Experimental intracerebral haemorrhage: the effect of nimodipine pretreatment

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SUMMARY The effect of pretreatment with the calcium antagonist nimodipine on the pathophysiological events which follow an intracerebral haemorrhage in rats was compared with a similar control group. Cerebral blood flow was higher and the amount of pathologically determined ischaemic damage measured by light microscopy was less in the nimodipine pretreated group. Bloodbrain barrier permeability was increased in the nimodipine group, but there was no evidence of cerebral oedema. Nimodipine appeared to have no effect on the intracranial pressure.

The management of intracerebral haemorrhage occurring either spontaneously or secondary to rupture of an aneurysm remains controversial and the mortality is often high.¹⁻⁵ Undoubtedly much tissue damage and distortion occur at the time of formation of the haematoma,^{6,7} but secondary ischaemic events may also be important,^{8,9} and may be susceptible to treatment.

The calcium antagonist nimodipine has been shown to be capable of increasing cerebral blood flow (CBF)^{10,11} without affecting oxygen uptake and glucose utilisation in different animal models of cerebral ischaemia.¹² Also it has been reported to reduce the amount of ischaemic damage following various periods of reduced CBF in animal models, particularly if treatment begins before the ischaemic event.¹³⁻¹⁵ In addition it has been used in clinical trials involving patients with the purpose of preventing or reversing delayed cerebral ischaemia following subarachnoid haemorrhage.¹⁵⁻¹⁹ However, the effects of nimodipine pretreatment on the pathophysiological events produced by an intracerebral haemorrhage have not yet been determined.

The aim of this study was to investigate the effect of nimodipine pre-treatment on regional cerebral blood flow (rCBF) following an intracerebral haemorrhage, and to correlate these changes in rCBF with any

changes in the volume of ischaemic damage, intracranial pressure (ICP), brain specific gravity (SG), and blood-brain barrier (BBB) permeability.

Materials and methods

General preparation

Experiments were performed on anaesthetised, physiologically monitored, adult male Sprague-Dawley rats weighing 360-439 g. The general preparation was identical to that previously described elsewhere.²⁰ After a 30-minute stabilisation period, in half the animals an intravenous infusion of nimodipine was commenced at the rate of $1 \mu\text{g kg}^{-1} \text{min}^{-1}$. In the remaining animals vehicle (polyethylene glycol-ethanol-water mixture) was infused at the same rate, this group serving as controls. Thirty minutes following the start of the infusion fresh, non-heparinised, autologous arterial blood was taken from a femoral artery and used to prime a blunted 25-gauge butterfly needle. This was then inserted stereotactically to a depth of 5.5 mm into the right caudate nucleus. The burr hole was sealed with dental cement and 100 μl of the arterial blood introduced into the right caudate nucleus in all animals at arterial pressure (100 mmHg) from a constant pressure reservoir. Following production of the intracerebral haemorrhage the infusion of nimodipine or vehicle was continued at the previously stated rate for 4 hours. During this time the PaO_2 was maintained above 100 mmHg, the PaCO_2 between 35 and 40 mmHg, the mean arterial blood pressure (MABP) above 80 mmHg, and the plasma glucose concentration and haematocrit were measured every 30 minutes. The temperature was monitored by means of a rectal thermistor probe and maintained at 37°C by means of an electric heating lamp. Any animal not fulfilling these physiological criteria was excluded from the series. The experiments were performed on a double-blind basis, the code remaining unbroken until all the experiments had been completed and the results analysed.

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Experimental groups

The animals were divided into four groups each containing an equal number of nimodipine and vehicle treated animals.

Group 1 (n = 12): Neuropathology

Four hours following production of the intracerebral haemorrhage the animals were perfusion-fixed for neurological purposes using the method of Brierley *et al.*²¹ The brains were removed and using the histological criteria of Brown and Brierley²⁷ the area of ischaemic damage at pre-determined coronal levels was calculated,²⁰ the anterior co-ordinates of which are given in table 1. The co-ordinates for the coronal levels were taken from the stereotaxic areas of König and Klippel.²³ An approximation to total volume of ischaemic damage was then achieved by integration of the areas with the distance between each level using a micro-computer. Great care was taken to exclude the volume of the needle and haematoma from the total. The amount of ischaemic damage was then expressed as a percentage of the volume of the cerebral hemisphere, cerebral cortex and caudate nucleus, as well as in the absolute volume (mm³).

