EFFECT OF ACUTE HYPOVOLAEMIA ON LIGNOCAINE ABSORPTION AND CARDIOVASCULAR RESPONSE FOLLOWING EPIDURAL BLOCK IN DOGS

K-I. MORIKAWA, J. J. BONICA, G. T. TUCKER AND T. M. MURPHY

SUMMARY

The effect of acute hypovolaemia (15% blood loss) on the absorption of lignocaine from the epidural space and on the cardiovascular response to epidural analgesia was studied in 10 dogs. After bleeding the net rate of systemic drug absorption was significantly reduced compared with the rate under normovolaemic conditions. Maximum blood concentrations of the drug were lower by about 30%. This finding emphasizes the importance of blood flow as a determinant of the pharmacokinetics of local anaesthetics. After bleeding, epidural injection of lignocaine caused considerable cardiovascular depression. Significantly greater decreases in arterial pressure and cardiac output occurred compared with those observed under normovolaemic conditions. These results emphasize the view that epidural anaesthesia should not be used in the presence of moderate hypovolaemia.

In a study of human volunteers, Bonica et al. (1972) observed severe circulatory depression during high (T5) epidural analgesia achieved after the acute removal of 13% of the blood volume. A 2% solution (10 mg/kg) of plain lignocaine hydrochloride (Xylocaine) was used. The degree of cardiovascular depression was nearly twice that seen in hypovolaemic subjects with high subarachnoid block produced with plain solution or with epidural block produced with 2% lignocaine with adrenaline 1:200,000. Although impairment of compensatory circulatory mechanisms would account for depression seen after hypovolaemia plus vasomotor block, it was suggested that the increased effect seen after epidural block without the use of adrenaline could be explained by lignocaine-induced myocardial depression resulting from greater blood and heart drug concentrations as a result of the hypovolaemic state. The present study was undertaken to investigate the influence of haemorrhage on the systemic absorption of lignocaine from the epidural space.

METHODS

Ten adult mongrel dogs (13.3 ± 0.5 kg) were anaesthetized with thiopentone 50–100 mg i.v., suxamethonium 10–20 mg and 75% nitrous oxide in oxygen using intermittent positive pressure ventilation with a tidal volume of 10–15 ml/kg. Five percent lactated Ringer’s solution was given intravenously at a rate of 7 ml/kg/hr. Central body temperature was maintained at 38 ± 0.5°C with two heating pads.

Following the induction of anaesthesia, catheters were inserted into the femoral artery and vein, and advanced to the mid-thoracic aorta and to the thoracic portion of the inferior vena cava, respectively. The catheters were connected to Statham strain gauges and the pressures recorded on a Gilson polygraph recorder. The zero reference point for all pressures was the sternal angle of the animals when in the right lateral position. The catheters were connected to Statham strain gauges and the pressures recorded on a Gilson polygraph recorder. The zero reference point for all pressures was the sternal angle of the animals when in the right lateral position. An indwelling epidural catheter was inserted through the L7 interspinous space using the “loss of resistance” technique, advanced 5 cm cephalad, and taped in place.

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A preliminary communication of part of these studies was presented at the 1973 Annual Meeting of the American Society of Anesthesiologists, San Francisco, and published in abstract at that meeting.
heart rate (HR), and electrocardiogram (e.g.); serial determination of cardiac output (CO) by dye-
dilution, arterial pH and blood gases; and calcula-
tion of total peripheral resistance (TPR) and stroke
volume (SV). In addition, the blood volume was
measured using RIHSA(I\textsuperscript{125}) and a Volemetron
(Ames Co., Indiana).

After control measurements were completed, 2%
lignocaine hydrochloride 7 mg/kg was injected over
a period of 1 min through the epidural catheter. For
120 min after this first epidural injection the cardio-
vascular and respiratory variables were measured
every 5–15 min. In addition, serial arterial whole
blood concentrations of lignocaine were determined
by gas chromatography (Tucker, 1970). At 120 min,
a second series of control measurements was made
(second control, C\textsubscript{2}). This was followed by removal
of 15% of the total blood volume over 5 min in 6
of the dogs (Group A), while in the other 4 dogs no
blood was withdrawn (Group B).

After observation of the same variables for 30
min, the third set of control measurements (C\textsubscript{3})
was made. This was followed by the second epidural
injection of the same dose of lignocaine and further
measurements for another 45 min.

The significance of any changes in the physio-
logical variables was determined: (a) within animals,
by the Student paired t-test using each animal as its
own control (each measurement was compared with
the preceding control value); and (b) between Group
A and Group B animals, by the unpaired t-test.
Non-parametric tests equivalent to (a) and (b) were
also applied using the Wilcoxon signed rank test and
the Mann-Whitney U-test, respectively.

