Effect of Topical Nimodipine Versus Its Ethanol-Containing Vehicle on Cat Pial Arteries

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SUMMARY Nimodipine and its solvent containing ethanol were tested in a randomized in vivo study by local administration to the outer vessel wall surface of pial arteries and veins in 15 anesthetized cats. Reactions were studied through a cranial window. Diameter variations of 90 arterial and 78 venous vessel segments were continuously analyzed using a multichannel videoangiometer. The solvent alone caused minor though statistically significant (p < 0.001) 7.6% dilatation, 8% in small and 7% in large arteries, which returned to their resting state after stopping treatment. 2.4 x 10^{-5} M nimodipine plus solvent induced a 21% pial arterial dilatation (p < 0.001), 26% in small and 17% in large arteries; dilatation induced by nimodipine plus solvent was significantly greater than dilatation by the solvent alone (p < 0.001). After ceasing topical administration, arteries remained dilated by some 5%.

Pial veins exhibited only minor reaction, i.e. a 6% (statistical n.s.) dilatation of large veins during nimodipine, and an 8% dilatation of small veins 20 minutes after stopping nimodipine. During solvent-administration rCBF, as estimated with the hydrogen clearance technique, remained unchanged. It is concluded that the dilatatory effect of the investigated compound on pial arteries is predominantly due to nimodipine.

CALCIUM ANTAGONISTS as cerebrovascular dilators have recently come into discussion for a potential protective effect against cerebral vasospasm, a threatening complication from a ruptured cerebral aneurysm. Thus, the lipophilic compound nimodipine (Bay e 9736) has been shown to dilate pial arteries in vitro and in vivo both in animal experiments and in man during intravenous administration. This dilatation of resistance vessels results in a selective increase of cerebral and myocardial blood flow which is even more pronounced after opening of the blood-brain barrier.

Perivascular administration of the drug, therefore, appeared to be a promising clinical approach. Since nimodipine is dissolved in ethanol and propylene glycol, it has been suggested that the main protective effect of the compound was due to its content of ethanol. The present study was, therefore, undertaken to separate the vascular effects of nimodipine and ethanol when topically applied in concentrations currently routinely used in clinical neurosurgery. Only one concentration of nimodipine was used for testing against the solvent, since it had previously proven satisfingly effective in vitro as well as during aneurysm surgery.

Materials and Methods

Experiments were performed in 15 cats of either sex with a body weight of 1.5–3 kg. The animals were anesthetized with 30 mg kg^{-1} sodium pentobarbital, relaxed with 6 μg kg^{-1} pancuronium bromide and respired with a 3:1 mixture of N₂O:O₂, using a Loosco baby respirator. A femoral vein and artery were cannulated with PVC catheters for blood pressure monitoring and blood gas sampling. With the animal in sphinx position, a closed cranial window was made in the left parietal region as described in detail earlier. In addition, a plastic cannula was placed under the glass window for irrigation of the subarachnoid space and a second one was placed into the cisterna magna to allow fluid to escape and maintain a normal ICP. Body temperature was continuously monitored with a Philips rectal thermosensor unit. Blood pressure (mean arterial pressure, MAP) and intracranial pressure (ICP) via a second needle in the cisterna magna were registered with Statham P23dB transducers and Hellige 1214 electromanometers. Frequent arterial blood gas checks were made with an AVL type 937C blood gas analyzer.

Initially, a short period of hypercapnia was induced by adding CO₂ to the respired gas mixture to check the normal regulatory response of the pial vessels.

Pial arteries and veins were observed using a Leitz intravital microscope and their absolute diameter variations were continuously recorded using a multichannel videoangiometer device as described elsewhere in detail. Vessels were grouped into those with a resting diameter up to 100 μm and larger vessels to demonstrate differences in behavior. Nimodipine or the solvent were applied to the pial surface in a randomized manner; experimenters were unaware of the random pattern.

In a first group of five animals, the subarachnoid space was irrigated with 6 ml/h or mock CSF for 40 minutes under steady state conditions of intracranial pressure and temperature of the irrigation fluid, the latter maintained constant at 37°C using a YSI microthermiosensor unit. The pH of mock CSF varied between 7.409 and 7.487, and was 7.44 ± 0.01 SEM on average. Addition of nimodipine in its solvent or the solvent alone increased pH by 0.06. The artificial CSF had the following composition: Na⁺, 156 mM; K⁺, 3 mM; Ca²⁺, 1.5 mM; HCO₃⁻, 15 mM; Cl⁻, 147 mM and was bubbled with 95% O₂ and 5% CO₂.

In five animals, the same procedure was performed using 2.4 x 10^{-5} M nimodipine in mock CSF for 10 minutes (i.e. a total dose of 10 μg in 50 μl solvent and 1 ml mock CSF), followed by mock CSF alone for further 30 minutes; and in a third series of five animals, the solvent of nimodipine dissolved in the same quanti-
ty of mock CSF was superfused again at a rate of 6 ml/h for 10 minutes (i.e. 50 μl solvent and 1 ml mock CSF), followed by mock CSF for 30 minutes. The solvent contains 200 g/l ethanol, 170 g/l polyethyleneglycol, 2 g/l Na-citrate, 0.3 g/l citric-acid in distilled water.