Group 2 (n = 12): Measurement of intracranial pressure, brain specific gravity, and repeated measurement of cortical blood flow using hydrogen clearance

In this group of animals intracranial pressure was measured continuously during the course of the experiments via a ventricular catheter.²⁰ In addition, to allow repeated measurement of cerebral blood flow using hydrogen clearance, two further burr holes were made one on either side of the sagittal suture 2.8 mm lateral and 4 mm anterior to the bregma. Platinum electrodes (external diameter 200 mm) were inserted stereotactically under direct microscopic vision to a depth of 1 mm into the frontal cortex (1 electrode per burr hole). A silver/silver chloride reference electrode was inserted subcutaneously in the dorsal thoracic region and a polarising voltage of 700 mV applied. Hydrogen was introduced into the system at a concentration of 12% of inspired gases and discontinued once saturation had occurred, usually after 5 minutes. CBF was calculated by analysis of the initial slope of the clearance curve.²⁴ Flows were measured initially at rest, 30 minutes after the start of infusion of nimodipine or vehicle, 5 minutes after production of the haematoma and thereafter every 30 minutes until the end of the experiment. Four hours following the production of the intracerebral haemorrhage, asystole was

produced with an intravenous bolus of potassium chloride and Euthatal, and brain specific gravity measured using a microgravimetric method.²⁵

Group 3 (n = 12): Measurement of regional cerebral blood flow at 4 hours

Regional cerebral blood flow (rCBF) was measured at the end of 4 hours using the ¹⁴C iodo-anti pyrene technique²⁶ as described previously.²⁰ For analysis of the CBF data both the standard method of microdensitometry and an area based method were used.²⁰ When using the area based method great care was taken to exclude the area of the needle and haematoma. The percentage area of cerebral cortex, cerebral hemisphere, and caudate nucleus with the rCBF below a particular range was then calculated for flow ranges of 10 ml. 100 gm⁻¹ min⁻¹ up to and including 200 ml. 100 gm⁻¹ min⁻¹ in increments of 10 ml. 100 gm⁻¹.

Group 4 (No 12): Measurement of blood-brain barrier permeability at 4 hours using the aminoisobutyric acid autoradiographic technique

The general preparation was the same as already described. At the end of 4 hours the blood-brain barrier (BBB) permeability was measuring using the ¹⁴C- α aminoisobutyric acid (AIB) technique described by Blasberg *et al.*²⁷ An infusion of 75 μ Ci of ¹⁴C AIB, made up to a total volume of 1.5 ml with normal saline, was given over 25 seconds. Simultaneously, commencing at the start of the infusion serial samples of arterial blood were taken (100–150 μ l) and rapidly centrifuged. Frequent blood samples were drawn early in the experimental time course (0, 0.25, 0.5, 0.75, 1.0, 2.0, 3.0, 5.0, 7.5 and 10 min) as the plasma levels of isotope were changing rapidly during this period. Later plasma samples changed more slowly and the sampling interval was lengthened correspondingly (12.5, 15.0, 20.0 min). Subsequently 27.5 μ l of plasma was pipetted into counting vials for determination of radioactivity by liquid scintillation counting. Immediately after the last sample had been taken, asystole was produced with an intravenous bolus of potassium chloride/euthatal. Circulatory failure was taken from the time when the MABP had been reduced to 50 of baseline and the time noted. The brain was rapidly removed and frozen in isopentane at -45°C, following which 20 μ m thick sections were cut in a cryostat at -22°C. Three adjacent sections every 400 μ m were saved, increasing to three sections every 200 μ m in the region of the lesion. The sections were mounted on glass cover slips and immediately dried on a hotplate. Autoradiographs were prepared by exposing the sections together with a set of plastic standards of known ¹⁴C concentration (44–1175 μ Ci g⁻¹) to single-coated x-ray film (Kodak SB5) for 6 weeks.

