Increase in Cerebral Blood Flow in the Rabbit by Viquidil

BY J. C. DE VALOIS, M.D.

Abstract:
The effect of viquidil, an isomer of quinidine, on the cerebral blood flow of the rabbit was determined using the \(^{85}\)Krypton clearance technique. The experimental animals had a thin polyethylene catheter chronically implanted in one of the internal carotid arteries to facilitate injection of the isotope into the cerebral circulation. At the time of the measurements the animals were artificially ventilated to control arterial \(P_{\text{CO}_2}\). Viquidil was administered via the implanted catheter at a dose of 5 mg/kg body weight. Cerebral blood flow was measured before injection of the drug (two control measurements of CBF) and ten minutes and 40 minutes after administration of viquidil. This drug causes an increase in cerebral blood flow of about 50 percent, which lasts at least one hour after administration. This increase in CBF was statistically significant \((P < 0.02)\).

Additional Key Words
- cerebrovascular resistance
- isotope clearance method
- two-compartmental analysis
- \(^{85}\)Krypton

Introduction

The pharmacological study of viquidil, an isomer of quinidine, has shown that this substance possesses some similarity with papaverine in its spasmyloytic and smooth muscle relaxant effect. A radioisotopic investigation of the metabolism of this compound in animals has demonstrated a strong affinity of viquidil for tissue proteins, which is probably in relation with the presence of a quinoline nucleus, and a noteworthy fixation on smooth muscles in particular on the walls of blood vessels.

Preliminary clinical trials of viquidil with the aid of radiocirculography using \(^{131}\)Iodine-labeled human serum albumin have provided evidence of a restoring effect of this agent on some aspects of the cerebral circulation in cases of cerebrovascular insufficiency. In consideration of the aforementioned findings, it appeared of interest to ascertain the activity of viquidil at the level of the cerebral circulation, and a study was undertaken to determine its effects on the cerebral blood flow (CBF) of the rabbit.

Methods

Five adult male rabbits (Alaska F1 bastards, TNO Central Proefdieren Bedrijf at Zeist, The Netherlands), weighing about 2.5 kg, were used for this study. In each animal a thin polyethylene catheter with an outer diameter of 0.65 mm was inserted into the right internal carotid artery one day before the pharmacological study. On the day of the experiments the animals were intubated, treated with succinylcholine (20 mg/kg/hr) to obtain muscular relaxation, and ventilated with a mixture of nitrous oxide and oxygen (ratio 2:1) with the Amsterdam Infant Ventilator (Loosco, Amsterdam). Under general anesthesia the femoral artery on one side was cannulated and connected to a Statham pressure transducer. EEG electrodes were placed over the sensorimotor cortex and a hollow screw was placed in the confluens sinuum for the sampling of cerebral venous blood. After completion of surgery, nitrous oxide was disconnected and artificial ventilation continued with pure oxygen at a rate of 32 per minute and a respiratory minute volume of approximately 1.4 liters.

The cerebral blood flow was measured by the method of Lassen and Ingvar, using \(^{85}\)Krypton instead of \(^{133}\)Xenon. The isotope, dissolved in saline to an activity of about 1 mCi/ml, was injected into the right internal carotid artery catheterized the day before. The clearance of the isotope from the brain was measured with a two-inch scintillation counter placed over the head of the animal. The clearance curves were subjected to two-compartmental analysis with the aid of an 1130 IBM computer. Details of the program used can be found elsewhere. At least four CBF measurements were performed in each animal, with an interval of 30 minutes. Two control measurements preceded the administration of the drug and two measurements followed 10 and 40 minutes after the injection of the drug, respectively. Viquidil was introduced at a dosage...
INCREASE IN CBF BY VIQUIDIL

TABLE 1
Effects of Viquidil on CBF

<table>
<thead>
<tr>
<th>Animal number</th>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 gm/min)</th>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>40</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>92</td>
<td>34</td>
<td>90</td>
<td>29</td>
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<td>3</td>
<td>90</td>
<td>46</td>
<td>98</td>
<td>38</td>
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<tr>
<td>4</td>
<td>90</td>
<td>51</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>55</td>
<td>95</td>
<td>43</td>
</tr>
</tbody>
</table>

MAP measurement:
1. (30 min) 2. (30 min) 3. (10 min) 4. (30 min)

Injection of viquidil

of 5 mg/kg body weight* into the cerebral circulation via the catheter mentioned before. In addition to the measurement of the CBF the following parameters also were recorded: EEG, ECG, cardiac pulse rate, and arterial blood pressure (mean pressure, systolic and diastolic pressures). From time to time arterial and cerebral venous blood samples were obtained and analyzed for pH, P<sub>CO₂</sub>, P<sub>O₂</sub>, buffer base, standard bicarbonate and base excess using the Astrup micro-method, and also analyzed for glucose with a standard Boehringer test kit.