In 4 solvent-only treated cats, regional cortical blood flow was measured before starting and shortly before stopping the solvent-superfusion. The hydrogen clearance technique \(^{14,15}\) was employed using 50 μm platinum electrodes insulated with resin inserted into the cortex in the cranial window under observation. Furrows were made in the edge of the trepanation to guide the wires extracranially underneath the glass window.

Statistical evaluation of pial arterial and venous diameter variations were performed using Friedman’s Chi-square Test.

Results

In the total of 15 animals, 87 pial arterial segments with resting diameters between 40 and 268 μm and 78 pial venous segments with resting diameters between 42 and 366 μm were analyzed.

Arteries (fig. 1a–c)

Within ten minutes of nimodipine administration, arteries showed a significant dilatation, maximal after 10 minutes with +21% ± 2.6 SEM, stronger in small (+26% ± 4 SEM) than in large arteries (+17% ± 3 SEM).
DILATORY EFFECT OF NIMODIPINE/Auer and Mokry

TOP. NIMO SOLVENT A MOCK-CSF

Diagram of dilatory effect of nimodipine and solvent on pial arteries.

- Nimodipine-treated arteries remained significantly wider than solvent-treated arteries.
- Mock CSF induced slow dilatation of large and small arteries.

Veins (fig. 2a-c)

- Only in the veins larger than 100 μm did nimodipine show a significant dilatation of 6 ± 1.6% SEM within 10 minutes of application.

Table 1: Blood Gas Values in the Three Treatment Groups before and 10' and 40' after Start of Treatment

<table>
<thead>
<tr>
<th></th>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>PaO₂</th>
<th>PaCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mock CSF</td>
<td>106.2±2.3</td>
<td>29.8±0.5</td>
<td>104.1±2.2</td>
<td>29.6±0.2</td>
<td>105.5±4.0</td>
<td>29.4±0.4</td>
</tr>
<tr>
<td>Solute</td>
<td>101.1±2.9</td>
<td>30.3±0.7</td>
<td>97.7±1.4</td>
<td>29.8±0.3</td>
<td>98.8±2.8</td>
<td>30.1±0.4</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>101.6±2.2</td>
<td>29.1±0.6</td>
<td>97.2±1.7</td>
<td>29.2±0.5</td>
<td>99.2±2.5</td>
<td>29.9±0.5</td>
</tr>
</tbody>
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Discussion

The present data demonstrate that nimodipine, when locally applied, dilates pial arteries to a significant extent. The smaller arteries are more affected than...
larger ones. Only a minor part of this effect is due to the solvent.

The present findings are similar to the reactions of pial arteries to topically applied nifedipine which is also diluted in an ethanol-containing vehicle. In contrast to nifedipine, nimodipine has no effect on pial veins, as has previously been observed in experimental studies and in clinical studies. The proportion of drug versus solvent effect was, however, dose-dependent in the study of Brandt et al. The solvent of nimodipine, known to contain ethanol and propylene glycol, was considered to be the main substance responsible for the reactions of cerebral vessels, when compared to the reactions of nifedipine plus solvent. A significantly higher increase in the tolerance of mice to hypoxia was described in tests of pretreatment with ethanol using doses of 0.2–2.1 mmol/animal intravenously and 0.2–4.2 mmol/animal intraperitoneally in comparison to the effects of nimodipine in its vehicle substance. The finding that "nimodipine does not add to the protective effects of ethanol" is not comparable with the present results, because of different doses used.

In another study by Altura et al. topical administration of doses between 10 to 500 mg/dl ethanol caused distinct constriction. Ethanol thus seems to exert a dose-dependent dilatatory or constrictor effect on cerebral vessels which plays a very minor role when compared to the reactions of nimodipine plus solvent. A significantly higher increase in the tolerance of mice to hypoxia was described in tests of pretreatment with ethanol using doses of 0.2–2.1 mmol/animal intravenously and 0.2–4.2 mmol/animal intraperitoneally in comparison to the effects of nifedipine in its vehicle substance. The finding that "nimodipine does not add to the protective effects of ethanol" is not comparable with the present results, because of different doses used.

The delayed reaction of small veins to nimodipine is as yet unexplained. A similar trend has been observed during intravenous administration of nimodipine in patients. On the one hand, this effect could add to an increase in CBF due to reduction of peripheral resistance in the cerebral venous compartment; on the other hand, caution seems advisable in situations of increased ICP, where the increment in cerebral blood volume might cause a steep further rise of ICP, according to the intracranial volume-pressure relationship.

Pial arteries show significantly smaller calibers 15 minutes after administration of solvent than both after nimodipine and after mock-CSF, although MAP was significantly higher during this period in the solvent-group than in the other groups. The significant difference would suggest a constriction effect of the solvent. Alternatively, the reaction could be interpreted as an autoregulatory response to the parallel 6% increase of MAP in the solvent-group.
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