Changes in BBB permeability were then assessed from the resulting ¹⁴C- α AIB autoradiographs (fig 6). Sample readings were taken at 17 discrete neuroanatomically determined loci, with reference to the ¹⁴C standards, using a computer-based densitometer (Quantimet 720, Cambridge Instruments). The capillary transfer constant (K₁) for ¹⁴C- α AIB was then calculated at each locus.

Statistics

All values are expressed as means and the standard error of the mean. The means were compared using both Scheffe and

Table 1 Anatomical landmarks

	Level	Anterior Co-ordinates (mm)
Caudate nucleus	1	9.65
Genu corpus callosum	2	8.92
Nucleus accumbens	3	8.38
Septal nuclei	4	7.47
Anterior commissure	5	7.02
Fornix	6	6.79
Globus pallidus	7	6.36
Commissure of the fornix	8	5.91
Habenula	9	5.34
Fimbria hippocampi	10	4.62
Lateral habenula	11	4.11

Anatomical landmarks of coronal sections of the rat brain from König and Klippel, 1974.

Table 2 Physiological variables in the two groups (N = 48: mean values, SEM)

	Arterial pH		Arterial PaO ₂ mmHg		Arterial PaCO ₂ mmHg	
	Nimodipine	Vehicle	Nimodipine	Vehicle	Nimodipine	Vehicle
Resting	7.424, 0.007	7.420, 0.022	145.9, 7.7	140.2, 12.2	38.9, 0.4	37.1, 0.9
Infusion for 30 minutes	7.428, 0.014	7.407, 0.035	148.5, 7.0	137.2, 9.2	37.7, 0.7	36.6, 1.1
5 min post haemorrhage	7.434, 0.009	7.462, 0.018	160.0, 5.6	151.6, 7.3	37.6, 0.8	37.6, 0.5
30 min	7.429, 0.009	7.448, 0.020	162.6, 6.1	144.7, 6.6	38.5, 0.5	37.7, 0.6
60 min	7.438, 0.012	7.438, 0.019	162.8, 5.2	141.0, 10.5	37.6, 0.6	38.0, 0.8
90 min	7.441, 0.013	7.436, 0.026	160.7, 4.2	145.9, 6.8	37.2, 0.7	37.9, 0.7
120 min	7.400, 0.020	7.436, 0.022	163.2, 4.9	147.5, 9.2	37.3, 0.8	36.8, 0.8
150 min	7.399, 0.021	7.459, 0.025	170.2, 5.9	146.7, 8.2	36.6, 0.4	36.6, 0.6
180 min	7.434, 0.013	7.463, 0.012	169.5, 7.4	148.0, 6.2	37.7, 0.5	36.9, 0.6
210 min	7.416, 0.009	7.457, 0.013	144.2, 8.2	140.6, 8.4	36.6, 0.5	36.8, 0.3
240 min	7.431, 0.014	7.440, 0.012	161.7, 8.6	145.4, 4.4	37.0, 0.3	37.6, 0.3
Resting	98.3, 1.4	95.8, 3.7	9.8, 0.4	9.8	46, 1.0	44, 1.1
Infusion for 30 minutes	92.2, 3.5*	100.6, 4.2	11.6, 0.3†	9.1, 0.5	47, 1.1	45, 1.0
5 min post haemorrhage	93.6, 3.2	101.8, 3.9	11.2, 0.4†	9.4, 0.4	45, 0.4	45, 1.3
30 min	101.5, 8.3	100.0, 1.9	11.4, 0.2†	9.1, 0.4	48, 0.7	46, 0.3
60 min	111.5, 6.3	99.3, 2.8	11.2, 0.6	9.3, 0.3	47, 1.0	45, 1.3
90 min	111.0, 5.7	97.5, 3.5	11.2, 0.5	9.7, 0.5	44, 1.2	44, 1.7
120 min	109.7, 4.0	102.5, 4.1	11.3, 0.6	8.9, 0.3	45, 1.1	44, 1.7
150 min	107.2, 2.0	105.2, 3.7	11.3, 0.5	9.2, 0.5	46, 1.4	46, 1.1
180 min	99.3, 2.0	103.8, 1.8	10.9, 0.5	9.6, 0.4	47, 0.9	46, 1.1
210 min	95.8, 1.7	97.7, 0.7	10.8, 0.4†	9.2, 0.2	50, 0.7	48, 0.8
240 mins	97.5, 1.3	94.5, 1.8	10.9, 0.4†	9.0, 0.2	49, 0.9	50, 1.1

