Intracranial effects of nicardipine

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1 Preliminary investigations indicated that the calcium antagonist nicardipine improved cerebral vascular circulation and cerebral metabolism. Therefore we examined the effect of nicardipine on the cerebral vessels, cerebral oxygen tension, and intracranial pressure (ICP) in patients with cerebrovascular disturbances.

2 In patients with previous minor stroke undergoing surgery for extra-intracranial anastomosis, we applied nicardipine topically to the operation site by means of a perfusor and measured the diameter of the cerebral vessels.

3 After several minutes, the topically applied nicardipine produced marked dilatation in the small arterial cortical vessels and relaxation of vasospasm. In the two patients studied so far, we observed a rapid increase in the cerebral PO_2 , which remained elevated after the initial peak as long as the infusion continued.

4 With a lower dose the increase in the intracranial pulse amplitude (PA_{ICP}) was antagonized by the considerable drop in blood pressure which occurred after 10 mg h⁻¹ nicardipine.

5 The results indicate that nicardipine dilates the cerebral vessels and increases the cerebral oxygen tension

Keywords calcium antagonism cerebral oxygen tension cerebral vessels intracranial pressure nicardipine

Introduction

The therapeutic application of calcium antagonists has become increasingly important within the last 15 years (Fleckenstein, 1981). Because of the relaxant effect on the smooth muscle of the coronary vessels, the inhibitory effect on the contractile force of the cardiac muscle, and the fact that they reduce the calcium-dependent activity of cardiac pacemakers (Hoffmeister, 1984), calcium antagonists are today one of the first choice therapies for coronary heart disease, especially coronary spasm (Stone *et al.*, 1980; Yasue, 1980).

Successful therapy with calcium antagonists also has been reported increasingly in disturbances of the cerebral circulation. The new 1,4-dihydropyridine-derivatives have a pronounced

effect on the cerebral vessels. We have found a significant increase in the cerebral circulation following treatment with nimodipine, especially in the presence of cerebral vasospasm (Gaab *et al.*, 1984); in a double-blind study the clinical improvement seen after subarachnoid haemorrhage also was significant (Allen *et al.*, 1983). Experiments have shown that nicardipine markedly dilates the cerebral vessels and in particular relaxes cerebral vasospasm (Handa *et al.*, 1975; Matsui *et al.*, 1979; Nakayama *et al.*, 1983). Intravenous and intra-arterial infusion of nicardipine considerably increased the cerebral circulation rate of patients (Takenaka & Handa, 1983). Clinical improvement also has been reported in cerebrovascular disorders (Fujiwara *et al.*, 1980).

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Figure 1 Effect of nicardipine on the cerebral vessels (a before, b after nicardipine). Marked dilatation of the cortical artery after 8 min topical application of nicardipine. The spastic segment is widened (solid arrow) and there is a pronounced dilatory effect on the small arterioles (open arrow).

We therefore examined the effects of nicardipine on the cerebral vessels, the cerebral oxygen supply, and the intracranial pressure (ICP) in patients undergoing neurosurgery, and present our first findings in the following report.

Methods

The effects of nicardipine on the morphology of the cerebral vessels and on the cerebral oxygen tension were examined during and after neurosur-

gical intervention. Simultaneous measurement of ICP, systemic arterial blood pressure (MAP), and computation of the cerebral perfusion pressure (CPP) were made to show if and how vascular effects of nicardipine may affect the balance of the intracranial volume (Gaab & Heissler, 1985).

The study protocol received peer review and approval in the University of Vienna. Informed consent was obtained by the investigators from the patients, or the families of those who were unable to give consent. During the study, intensive monitoring by EEG, ECG, and measurement of blood pressure was carried out in all patients. A 10% calcium injection was at hand.

Effect of the local application of nicardipine on the cerebral vessels

In patients with cerebral arteriosclerosis and previous stroke who were undergoing surgery for extracranial anastomosis (EIA), the vascular reaction was studied using the surgical microscope (Figures 1 and 2). To avoid possible interactions between the drug and the anaesthetic agents nicardipine was applied topically as described in other studies by Auer *et al.* (1982).

Nicardipine was diluted 1:19 with mock cerebrospinal fluid at 37°C to give a concentration of 0.05 mg ml⁻¹ and was then perfused at the site, 5 ml bolus then 3 ml min⁻¹. The effect of nicardipine on the local vascular spasm was evaluated for 10 min with photographs being taken through the surgical microscope every 30 s. Identical enlargement of these photographs enabled relative changes in vessel size to be measured. Drug effect on the spasm induced by the mechanics of the surgery was studied in the same way.

