The Effects of Epinephrine on Mepivacaine Absorption from the Spinal Epidural Space

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The effect of epinephrine on the venous absorption of a local anesthetic (mepivacaine) from the epidural space of the dog was investigated by comparing the concentrations of mepivacaine in the ayzygos vein after epidural injection of 100 mg of 2 per cent mepivacaine with and without epinephrine 1:200,000. Blood flow in the ayzygos vein averaged 100 ml per minute. Concentrations of mepivacaine in the ayzygos vein reached a maximum of 10 μg/ml. At least 9 per cent of the dose of local anesthetic was removed in 30 min via the ayzygos vein; this was reduced to 3 per cent when epinephrine 1:200,000 was added to the anesthetic solution. It is concluded that the addition of small amounts of epinephrine to epidural local anesthetics is valuable to reduce venous absorption and favor neural blockade. (Key words: Epidural; Epinephrine; Local anesthetic.)

The efficiency of conduction blockade by local anesthetics depends on the amount of drug reaching the axonal membranes. In any local anesthetic technique there is a concentration gradient of the injected compound from the site of injection to the target axons. At the same time there are similar gradients into surrounding tissues, and much of the dose is wasted, especially by uptake into neighboring blood vessels.

Vascular absorption is a notable problem in epidural analgesia because the surface area of the epidural venous plexus is large. An increase in the dose injected ensures an increase in the amount of drug reaching neuronal tissue, but the dangers of excessive vascular absorption and systemic toxic effects limit the total dose. Vascular losses can be reduced, and blockade enhanced, by local vasoconstrictor agents which slow systemic uptake by reducing the surface area for vascular absorption.

The dynamics of vascular absorption from the epidural space cannot be studied directly in man because of the technical difficulty of cannulating the internal vertebral plexus, so measurements of concentrations of local anesthetics in blood have had to be confined to peripheral venous and arterial samples. This paper describes a radiometric method for measuring the vascular clearance of mepivacaine from the epidural space of the dog.

The principal venous drainage from the spinal canal passes from the internal vertebral plexus into the ayzygos system and thence into the superior vena cava.† Thus, simultaneous measurements of local anesthetic concentrations in ayzygos and peripheral venous blood should give an indication of the way these drugs are removed from the epidural space. Measurements of ayzygos venous flow would then indicate venous clearance.

Methods

Experiments were performed on 13 large dogs. In each of eight dogs a polyethylene catheter 1.7 mm in outside diameter was introduced into the epidural space through a burr hole in the sacrum and the tip was advanced until it lay at the thoracolumbar junction. The superior intercostal vein was cannulated with a no. 8 French catheter through a right thoracotomy incision and the tip arranged to lie pointing caudally just within the ayzygos vein. The thorax was closed around the catheter.

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Epidural Mepivacaine Absorption

Two per cent $^{14}$C-labelled mepivacaine (Carbocaine, Boors) of either 2 or 20 $\mu$Ci/ml specific activity, 100 mg, was injected via the epidural catheter. Four of the eight dogs also received epinephrine, 1:200,000, added to the solution. One-milliliter samples of both azygos and limb peripheral venous blood were collected simultaneously every 3 min for the first 15 min after injection, and thereafter at 8-min intervals for the next 45 min.

Samples were digested with 15 per cent tri-chloroacetic acid, neutralized with excess 10 N sodium hydroxide, and extracted with ethylene dichloride. Then 2-ml samples of the ethylene dichloride phase were evaporated to dryness in a scintillation counting vial and phosphor (2,5-diphenyloxazole and 4-methyl, 5-phenyloxazol benzene), 15 ml, was added. Radioactivity was measured in a Packard Tri-Carb scintillation counter and the counts per minute converted to mass of drug per milliliter of blood.

Estimations of blood flow in the azygos veins of five dogs were made using a simple technique of collection and reinfusion. The dogs were prepared as described above, and the small azygos sampling catheter was replaced by a large no. 22 French catheter tied directly into the azygos vein; the distal end of this catheter was clamped at the same height as the azygos vein. To inhibit clotting, heparin was given intravenously in a dose of 3 mg/kg. Azygos flow was measured directly by releasing the rubber catheter and allowing the blood to run into a graduated cylinder for 1-min periods; the blood was then returned to the circulation via a peripheral vein. Resting azygos flow was recorded several times until a stable value was reached. Epidural blockade was then induced with 100 mg of unlabelled lidocaine plus 1:200,000 epinephrine, and flow was measured at intervals during the next 30 min. Epinephrine, 1:200,000 in 5 ml of physiologic saline solution, was injected into one dog, followed by lidocaine, 100 mg, 20 min later: azygos flow was measured before and after both injections.