To show the contribution of the second epidural
injection to lignocaine blood concentrations, estima-
ted residual blood drug concentrations from the first
injection were subtracted from the observed values.
Residual concentrations were determined by extrap-
olation of the exponentially decaying concentration-
time curve from the first injection.

RESULTS

Blood lignocaine concentrations.

Changes in blood concentrations of lignocaine in
Group A and Group B dogs are shown in figure 1.
After the first epidural injection the maximum blood
lignocaine concentrations were 2.79 ± 0.29 (SEM)
μg/ml at 13.3 ± 1.7 (SEM) min in Group A and
2.58 ± 0.33 μg/ml at 13.8 ± 2.4 min in Group B.
Following the second epidural injection, the maxi-
mum blood drug concentrations were 2.25 ± 0.28
μg/ml and occurred at 18.3 ± 2.8 min in the hypo-
volaeamic (Group A) dogs, while in the normo-
volaeamic (Group B) dogs, maximum concentrations
were 3.59 ± 0.53 μg/ml at 10.0 ± 0 min. Correcting
for estimated residual blood concentrations from the
first injection, bleeding reduced the mean maximum
lignocaine concentration to 68% of the control
maximum concentration developed after the first
injection in the same animals (Group A), and to
59% of the mean peak after the second injection in
the normovolaemic (Group B) animals. Whereas in
Group A corrected lignocaine levels were always
less on the second injection compared with the first,
the opposite was observed in Group B. This differ-
ence was statistically significant (P<0.001) (Mann-
Whitney U-test). Maximum blood drug concentra-
tions also occurred significantly later in the hypo-
volaeamic state compared with those observed during
normovolaemia (P<0.05).

Cardiovascular function.

The mean total blood volume of the dogs was
76 ± 12 (SD) ml/kg measured after placement of
catheters.

The mean circulatory and blood gas values are
listed in table I. In figure 2 values of the variables
are shown as mean per cent changes from control
values (C\textsubscript{0}).

Following the first injection in both groups, MAP
decreased by 20–30%; CO decreased by about
20%; and c.v.p. increased. TPR decreased by about
10% in Group A and varied around baseline values
in Group B. Most of these changes were not statisti-
### Table I. Circulatory and blood-gas response to epidural analgesia with lignocaine before and after haemorrhage. Mean ± SE. The values in brackets relate to the non-bled animals.

