Pial Vascular Reaction to Intravenous Dihydralazine in the Cat

BARBRO B. JOHANSSON, M.D., LUDWIG M. AUER, M.D., AND ULRIKE G. TRUMMER

SUMMARY The diameters of pial vessels in the cat were measured through a closed cranial window after i.v. injection of dihydralazine (250 μg or 1 mg·kg⁻¹). The intracranial pressure was recorded from a needle in the cisterna magna. In 7 cats given 1 mg·kg⁻¹ dihydralazine, arterial vessels with a resting diameter of 72 ± 24 μm (SD) dilated by 58 ± 21% (p < 0.01), with no significant change seen in the veins. The intracranial pressure increased by 95 ± 30%. The maximum increase in intracranial pressure and arterial diameter was observed before the blood pressure had reached its lowest level. The dilatation far exceeded the autoregulatory dilatation observed at corresponding pressure reductions induced by bleeding. It is concluded that dihydralazine dilates pial arterial vessels.

HYDRALAZINE AND DIHYDRALAZINE have been shown to dilate precapillary resistance vessels but are considered to have little or no effect on systemic veins. Based on a study of cerebral blood flow (CBF) and intracranial pressure (ICP) in some patients with neurological diseases, Overgaard and Skinhøj concluded that, “hydralazine is a cerebral vasodilator acting first upon cerebral capacitance vessels but later upon the resistance vessels as well.” However, the evidence for a dilatatory effect on cerebral veins was indirect and in our opinion not conclusive — the interpretation of the results being particularly difficult since cerebral autoregulation was disturbed in most of the CBF studies. A better knowledge of the action of dihydralazine and hydralazine on cerebral vessels seems important, since drugs of this type are commonly used to decrease the blood pressure acutely in neurological and neurosurgical patients. In the present study the effect of dihydralazine on the diameters of pial arteries and veins was measured in the cat through a closed cranial window. ICP was continuously recorded from a needle in the cisterna magna.

Material and Methods

Thirteen experiments were performed in 11 cats with a body weight of 2–3.4 kg. The cats were anesthetized with 40 mg · kg⁻¹ sodium pentobarbital, intubated endotracheally and respired with a 3:1 mixture of N₂O:O₂. Both femoral arteries and one femoral vein were cannulated with PVC catheters for continuous monitoring of mean arterial pressure (MAP), removal of blood for blood gas analyses and for administration of drugs. MAP was measured with a Statham P23dB transducer connected with a Hellige electromanometer and recorded with a Rikadenki 2-channel writer. EKG and pulse frequency were continuously monitored with a Philips unit. Paco₂ and Pao₂ were frequently measured in an AVL gas check and maintained on normal and stable levels (Paco₂ 25–35 mm Hg). Body temperature was controlled by a Philips rectal thermosensor unit and maintained during the experiments between 37 and 38°C by aid of a heating pad. The head was fixed in a stereotaxic holder and a parasagittal parietal window inserted. A modification of the technique described by Forbes was used. Pial vessels were observed through the closed cranial window with the aid of a Leitz intravital microscope. Diameter variations were measured with a multichannel videoangiometer, or by aid of an image splitting eyepiece every 15 seconds within the first minute, every 30 seconds during the following 4 minutes and, later, every minute until the end of the experiment.

Dihydralazine, 250 μg · kg⁻¹, was given intravenously in 6 experiments to 4 cats, and venular diameters were then recorded for 15–20 minutes. Seven other cats were given 1 mg · kg⁻¹ dihydralazine. In these experiments both the diameters of veins and arteries were recorded. ICP was monitored in 5 of the cats by inserting a needle into the cisterna magna and connecting it to a Statham P23dB transducer and a second Hellige unit. Statistical evaluation was performed with the Wilcoxon signed rank test.

Results

MAP, ICP and vascular diameters are given in the table. Figure 1 shows the mean value curve of MAP and venous diameter reactions after injection of 250 μg · kg⁻¹. All arterial vessels studied, i.e. 8 vessels with resting diameter 49–102 μm, reacted with a pronounced dilatation (p < 0.01) after injection of 1 mg · kg⁻¹ dihydralazine. The diameters of the veins were essentially unchanged, whereas ICP increased by 95% within 7 minutes (table). Examples of individual experiments are presented in figures 2 and 3.

