 ml/kg
into the scalp by an anesthesiologist over a period of 5
min. Half of the solution was deposited beneath the
aponeurosis, followed by infiltration of the remaining
half into the subcutaneous tissue. When using the solu-
tions not containing lidocaine, nerve block or field
block of the scalp was performed with a 0.25% bupiva-
caine solution prior to epinephrine injection to mini-
mize the surgical stress. Arterial blood for analysis of
the epinephrine concentration was obtained five times,
\text{i.e.}, before injection and 1, 5, 10, and 20 min after
completion of the injection. The sampled blood was
treated with ethylene-diamine-tetra-acetic acid (EDTA)
and centrifuged immediately. The plasma was stored in
a freezer at \(-25^\circ\) C and analyzed within 3 days. Ep-
epinephrine was measured by the same method as reported
previously.\(^3\) The limit of sensitivity of the method was
0.01 ng/ml.

The results were expressed as the mean ± SEM. Com-
parison of variables among groups was made by analysis
of variance (ANOVA), and within groups by the paired
Student's \( t \)-test. Linear correlations between the vari-
ables were calculated by the method of least squares,
and the equations were compared by regression analy-
sis. \( P \) values of less than 0.05 were considered signifi-
cant.

RESULTS

The physical status of the five groups of patients is
shown in table 1. They were comparable with respect to
age and body weight. Table 2 shows the \( \text{pH} \) and sodium
concentration of the prepared solutions, and hemody-
namic changes at 5 min after the epinephrine injection.
The differences in the sodium concentration among
groups LE were significant (\( P < 0.01 \)). Hemodynamic
changes produced by the injection of epinephrine were
significant (\( P < 0.01 \)) at 5 min after the injection in
group LE 4.9. None of the patients in this study devel-
oped circulatory complications, such as dysrhythmias or
hypertensive episodes, due to the use of epinephrine.

The time courses of the plasma epinephrine levels of
the five groups of patients are shown in figure 1. The
control value of plasma epinephrine was less than 0.01
ng/ml in all cases. One minute after the injection of
epinephrine, the plasma epinephrine level increased sig-
ificantly (\( P < 0.005 \)) in all groups. Compared with the

<p>| TABLE 1. Physical Status of the Studied Patients (Mean ± SEM) |
|---------------------|---------------------|----------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Age (Y)</th>
<th>Body Weight (kg)</th>
<th>Male/Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE 4.9</td>
<td>8</td>
<td>54 ± 2</td>
<td>61 ± 2</td>
<td>7/3</td>
</tr>
<tr>
<td>LE 6.4</td>
<td>8</td>
<td>51 ± 5</td>
<td>55 ± 2</td>
<td>4/6</td>
</tr>
<tr>
<td>LE 7.6</td>
<td>8</td>
<td>54 ± 4</td>
<td>57 ± 2</td>
<td>2/6</td>
</tr>
<tr>
<td>E 6.1</td>
<td>8</td>
<td>54 ± 4</td>
<td>53 ± 2</td>
<td>5/5</td>
</tr>
<tr>
<td>E 7.6</td>
<td>8</td>
<td>58 ± 6</td>
<td>57 ± 4</td>
<td>5/5</td>
</tr>
</tbody>
</table>

LE = lidocaine—epinephrine; E = epinephrine.

<p>| TABLE 2. The pH and Sodium Concentration of the Prepared Solutions, and Hemodynamic Changes at 5 Min After the Epinephrine Injection (Mean ± SEM) |
|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>( \text{pH} )</th>
<th>Sodium Concentration (mEq/l)</th>
<th>Percent Changes</th>
<th>Heart Rate</th>
<th>Systolic Arterial Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE 4.9</td>
<td>4.90 ± 0.00</td>
<td>138 ± 0*</td>
<td>+15 ± 5†</td>
<td>+23 ± 7†</td>
<td></td>
</tr>
<tr>
<td>LE 6.4</td>
<td>6.41 ± 0.01</td>
<td>128 ± 0*</td>
<td>0 ± 2</td>
<td>+7 ± 2</td>
<td></td>
</tr>
<tr>
<td>LE 7.6</td>
<td>7.58 ± 0.03</td>
<td>150 ± 0*</td>
<td>+4 ± 2</td>
<td>-3 ± 3</td>
<td></td>
</tr>
<tr>
<td>E 6.1</td>
<td>6.11 ± 0.00</td>
<td>150 ± 0</td>
<td>+1 ± 5</td>
<td>-2 ± 3</td>
<td></td>
</tr>
<tr>
<td>E 7.6</td>
<td>7.38 ± 0.06</td>
<td>149 ± 0</td>
<td>-2 ± 2</td>
<td>-5 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

LE = lidocaine—epinephrine; E = epinephrine.

\( P < 0.01 \). *among groups, †as compared with the values prior to the injection.
values at 1 min, a significant ($P < 0.025$) increase in the plasma epinephrine concentration occurred in groups LE 4.9, LE 6.4, and LE 7.6 5 min after the injection, whereas the changes in the plasma epinephrine levels in groups E 6.1 and E 7.6 were insignificant. In 28 of 40 cases, the plasma concentration of epinephrine peaked 5 min after the injection. In seven of the 40 cases, two in each of groups LE 4.9, E 6.1, and E 7.6, and one in group LE 7.6, the concentration of epinephrine peaked at 1 min. In the five remaining cases, one in each of groups LE 6.4 and LE 7.6, and three in group E 7.6, the concentration of epinephrine peaked at 10 min. The differences in the plasma level of epinephrine among all the groups were significant ($P < 0.001$) throughout the study.