*p < 0.05 (unpaired *t* test)

†p < 0.01 (unpaired *t* test)

‡significant difference between the two groups

Student's unpaired *t* tests. Student's tests were used where a priori hypotheses were recorded before the experiments were conducted; Scheffe tests, being more rigorous and less likely to show up differences, were used for all other comparisons. Significance was taken as *p* < 0.05.

Results

Physiological variables

Table 2 shows the physiological variables in the two groups of animals. There was not a significant difference in the PaO₂, PaCO₂, pH or the haematocrit between the two groups during the course of the experiments. Thirty minutes following the start of the infusion the MABP in the nimodipine group had fallen to 92.2, 3.5 mmHg compared with 100.6, 4.2 mmHg in the vehicle group. This difference was statistically significant (*p* < 0.05, unpaired *t* test) and remained so until 30 minutes after the production of the ICH. Thirty minutes following commencement of the infusion the arterial plasma glucose concentration had risen significantly (*p* < 0.01, unpaired *t* test) to 11.6, 0.3 mmol/l in the nimodipine group compared with 9.1, 0.5 mmol/l in the vehicle group. The difference between the two groups remained significant until the end of the experiment.

Neuropathological findings

Perfusion fixation was excellent in all animals, as shown by the absence of intravascular blood, good neuronal morphology and the lack of cytological artefacts such as "dark cell" and "hydropic cell"

changes. All the brains examined had an intracerebral haematoma present in the ipsilateral caudate nucleus, although the configuration varied from animal to animal. Three animals in each group had a small haematoma overlying the ipsilateral cerebral cortex adjacent to the needle tract. No animal in either group had a haematoma in the contralateral cerebral hemisphere or overlying the contralateral cerebral cortex.

Each of the brains examined had some degree of ischaemic damage adjacent to the needle track in the ipsilateral cerebral cortex, the degree of damage being similar in both groups. However the amount of cortical damage was greatly increased in the six animals that had cortical haematomas present. Around each intracaudate haematoma was a zone of ischaemic damage varying in shape according to the configuration of the haematoma. No animal in either group had evidence of ischaemic damage in the contralateral cerebral hemisphere. Figure 1 shows the typical appearance of an animal pre-treated with nimodipine and one receiving vehicle.

Quantification of the volume of ischaemic damage from the brain maps (fig 2) showed that in the vehicle group 15 ± 4% of the ipsilateral caudate nucleus showed signs of ischaemic damage compared with only 7 ± 2% in the nimodipine group, a difference of 113% (table 3). Despite this definite trend, there was some variability in the volume of ischaemic damage from animal to animal. This resulted in the difference in mean values not being statistically significant (*p* > 0.05 < 0.1, unpaired *t* test). However, quantification of the area of ischaemic damage at each

Fig 1 Histological sections of the ipsilateral cerebral hemisphere at the level of the caudate nucleus. The sections show the typical appearance of an animal pre-treated with vehicle (a) and one with nimodipine (b). Present in each caudate nucleus is a haematoma, although its visible size in these illustrations is reduced by the decolourising effect of FAM. Note the area of ischaemia around the haematoma ($H \& E \times 10$).

area of the coronal levels (fig 3) revealed that anteriorly at level 1 (caudate nucleus), at which damage was maximum, there was a significant reduction in the amount of ischaemic damage in the nimodipine group compared to the vehicle group ($p < 0.05$, unpaired t test). Similar differences were seen in the volume of ischaemic damage in the cerebral cortex and cerebral hemisphere between the two groups (table 3), but these differences were not significant.