Discussion

The increase in ICP induced by dihydralazine agrees with data presented by Overgaard and Skin-
TABLE Mean Arterial Blood Pressure (MAP), Intracranial Pressure (ICP) and Diameter of Arterial Vessels ($\phi$ A) and of Venous Vessels ($\phi$ V) Before and After i.v. Injection of Dihydralazine. Time Represents Interval Between Injection of Drug and Maximum Change Obtained (in minutes). Mean Values ± SD

<table>
<thead>
<tr>
<th></th>
<th>Dihydralazine 250 $\mu g \cdot kg^{-1}$</th>
<th>1 mg $\cdot kg^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi$ A (µm)</td>
<td>Resting</td>
<td>71.6 ± 23.7</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>111.5 ± 33.4</td>
</tr>
<tr>
<td></td>
<td>$\Delta %$</td>
<td>58.0 ± 21.1</td>
</tr>
<tr>
<td></td>
<td>Time (min)</td>
<td>12.6 ± 2.7</td>
</tr>
<tr>
<td>$\phi$ V (µm)</td>
<td>Resting</td>
<td>82.6 ± 15.2</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>94.5 ± 23.9</td>
</tr>
<tr>
<td></td>
<td>$\Delta %$</td>
<td>3.0 ± 10.9</td>
</tr>
<tr>
<td></td>
<td>Time (min)</td>
<td>3.5 ± 2.7</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>Resting</td>
<td>144.5 ± 19.7</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>128.6 ± 21.6</td>
</tr>
<tr>
<td></td>
<td>$\Delta %$</td>
<td>-12.3 ± 6.8</td>
</tr>
<tr>
<td></td>
<td>Time (min)</td>
<td>6.6 ± 2.9</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>Resting</td>
<td>8.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>16.6 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>$\Delta %$</td>
<td>95.2 ± 29.7</td>
</tr>
<tr>
<td></td>
<td>Time (min)</td>
<td>7.0 ± 3.9</td>
</tr>
</tbody>
</table>

However, our results do not support the hypothesis that drugs of this type dilate cerebral veins. Dihydralazine markedly dilated pial arteries as it does in other vascular beds. The maximum change in arterial diameter was reached somewhat later than the maximum increase in ICP but earlier than the lowest blood pressure levels.

The dilatation obtained after dihydralazine administration far exceeds that seen as a result of autoregulation with a corresponding reduction in blood pressure. In a recent study, briefly reported by Johansson et al., 10 arteries from 8 cats were measured with the same technique as in the present study during hypotension induced by withdrawal of blood. Lowering of MAP from 121 ± 24 (SD) mm Hg to 68 ± 3.5 mm Hg, i.e. a 44% decrease in pressure, reduced the diameter of arterial vessels with an initial diameter 46-184 µm by 10% only. This is in agreement with the classical study by Fog 4 whose data showed that arterioles with a resting diameter of 32-57 µm increased 11% (range 9-22%) when MAP was lowered from 80-110 to 70-85 mm Hg by bleeding (mean decrease 18%). [Data taken from Table V in Fog.] Animals with blood pressure outside the range of autoregulation, i.e. MAP after bleeding < 40 mm Hg or initial MAP > 190 mm Hg were excluded.] Kontos et al., also using a cranial window technique, reported that only arteries with diameter > 200 µm dilated within the pressure range of MAP 110-160 mm Hg; arteries < 200 µm started to dilate below 110 mm Hg and vessels < 75 µm did not dilate until MAP decreased below 90 mm Hg. However, it can not be excluded that the lack of responsiveness of smaller arteries in their study could be associated with the fact that they kept the intracranial pressure constant which is likely to influence the hemodynamics of the microvessels. The above quoted results show that the dilatation of pial arteries within the autoregulatory range is of a much lower magnitude than the 50% increase of diameter obtained in our study with a moderate lowering of MAP. It seems fair to conclude that dihydralazine is, to a large extent, responsible for the dilatation in the present study.

Antihypertensive drugs have been studied surprisingly little for their effects on the cerebral circulation. It seems possible that dihydralazine, because of the increase in ICP, can be hazardous to patients with preexisting intracranial hypertension. In addition to an effect on ICP, the vasodilatory action per se can be potentially harmful, particularly when it occurs earlier.
than the decrease in systemic MAP. Dilatation enhances pressure-induced extravasation of protein into the brain and results in leakage at lower pressure levels.\textsuperscript{10, 11} Even if results obtained from animals with intact cerebral circulation obviously cannot be directly applied to patients with cerebrovascular disease, it should theoretically be better to decrease the blood pressure with drugs that do not preferentially dilate cerebral resistance vessels in patients with manifest or suspect increase of ICP.

References


\textbf{Figure 2.} Intracranial pressure (ICP), pial arterial diameter (\(\phi A\)), pial venous diameter (\(\phi V\)) following injection of 1 mg \(\cdot\) kg\(^{-1}\) dihydralazine. Mean arterial pressure (MAP) starts to decrease slowly, while the artery dilates markedly within a few minutes. The diameter of the vein remains essentially unchanged. ICP slowly increases.

\textbf{Figure 3.} After injection of 1 mg \(\cdot\) kg\(^{-1}\) dihydralazine, mean arterial pressure (MAP) falls markedly, and the artery simultaneously dilates (\(\phi A\)). The vein does not dilate (\(\phi V\)). Intracranial pressure (ICP) shows an initial rise.
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