The plasma epinephrine level at 5 min after injection was plotted against the $pH$ of the solution, as shown in figure 2. Each of the three regression equations demonstrates a significant correlation between the plasma epinephrine level and the $pH$ of the injected solution. The regression equation obtained from the values of groups LE 6.4 and LE 7.5 was significantly ($P < 0.005$) different from the equation of groups E 6.2 and E 7.5. There was an insignificant ($0.7 < P < 0.8$) difference between the equation obtained from the values of groups LE 6.4 and LE 7.6, and the equation obtained from the values of groups LE 4.9, LE 6.4, and LE 7.6.

**DISCUSSION**

Epinephrine has vasoconstricting action which retards its own absorption when injected locally. We demonstrated that the rate of absorption of injected epinephrine is inversely correlated with the $pH$ of the prepared solution of epinephrine. This is due to changes in the tissue blood flow arising from the $pH$. A decrease in $pH$ causes the tissue blood flow to increase, thereby accelerating absorption of injected substances. Besides the vasodilating action of halothane, arterial blood pressure, the sodium concentration of the solution, and the effect of $pH$ on the action of epinephrine might have an effect on the transfer of locally injected epinephrine to the blood in this study. The circulatory status of the patients was stable under relatively deep halothane anesthesia. The effect of anesthesia on the absorption of epinephrine should be the same in all groups when the injection of epinephrine was performed. The injected epinephrine, however, changed the hemodynamics in group LE 4.9. This might have increased the blood flow to the scalp, thereby causing further acceleration of epinephrine absorption.

The results of this study confirmed that lidocaine accelerates the absorption of epinephrine, and lidocaine's ability to increase epinephrine absorption was enhanced

**FIG. 1.** The time courses of the plasma epinephrine levels of the five groups of patients. The levels at 1 min are significantly ($P < 0.005$) higher than that of the control in all groups. The levels at 5 min are significantly ($P < 0.025$) higher than those at 1 min in groups LE 4.9, LE 6.4, and LE 7.6. The differences in the level among all the groups were significant ($P < 0.001$) throughout the study.

**FIG. 2.** The plasma epinephrine level at 5 min after injection was plotted against the $pH$ of the solution. Each of three regression equations represents a significant relation. There is a significant ($P < 0.005$) difference between the equations of $Y = -0.21X + 1.9$ and $Y = -0.03X + 0.30$. The difference between the equations of $Y = -0.21X + 1.9$ and $Y = -0.25X + 2.2$ is insignificant ($0.7 < P < 0.8$).
by a reduction in the pH of the solution. The pKa of lidocaine is 7.91 at 25° C and 7.57 at 38° C.4 The order of the percentage of the ionized forms of lidocaine existing in the solutions should be LE 4.9 > LE 6.2 > LE 7.5, and this should be the reverse in order of the anesthetic potency and the speed of onset of the anesthetic action of the solution.5,6 The mechanism of action of lidocaine in accelerating epinephrine absorption is not known. Possible mechanisms are local tissue irritation6,7 and vasodilating action.6,7 Enhancement of the action of lidocaine in tissue irritation is reported to be correlated with a reduction in the pH of the solution, which increases the percentage of the ionized forms of lidocaine.8 Vasodilation by lidocaine is expected at the concentration used in this study, but further studies will be needed to elucidate the effect of pH on vasodilating activity of lidocaine. Provided that the mechanisms are the local tissue irritation and the vasodilating action, which would increase the blood flow and the permeability of the blood vessels, the effect of molarity of the solution on the rate of absorption of an injected substance may be diminished.9 The regression equations obtained from the values of groups LE may indicate that the effect of sodium concentration on the rate of absorption of epinephrine is less obvious than that of pH in the presence of lidocaine.

Commercial preparations of lidocaine with epinephrine have a pH lower than 5. Lidocaine and epinephrine in such a low pH solution not only promote the increase in the blood level of epinephrine, but also reduce the anesthetic action.5,10 Epinephrine should be added to plain lidocaine prior to use to avoid increasing the acidity of local anesthetic solutions containing epinephrine. Sodium bicarbonate can also be used to increase the pH of the anesthetic solution.5,8

REFERENCES


Anesthesia-related Complications in Children with Duchenne Muscular Dystrophy

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Duchenne Muscular Dystrophy (DMD) is the most common and severe form of childhood myopathy. Pa-

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patients suffering from this disease often require anesthesia to obtain a muscle biopsy or to correct orthopedic deformities. Occasional case reports have described perioperative complications in these patients.14 This study was designed to determine the incidence and type of anesthesia-related complications occurring in these children and identify risk factors.

METHODS

The medical records were reviewed retrospectively of all patients with DMD who were known to have had surgery with general anesthesia at our institution during a 5 yr period ending January, 1985. The diagnosis of DMD was based upon: 1) a characteristic history and