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 × 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.

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. The animal was previously proven satisfingly effective in vitro as well as during aneurysm surgery.

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.

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Initials, 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 microthermosensor 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 × 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 polyethylene-glycol, 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 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

After stopping superfusion, calibres returned to some +5% above resting within a further 15 minutes. Nimodipine-treated arteries thus remained significantly wider than solvent-treated arteries.

The solvent dilated arteries significantly more than the mock CSF controls. A maximal dilatation of +8% ± 2.4 SEM in small arteries was achieved after 15 minutes, i.e. 5 minutes after stopping superfusion. Thereafter arteries of all sizes returned to their resting calibres.

Mock CSF induced a slow dilatation of large and small arteries amounting to +7% ± 2.3 SEM and +6% ± 3.2 SEM respectively, after 25 to 30 minutes. Thereafter small arteries returned to around 2% above their resting calibres, whereas large arteries remained approximately +6%, i.e. significantly wider than controls.

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.

Both the solvent and the mock CSF superfusion group showed no venous reactivity. After stopping nimodipine, small veins started to show a tendency to dilate, culminating in a significant 8% ± 0.8 SEM dilatation after 20 minutes; the two other groups remained unreactive.

During administration of nimodipine, its solvent alone, or mock CSF, PaO₂ and PaCO₂ were kept at constant normal level (table 1). The mean resting MAP (fig. 3) was 114 mm Hg in the control group with variations during superfusion of not more than −3.5% to +0.6%. Solvent MAP was 110 mm Hg varying from −1.7% to +6.4% during superfusion, the nimodipine plus solvent MAP was 106 mm Hg with a range of −2.9% to +0.2% during superfusion.

Regional cerebral blood flow was measured in four of the solvent perfused cats by hydrogen clearance. Mean rCBF was 94.7 ml/100 g tissue/min at the beginning of the experiments and rose 2.9% by the end of the solvent superfusion period. ICP remained constant within a range of 0.3 to 10.3 mm Hg (nimodipine group 1–8.3 mm Hg; solvent group 0.8–10.3 mm Hg; and control group 0.3–3.8 mm Hg).

Discussion

The present data demonstrate, that nimodipine, when locally applied, dilates pial arteries to a significant extent. The smaller arteries are more affected than

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<th>Table 1 Blood Gas Values in the Three Treatment Groups before and 10' and 40' after Start of Treatment</th>
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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 and in clinical studies. The proportion of drug versus solvent effect was, however, dose-dependent in the study of Brandt et al.1

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 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 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.1983 topical administration of doses between 10 to 500 mg/dl ethanol caused distinct constriction. Ethanol thus seems to exert a dose-dependent dilator or constrictor effect on cerebral vessels which plays a very minor role when the concentrations used for topical administration in the present study are employed. Thus, the cerebral blood flow in 4 animals remained unchanged. Intravenous administration of clinically used concentrations of the compound does not induce any effect related to the ethanol-containing solvent.

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 calibres 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.

**References**


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