*Chosen on the basis of preliminary tolerance tests in the rabbit.

TABLE 2
Mean CBF Parameters of Ten Determinations (± Standard Deviation)

<table>
<thead>
<tr>
<th>P&lt;sub&gt;CO₂&lt;/sub&gt;</th>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 gm/min)</th>
<th>CVR (PRU)</th>
<th>RW (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before viquidil</td>
<td>39 ± 9.7</td>
<td>88 ± 7.6</td>
<td>42 ± 7.6</td>
<td>2.1 ± 0.48</td>
</tr>
<tr>
<td>After viquidil</td>
<td>40 ± 7.6</td>
<td>96 ± 16.0</td>
<td>57 ± 22.6</td>
<td>1.9 ± 0.45</td>
</tr>
</tbody>
</table>

P<sub>CO₂</sub>: arterial CO₂ tension (mm Hg),
MAP: mean arterial blood pressure (mm Hg),
CBF: mean cerebral blood flow (ml/100 gm/min),
CVR: mean cerebrovascular resistance (PRU),
RW: relative weight of fast perfused compartment (percent).

TABLE 3
Mean CBF Parameters of Five Determinations (± Standard Deviation)

<table>
<thead>
<tr>
<th>P&lt;sub&gt;CO₂&lt;/sub&gt;</th>
<th>MAP (mm Hg)</th>
<th>CBF (ml/100 gm/min)</th>
<th>CVR (PRU)</th>
<th>RW (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ten minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After viquidil</td>
<td>40 ± 8.7</td>
<td>97 ± 15.8</td>
<td>65 ± 25.9</td>
<td>1.9 ± 0.45</td>
</tr>
<tr>
<td>40 minutes</td>
<td>41 ± 7.3</td>
<td>96 ± 18.1</td>
<td>49 ± 16.8</td>
<td>1.9 ± 0.50</td>
</tr>
</tbody>
</table>

*See table 2.

Results
The results obtained after intra-arterial administration of a dose of 5 mg/kg of viquidil are summarized in tables 1 through 4. This dose causes a very characteristic change in blood pressure which is three-phasic in nature: increase, decrease and, again, an increase in pressure. The first two changes take place between 30 and 40 seconds after injection; the third is of longer duration. In all cases an increase in mean arterial pressure of about 10%, which lasts one to two hours, can be observed (tables 2 and 3).

The cerebral blood flow shows a considerable increase under the influence of viquidil, with an
TABLE 4

Results of Compartmental Analysis

<table>
<thead>
<tr>
<th></th>
<th>Flow fast</th>
<th>Flow slow</th>
<th>CVRfast</th>
<th>CVRslow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before viquidil</td>
<td>105</td>
<td>27</td>
<td>0.90</td>
<td>3.45</td>
</tr>
<tr>
<td>10 minutes after viquidil</td>
<td>145</td>
<td>22.5</td>
<td>0.79</td>
<td>4.52</td>
</tr>
<tr>
<td>40 minutes after viquidil</td>
<td>166</td>
<td>26</td>
<td>0.68</td>
<td>3.84</td>
</tr>
</tbody>
</table>

Flow fast: cerebral blood flow through superficial layers (ml/100 gm/min), flow slow: cerebral blood flow through deep subcortical structures, CVR: cerebrovascular resistance.

The greatest increase in CBF occurs in the first half-hour after administration of viquidil, although the effect can still be traced after a period up to 40 minutes (tables 2 and 3). Compartmental analysis of the clearance curves elicits that the increase in blood flow mainly takes place in the fast perfused compartment, i.e., in the gray matter of the brain (table 4), and this also can be seen in a small shift in the values of the relative weights of this compartment.

The observed changes in response to viquidil were statistically significant (P < 0.02, Wilcoxon matched pair test). The biochemical data that were obtained did not show significant differences between the control values and the values under the influence of viquidil.

Discussion

Viquidil increases the cerebral blood flow in the rabbit considerably. The properties of viquidil in the present investigation distinguish it from other vasodilators previously studied by the same method. In that study we did not find an effect of intrarterially injected papaverine, which is in contrast to the conclusions of Olesen et al. They found an increase in regional CBF with intraarterially injected papaverine in patients with cerebrovascular disorders and tumor cases up to 90%. The reason for this discrepancy might be the fact that the duration of the vasodilatory action of papaverine is rather short, about ten minutes, which is the time lag we normally wait before starting CBF measurements in drug studies. Although viquidil and papaverine show some similarity in structural and in functional respect, one of the interesting differences might be the longer duration of the vasodilatory action of viquidil. Further research on the effect of this drug on cerebral hemodynamics will be centered on the duration of the effects on smooth muscle, the effects of chronic parenteral administration on CBF, and the ability of the drug to relieve experimentally produced spasms in the basilar artery of the rabbit.

References

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