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>CO (l/min)</th>
<th>HR (beats/min)</th>
<th>SV (ml)</th>
<th>CVP (cm H2O)</th>
<th>TPR (dynes/sec/cm2)</th>
<th>PaO2 (mm Hg)</th>
<th>PaCO2 (mm Hg)</th>
<th>pH</th>
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</thead>
<tbody>
<tr>
<td>Control (1)</td>
<td>143±9 (147±8)</td>
<td>1.87±0.27 (2.20±0.58)</td>
<td>148±15 (155±13)</td>
<td>13.4±1.4 (14.2±5.5)</td>
<td>3.5±1.5 (2.0±0.6)</td>
<td>6661±1023 (6136±1063)</td>
<td>88.1±2.7 (85.0±1.5)</td>
<td>32.2±3.3 (33.0±2.4)</td>
<td>7.39±0.03</td>
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<td>After 1st injection</td>
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<tr>
<td>15 min</td>
<td>113±14 (124±19)</td>
<td>1.42±0.20 (1.74±0.66)</td>
<td>149±16 (158±19)</td>
<td>10.3±0.3 (12.4±6.1)</td>
<td>5.3±1.7 (2.7±0.7)</td>
<td>6760±1171 (6142±1070)</td>
<td>97.5±9.6 (97.9±18.0)</td>
<td>30.8±3.2 (34.9±3.2)</td>
<td>7.37±0.03</td>
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<td>30 min</td>
<td>109±15 (120±21)</td>
<td>1.64±0.17 (1.76±0.47)</td>
<td>149±16 (158±19)</td>
<td>9.8±0.7 (11.7±4.5)</td>
<td>5.8±1.6 (4.0±0)</td>
<td>5972±983 (6901±1108)</td>
<td>94.3±9.1 (104.2±13.4)</td>
<td>32.1±3.5 (37.3±4.0)</td>
<td>7.36±0.03</td>
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<tr>
<td>45 min</td>
<td>102±14 (118±24)</td>
<td>1.40±0.14 (1.69±0.48)</td>
<td>133±17 (135±16)</td>
<td>11.3±2.0 (12.8±3.5)</td>
<td>4.8±1.7 (4.7±0.3)</td>
<td>6112±1052 (5895±1033)</td>
<td>93.6±10.3 (103.7±13.8)</td>
<td>33.7±4.2 (40.0±6.0)</td>
<td>7.35±0.04</td>
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<tr>
<td>60 min</td>
<td>108±14 (113±24)</td>
<td>1.48±0.16 (1.65±0.49)</td>
<td>129±17 (128±16)</td>
<td>11.6±1.7 (12.0±3.5)</td>
<td>5.1±1.8 (3.3±1.3)</td>
<td>6080±1023 (5822±1069)</td>
<td>99.1±11.4 (112.5±26.3)</td>
<td>36.2±5.8 (39.7±3.7)</td>
<td>7.31±0.08</td>
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<tr>
<td>90 min</td>
<td>104±11 (124±19)</td>
<td>1.50±0.19 (1.85±0.67)</td>
<td>132±17 (137±18)</td>
<td>10.9±1.1 (12.5±4.8)</td>
<td>4.5±2.6 (3.5±1.9)</td>
<td>5917±1076 (6780±2093)</td>
<td>94.2±14.7 (114.0±24.7)</td>
<td>35.0±4.7 (35.3±6.0)</td>
<td>7.31±0.04</td>
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<tr>
<td>120 min</td>
<td>118±10 (128±22)</td>
<td>1.51±0.18 (2.01±0.80)</td>
<td>132±17 (137±22)</td>
<td>11.3±1.6 (13.7±5.3)</td>
<td>4.0±1.6 (4.0±2.0)</td>
<td>6685±1147 (6638±1899)</td>
<td>99.0±13.8 (125.0±3.2)</td>
<td>32.3±5.5 (37.1±8.5)</td>
<td>7.38±0.05</td>
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<td>Control (2)</td>
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<tr>
<td>15 min</td>
<td>107±7 (136±17)</td>
<td>1.40±0.19 (2.06±0.67)</td>
<td>138±16 (140±20)</td>
<td>9.8±1.1 (13.5±4.2)</td>
<td>2.8±1.2 (3.7±1.7)</td>
<td>6707±1225 (6567±1860)</td>
<td>103.1±15.5 (114.1±18.7)</td>
<td>31.1±6.2 (41.0±6.6)</td>
<td>7.38±0.06</td>
</tr>
<tr>
<td>30 min</td>
<td>111±8 (139±17)</td>
<td>1.38±0.11 (2.23±0.77)</td>
<td>132±19 (150±20)</td>
<td>11.0±1.2 (12.8±4.5)</td>
<td>2.5±1.5 (3.3±1.3)</td>
<td>6666±888 (6364±1880)</td>
<td>103.0±14.3 (112.9±20.3)</td>
<td>30.0±6.1 (40.2±6.1)</td>
<td>7.38±0.06</td>
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<td>Control (3)</td>
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<td>After 2nd injection</td>
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<tr>
<td>15 min</td>
<td>84±14 (136±21)</td>
<td>0.98±0.12 (1.98±0.55)</td>
<td>135±18 (155±19)</td>
<td>6.7±1.1 (12.1±3.9)</td>
<td>3.5±0.7 (3.7±1.7)</td>
<td>6643±1855 (6240±1492)</td>
<td>101.2±13.9 (117.2±18.7)</td>
<td>34.1±5.9 (36.3±2.6)</td>
<td>7.33±0.06</td>
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<tr>
<td>30 min</td>
<td>79±14 (126±19)</td>
<td>1.00±0.11 (1.86±0.72)</td>
<td>129±20 (150±30)</td>
<td>8.9±1.2 (15.3±6.3)</td>
<td>3.8±1.2 (4.3±1.9)</td>
<td>6118±1085 (6308±2886)</td>
<td>100.6±14.0 (101.0±19.2)</td>
<td>36.1±2.6 (37.8±7.7)</td>
<td>7.30±0.06</td>
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<tr>
<td>45 min</td>
<td>73±18 (120±26)</td>
<td>1.04±0.21 (1.92±0.76)</td>
<td>108±18 (150±30)</td>
<td>10.9±2.0 (16.0±6.9)</td>
<td>3.7±1.8 (4.0±1.5)</td>
<td>5407±1028 (6192±1778)</td>
<td>107.1±18.2 (107.1±18.2)</td>
<td>46.0±3.5 (32.6±0.0)</td>
<td>7.24±0.05</td>
</tr>
</tbody>
</table>
Fig. 2. Circulatory responses of dogs to two epidural injections of 2% lignocaine hydrochloride (Δ% = per cent change). First injection at zero time; second injection at 150 min.