Effect of nicardipine on cerebral oxygen tension

In brain tissue with disturbed blood flow but not irreversibly damaged, for example in the 'penumbra' of a stroke, the oxygen tension (PO_2) is considerably reduced. Oxygen tension can be increased by surgical measures aimed at increasing the blood flow (Schuster & Gaab, 1985) and an improvement in cerebral PO_2 produced by nicardipine has been shown experimentally (Kosugi *et al.*, 1979). Using a micro- PO_2 -probe implanted simultaneously with the ICP sensor (Gaab, 1985) it has been possible to obtain stable measurement conditions and to follow in two patients the changes in PO_2 which occurred after intravenous injection of nicardipine 24 h after operation (Figure 3).

Effect of nicardipine i.v. on ICP, MAP, and CPP

As nicardipine produces dilatation in the cerebral vessels, an increase in ICP must be expected as the cerebral blood volume increases (Gaab *et al.*, 1984). We therefore continuously measured the ICP by use of miniaturized, epidurally-implanted pressure transducers (Gaab, 1981, 1985) in six patients and simultaneously measured the arterial pressure (MAP). The computerized neuromonitor described earlier (Gaab, 1985) computed the CPP continuously from the difference between MAP and ICP, and all data were evaluated by histogram statistics.

Additionally, the cerebral pulse amplitude (PA_{ICP}) also was recorded and evaluated (Figures 5, 6; Gaab *et al.*, 1984). The values measured in the six patients 1 h before nicardipine was infused, 1 h after i.v. infusion of nicardipine (5 mg h⁻¹), and 1 and 2 h after i.v. infusion of 10 mg h⁻¹, were compared by the paired *t*-test (Figures 4, 5 and 6). As all patients weighed between 64 and 79 kg, the dose of nicardipine was 1–1.2 or 2–2.4 $\mu\text{g kg}^{-1} \text{min}^{-1}$.

Results

Effects on the morphology of the cerebral vessels

After the topical application of nicardipine there was a latent period of at least 5 min (also reported to occur with nimodipine, Auer *et al.*, 1982)

Figure 2 Percentage increase in diameter of cortical vessels, 9 min after topical application of nicardipine during EIA surgery. Mean $\pm$ s.e. mean, $n = 4$ patients.

Figure 3 Changes in cortical PO_2 (single probe) following infusion of nicardipine 24 h after EIA surgery in one patient with a stroke.

before considerable dilatation of the cortical vessels occurred (Figures 1 and 2). The most obvious feature was the elimination of the local spastic vascular constrictions caused by the surgical intervention and the increase in the mean diameter of the cortical arteries. Dilatation of the smallest visible cortical arterioles by over 50% was considerably greater than that seen in the larger artery.

Effect of nicardipine on cerebral oxygen tension

As only two patients have been studied so far, trends must be interpreted cautiously. In both patients there was an increase in the cerebral oxygen tension which occurred soon after the infusion of nicardipine was started. After the initial peak the PO_2 level decreased slightly although it remained above the pretreatment level, and increased further as the dose of nicardipine was increased. After the infusion the PO_2 level fell once more (Figure 3).

ICP, MAP and CPP

The average values in the patients studied so far show no noticeable change in the mean ICP after nicardipine (Figure 4). However, in one patient with considerably reduced intracranial reserve volume and, therefore, increased ICP prior to nicardipine, as nicardipine was infused the ICP

further increased. The MAP and CPP were decreased following infusion of nicardipine (Figure 4), especially by the higher dosage of 10 mg h^{-1} . The decrease after 5 mg h^{-1} was not dangerous in any of the patients, as the CPP always remained above the critical level of 65 mmHg (Gaab, 1981, 1985).

With 10 mg h^{-1} , however, MAP and CPP dropped markedly, so that for three patients the infusion had to be discontinued. The values measured before the infusion was stopped were used in Figure 4. After the i.v. infusion was stopped, the MAP quickly rose again (Figure 4a), so that neither administration of calcium nor volume substitution was required.

In addition to the changes seen in ICP_{mean} , there were changes in the ICP_{diast} and ICP_{syst} , and thus the intracranial pulse amplitude PA_{ICP} that were just below the significance level. After nicardipine 5 mg h^{-1} the ICP_{diast} decreased, whereas the pulse amplitude increased; with 10 mg h^{-1} , however, the PA_{ICP} again decreased and dropped markedly after the nicardipine infusion was stopped (Figures 5 and 6).