**Results**

The concentrations of mepivacaine in azygos and peripheral venous blood after epidural injection of 100 mg of mepivacaine are plotted...
against time in figures 1 and 2. It can be seen 
that the presence of epinephrine, 1:200,000, 
in the epidural solution exerts considerable 
influence on azygos uptake; peak concentrations 
of mepivacaine are reduced by two thirds and 
asorption is delayed, as shown by a shift to 
the right of the peak in the curve with epinephrine added. Azygos venous concen-
trations were about three to four times higher 
than peripheral venous concentrations.

Recirculated peripheral blood contributes its 
portion to the total azygos concentration, so 
the net azygos uptake is shown more closely 
by subtracting peripheral venous concentrations from total azygos values (fig. 3).

Figure 4 shows the effect of epidural blockade 
on azygos flow and mean systemic blood pressure. Table 1, extracted from figure 4, 
shows that epidural blockade increased azygos flow by 35 per cent. Epinephrine, 1:200,000 
in physiologic saline solution, in the epidural space had no effect on azygos flow, nor did it 
modify the hemodynamic effects of a subsequent epidural injection of 100 mg lidocaine.

Approximate values for total azygos clearance of an epidural injection can be calculated by relating the values for uptake (fig. 3) to those for azygos flow (fig. 4). In these 
experiments approximately 9 per cent of the 
epidural dose passed into the azygos system within the first 30 min after injection, whereas
when epinephrine, 1:200,000, was added, only 3 per cent was cleared in the same time.

Discussion

The azygos vein collects most of the blood draining from the thoracic portion of the internal vertebral venous plexus; therefore, the amount of local anesthetic appearing in the vein is only an approximation of the total uptake by the epidural plexus. Nevertheless, the azygos vein is easy to cannulate and so provides the most practical indication possible of the pattern of vascular absorption from the spinal canal in the experimental animal.

There are at least two possible explanations for the increase in azygos blood flow observed after epidural blockade. First, the local anesthetic agent acting within the spinal canal may cause a direct depression of smooth muscle in the blood vessel walls, and hence increase arterial and venous diameters. Second, blockade of sympathetic impulses from the spinal cord may remove vasomotor tone in the extradural vessels, and so increase flow, provided systemic blood pressure remains reasonably constant.

High concentrations of local anesthetic cause vasodilation by a direct depressant effect on vascular smooth muscle; the precise depressant concentration, in vitro, for mepivacaine has not been established, but it probably lies in a range similar to that of lidocaine, i.e., 5–10 μg/ml.\textsuperscript{14,15} Table 2 shows that while vasodepressant concentrations may not be reached throughout the body as a whole after epidural injection, the azygos concentrations are 2½–3½ times higher than those in the peripheral blood, so a considerable degree of localized vascular depression may occur within the azygos system without comparable depression elsewhere.

Addition of epinephrine to the anesthetic solution markedly affects the quantity of local anesthetic removed by the azygos route. In these experiments epinephrine, 1:200,000, delayed the uptake of mepivacaine in the azygos vein and reduced the peak concentration by two thirds. The total amount removed by the azygos vein was also reduced by two thirds.

Although only 9 per cent of the injected dose was recovered from the azygos vein in an hour, this small proportion is not surprising in view of the fact that 2 per cent mepivacaine has an oil:water solubility ratio of 7:1 at pH 7.4.\textsuperscript{1} Therefore, approximately 86 per cent will be partitioned in the epidural fat and released slowly as the concentration in the local water phase declines. Under these circumstances a reduction in the azygos recovery rate from 9 to 3 per cent in an hour is more significant, and would appear to warrant the routine addition of epinephrine, 1:200,000, to epidural local anesthetic solutions in clinical situations.

\textsuperscript{1} Personal communication from Winthrop Laboratories, Aurora, Ontario, Canada.

Table 1. Changes in Blood Flow in the Azygos Vein following Epidural Injection of 100 mg Lidocaine with 1:200,000 Epinephrine in Five Dogs

<table>
<thead>
<tr>
<th></th>
<th>Resting Flow (ml/min)</th>
<th>Maximum Flow after Epidural Injection (ml/min)</th>
<th>Per Cent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog 1</td>
<td>63</td>
<td>94</td>
<td>+50</td>
</tr>
<tr>
<td>Dog 2</td>
<td>128</td>
<td>158</td>
<td>+19</td>
</tr>
<tr>
<td>Dog 3</td>
<td>120</td>
<td>112</td>
<td>−6</td>
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<tr>
<td>Dog 4</td>
<td>41</td>
<td>85</td>
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<td>Dog 5</td>
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<td>126</td>
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<tr>
<td>Mean</td>
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<td></td>
<td>+35</td>
</tr>
</tbody>
</table>

* Maximum concentrations with SD in azygos and peripheral venous blood after epidural injection of 2 per cent mepivacaine, with and without 1:200,000 epinephrine.
Supplies of "C-labelled mepivacaine were kindly supplied by AB Bofors, Nobeleut, Sweden.

References


5. Scott B: Plasma levels of lignocaine (Xylocaine) and prilocaine (Citanest) following epidural and interscalene nerve block. Acta Anaesth Scand suppl XVI:111–114, 1965