ICP Responses and brain specific gravity measurements

The changes in ICP in the two groups of animals during the course of the experiments are summarised in table 4. Before the start of infusion of nimodipine or vehicle the resting ICP was the same in both groups (4.0 and 4.1 mmHg respectively). After 30 minutes' infusion of nimodipine or vehicle, the ICP did not alter in either group. Immediately following production of the intracerebral haemorrhage there was a significant rise in ICP in both groups of animals to reach 41.6 mmHg in the nimodipine group and 44.6 mmHg in the vehicle group ($p < 0.01$, unpaired t test). ICP in both groups fell over the next 30 minutes before rising again but never attaining the level recorded immediately after production of the haemorrhage. At the end of the 4-hour period ICP in both groups remained significantly above resting levels ($p < 0.05$, unpaired t test). At no time was there a significant difference in ICP between the two groups.

Table 5 summarises the brain specific gravity (SG)

measurements in the two groups of animals. The SG measurements did not differ significantly between the two groups of animals at 4 hours following production of the intracerebral haemorrhage. None of the measurements were of an order which suggested that oedema formation had taken place.

Cerebral blood flow measurements from the ^{14}C IAP autoradiographs

Figure 4 shows the autoradiographic appearance of an animal receiving nimodipine and of one receiving vehicle, 4 hours following the production of an intracerebral haemorrhage.

(1) *Discrete anatomical loci* Table 6 shows the values of rCBF measured in 21 pre-determined neuroanatomical loci in both groups of animals. All measurements were made 4 hours following production of the intracerebral haemorrhage. Because of its size and because it was the site of the lesion, the caudate nucleus was divided into three regions: ante-

Table 3 Volume per cent of ischaemic damage ($N = 12$: mean values, SEM)

Volume %	Ipsilateral	
	Nimodipine	Vehicle
Cerebral hemisphere	2.6, 0.9	4.1, 1.3
Cerebral cortex	4.3, 1.7	6.0, 3.0
Caudate nucleus	7.2, 1.7	15.4, 3.8

Only ipsilateral structures are considered, contralateral structures being free from damage.

Fig 2 Diagram to show the extent of intracerebral haemorrhage and resulting ischaemic damage in a vehicle-treated animal (a) and one receiving nimodipine (b). In both groups the haematoma is confined mainly to the caudate nucleus, surrounded in turn by a zone of ischaemic damage. The dark areas represent the extent of the haematoma, the stippled area the extent of ischaemic damage.

rior, middle and posterior, areas of high and low flow being measured in each region. The rCBF in the ipsilateral caudate nucleus of both groups was reduced compared with that in the corresponding contralateral caudate nucleus. The reduction was significant at three levels (anterior low, middle low and posterior low) in the vehicle group, but at only two levels (anterior low and middle low) in the nimodipine group. In addition there was a trend for the reduction in rCBF in the nimodipine group to be less than in the vehicle group, in areas of both high and low flows. Anteriorly in areas of low flow the ipsilateral caudate nucleus of the nimodipine group had an rCBF of $70.17 \pm 6 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ compared with only $41.11 \pm 2 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ in the vehicle

Table 4 Intracranial pressure measurements in the two groups of animals during the course of the experiments.

Intracranial pressure (N = 12: mean values, SEM (mmHg))		
	Nimodipine	Vehicle
Resting	4, 0.4	4, 1.0
30 minutes of infusion	4, 1.0	4, 1.0
Production of haematoma	41, 6.0†	44, 6.0†
30 min post haematoma	16, 4.0	19, 4.0
60 min	17, 3.0	20, 3.0
90 min	19, 2.0	21, 3.6
120 min	22, 3.0	23, 2.0
150 min	23, 2.0	24, 1.2
180 min	20, 4.0	25, 2.4
210 min	22, 2.0	26, 4.0
240 min	21, 7.0*	25, 6.0*