Values at each time represent mean per cent change from control (C₀ at zero time).

* Significant difference from preceding control value (C₁, C₂, C₃); P<0.05 (paired t-test).
† Significant difference from preceding control value, P<0.05 (Wilcoxon signed rank test).
◊ Significant difference between value for control group and hypovolaemic group (unpaired t-test).

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DISCUSSION

Moderate haemorrhage produced a considerable reduction in the blood concentrations of lignocaine measured after subsequent epidural block in the dog. That this effect was a reflection of reduced systemic absorption of the drug, rather than a result of altered distribution and/or elimination, is substantiated by results of additional experiments involving intravenous infusion of the agent (Benowitz et al., 1973; Tucker et al., unpublished data). Under these conditions, haemorrhage produced the expected elevation of blood lignocaine concentrations. It might be anticipated that reduced drug absorption during hypovolaemia would result in prolonged duration of anaesthesia, because more drug is left in contact with neural structures. Our data lend support to the contention of Quimby (1965) that this situation explains his observation that patients undergoing thoracotomy with regional block and having more than 500 ml of blood loss during surgery had prolonged anaesthesia compared with those whose blood loss was less than 500 ml.

The slower net absorption of lignocaine during epidural analgesia in hypovolaemic animals is pre-
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sumably related to reduced perfusion of the epidural spaces as a result of acute blood loss. This decreased perfusion may be a consequence of local vasoconstriction or of a decrease in MAP, or both. It is well known that the increased sympathetic tone provoked by haemorrhage produces selective vasoconstriction (Chien, 1967). However, little is known about the reactivity of the epidural arterioles, precapillary sphincters and venules to increased sympathetic impulses. If one assumes that because the resistance vessels are branches of spinal arteries and the veins drain into the azygos system, they should be as reactive to sympathetic influences as vessels supplying the somatic structures and splanchnic region, respectively. On the other hand, the vasomotor blockade which accompanies epidural anaesthesia should completely eliminate vasoconstriction of these vessels. Since the nerve supply to the epidural vessels is segmental and each segment receives vasomotor fibres from the recurrent nerve, analgesia to T5 should be accompanied by vasomotor blockade to the same segment. In view of these considerations, one assumes that the observed decrease in drug absorption rate was related to a reduction of MAP.

The reductions of CO and MAP observed in our anaesthetised animals in response to epidural analgesia in the presence of acute hypovolaemia paralleled those noted in conscious volunteers (Bonica et al., 1972). However, several differences between the two sets of experiments were observed also. Thus, MAP and CO decreased more in the dogs than in the humans before bleeding and the c.v.p. was increased in the dogs but reduced in humans. In the human experiments 5 of the 7 subjects collapsed after bleeding plus epidural block with plain lignocaine. The marked bradycardia, sometimes amounting to vagal arrest, seen in these subjects (and not in any of the dogs) suggested the superimposition of a vaso-vagal fainting attack. However, this phenomenon did not occur in volunteers with high subarachnoid block plus hypovolaemia (Kennedy et al., 1968) or in volunteers receiving epidural lignocaine with adrenaline plus hypovolaemia (Bonica et al., 1972). The absence of cardiovascular collapse in the latter group was attributed to the systemic absorption of the adrenaline preventing bradycardia.

The results of the present study indicate that the cause of additional cardiovascular depression produced by epidural analgesia with plain lignocaine plus hypovolaemia is not related to excessive blood concentrations of lignocaine, as was suggested initially. However, the data do not exclude the possibility of elevated lignocaine concentrations at receptors in myocardial tissue during hypovolaemia. This might result from changes in blood binding or binding at non-specific myocardial sites or from a reduction in cardiac perfusion resulting from hypovolaemia plus epidural block. The latter effect would tend to reduce clearance from the heart of drug accumulated during the first injection given in the normovolaemic state. A further possibility is an excessive heart drug concentration following the second injection, resulting from diversion of CO to the myocardium as a result of hypovolaemia. However, such diversion may be compromised when the splanchnic response to haemorrhage is reduced by sympathetic blockade. Furthermore, the reduced arterial blood drug concentrations observed after epidural block plus hypovolaemia, together with a presumed decrease in coronary blood flow, would tend to result in reduced drug concentrations in the myocardium. Consequently, changes in drug distribution may not be a factor. Alternatively, the myocardium may be more sensitive to the adverse effects of lignocaine during hypovolaemia plus vasomotor blockade.

Further studies are indicated to delineate the roles of altered drug disposition and altered myocardial and central sensitivity in the action of local anaesthetics in various patho-physiological conditions.

ACKNOWLEDGEMENTS

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