Discussion

The changes in diameter of the cerebral vessels induced by topical application of nicardipine are

Figure 4 Measurements of ICP, MAP and CPP after infusion of nicardipine (a) tracing made from one patient, showing small increase in ICP following nicardipine 10 mg h⁻¹ and (b) mean $\pm$ s.e. mean in six patients. + = $P < 0.05$.

clearly observed with the surgical microscope. The width of the cortical arteries increased, the increase being especially pronounced in small-diameter vessels, and mechanically-induced vascular spasm was eliminated. The effect was weaker and set in later than that seen with locally applied papaverine but was comparable to that produced by topical nimodipine (Auer *et al.*, 1982).

The delayed effect seen with the calcium antagonist suggests that the vascular contraction temporarily is maintained by the calcium that is present in the cells and, consequently, is not affected by the calcium antagonist (Fleckenstein, 1981; Hoffmeister, 1984). The smooth muscle relaxation produced by the inhibition of calcium

inflow would then appear only after exhaustion of the calcium stored in the cells.

Whether the effect of i.v. administration of nicardipine is as pronounced as with topical application cannot be answered by our studies, although measurement of P_{O_2} and ICP following i.v. infusion also suggested a dilating effect on the cerebral vessels. As the P_{O_2} and the ICP pulse amplitude increased very quickly after i.v. infusion, the effect might even be precipitated by i.v. dose.

The effect on cerebral oxygen tension remains to be ascertained in a larger number of patients with a variety of diagnoses; also it remains to be clarified whether or not the P_{O_2} increased merely

Figure 5 ICP and intracranial pulsation tracings made from one patient. Although the mean ICP remained unchanged the ICP pulse amplitude increased.

because of an effect on the vessels, or whether, in addition, the cerebral metabolism was involved. This latter is suggested by the experimental chemical studies of Borzeix & Cahn (1983) and the experimental measurements of the PO_2 histogram and O_2 consumption by Heller *et al.* (1983). A trophotropic effect could also explain the improvement in the depressive symptoms of aged people reported with the calcium antagonists (Eckmann *et al.*, 1984). One explanation might involve the 'second messenger system' of calcium and calmodulin, which probably plays a major role in the brain (Marmé, 1981; Epstein *et al.*, 1982).

The effect of nicardipine on ICP and CPP is shown by the combination of cerebral vascular dilatation and decreasing blood pressure. As found with nimodipine (Gaab *et al.*, 1984), the

cerebral pulse amplitude PA_{ICP} increased as nicardipine was given, mainly because of the increase in the cerebral vessel diameter. Because of the reduced arterial tone, the arterial pulsations were transmitted to a larger extent in the CSF and the intracranial space (normally the intracranial pulse amplitude is largely of arterial origin; Gaab, 1981; Gaab & Heissler, 1985). The ensuing increase in cerebral blood volume, however, was not very large; this is in line with the more pronounced effect on the arterial vessels without significant dilatatory effect on the cerebral veins, which contain a considerably higher blood volume (Gaab, 1981).

Thus, unless the intracranial compliance is impaired, the mean ICP does not increase markedly. An ICP increase can be expected only when the intracranial reserve capacity is restricted

Figure 6 Absolute (a) and relative (b) changes in diastolic ICP and ICP pulse amplitude. Mean $\pm$ s.e. mean.

and the ICP is already elevated; under such circumstances pressure-volume-slope is steep, and the small increase in cerebral blood volume occurring with arterial dilation will therefore significantly increase the ICP (Gaab, 1981; Gaab & Heissler, 1985). An intracranial space-occupying lesion or cerebral oedema therefore might constitute a contraindication for calcium antagonists (Gaab *et al.*, 1984), the more so as the CPP drops disproportionately because of the falling blood pressure. This hypotensive effect is already known with nicardipine and is even made use of in the treatment of hypertension (Aoki *et al.*, 1982; Iliopoulou *et al.*, 1982).

In patients with cerebral disease, however, a dose of 10 mg h⁻¹ i.v. is too high. As the hypotensive effect may become excessive, we no longer use more than 1.2 μ g kg⁻¹ min⁻¹ or

4–6 mg h⁻¹. The hypotension caused by a dose of 10 mg h⁻¹ also explains why the intracranial pulse amplitude decreases although cerebral vessels may continue to dilate: the 'input value' of the arterial pressure and arterial pulsation (Gaab, 1981) drops too much. In cerebrovascular disorders, a combination of calcium antagonist with rheological therapy (infusion of low molecular weight dextran or hydroxy-ethyl-starch, with peripheral α -adrenoceptor therapy) is suggested.

The effect of nicardipine on the brain must be investigated further in a larger number of patients. Based on the data collected so far, we plan further studies on the effect of nicardipine on cerebral oxygen metabolism and quantitative regional studies of the cerebral circulation using Xenon 133 and methods previously described (Gaab *et al.*, 1982, 1984).

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