*p < 0.05 (unpaired t test)

†p < 0.01 (unpaired t test)

†significant differences compared to the corresponding resting ICP

Fig 3 Area of ischaemic damage at each of the coronal levels. *significant difference between the groups ($p < 0.05$, unpaired t test). (All values, SEM).

group, a difference of 70.7%. Similar differences existed more posteriorly in the caudate nucleus (60, 15.6 ml 100 g⁻¹ min⁻¹ in the nimodipine group compared with 42, 12.8 ml 100 g⁻¹ min⁻¹ in the vehicle group, a 42.8% difference). Similarly rCBF in the ipsilateral frontal cortex of the nimodipine group was 150, 31.5 ml 100 g⁻¹ min⁻¹ compared to 117, 29.0 ml 100 g⁻¹ min⁻¹ in the vehicle group (a difference of 28%). However, owing to the high degree of variability in the two groups of animals, there were not

any significant differences between the two groups in the rCBF values in the caudate nucleus ($p > 0.05 < 0.1$, unpaired t test). Differences in the rCBF values between the two groups were also seen in the cingulate and frontal cortices but again did not reach significance (Scheffe test).

(2) *Range of flows* The range of flow values was analysed by measuring and calculating the percentages of each caudate nucleus, cerebral hemisphere and cerebral cortex having an rCBF within a particular range, as previously described. These results are shown graphically in fig 5. As with rCBF values measured at the pre-determined neuroanatomical loci, the overall picture was for structures ipsilateral to the lesion in the nimodipine group to have higher rCBF values than the corresponding side in the vehicle group. Thus 7.4, 3.2% of the ipsilateral caudate nucleus in the vehicle group had a flow less than 20 ml 100 g⁻¹ min⁻¹ compared with 4.9, 1.8% in the nimodipine group. In the vehicle group 7.5, 2.5% of the ipsilateral cerebral hemisphere had a flow less than 20 ml 100 g⁻¹ min⁻¹ compared with 3.5, 1.4% of the same side in the nimodipine group. In the cerebral cortex the values were similar in both groups: 3.8, 1.9% (vehicle) and 3.5, 1.1% (nimodipine).

Cortical blood flow measurements using the H⁺ clearance technique

Table 7 summarises changes in rCBF in the adjacent frontal cortex in both groups of animals during the course of the experiments using the H⁺ clearance technique. Measurement of rCBF at rest showed that there was not a significant difference between the two groups of animals (either ipsi- or contralaterally). Thirty minutes following the start of the infusion rCBF had risen significantly in the ipsilateral frontal cortex of the nimodipine group (69, 3.6 ml 100 g⁻¹ min⁻¹) compared with the same side in the vehicle group (51, 5.7 ml 100 g⁻¹ min⁻¹) ($p < 0.05$, unpaired t test).

Following production of the intracerebral haemorrhage there was a reduction in cortical rCBF bilaterally in both groups, although the reduction was

Table 5 Regional specific gravity measurements in the two groups of animals four hours following production of the intracerebral haematoma

	Regional specific gravity measurements (N = 12: mean values, SEM)			
	Nimodipine		Vehicle	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Frontal cortex	1.0610 0.0060	1.0531 0.0050	1.0487 0.0030	1.0526 0.0019
Sensorimotor cortex	1.0489 0.0016	1.0509 0.0028	1.0515 0.0015	1.0541 0.0029
Caudate nucleus	1.0503 0.0014	1.0463 0.0028	1.0480 0.0010	1.0530 0.0018
Occipital cortex	1.0576 0.0021	1.0533 0.0012	1.0519 0.0031	1.0491 0.0006

Fig 4 Autoradiograph at the level of the ipsilateral caudate nucleus in an animal receiving vehicle (a) and one receiving nimodipine (b). There is a reduction in rCBF in the ipsilateral caudate nucleus in both animals but more so in the animal receiving vehicle. The pale area represents reduced regional cerebral blood flow.

greater in the ipsilateral frontal cortex of the nimodipine group (69, 3.6 ml reducing to 35, 5.6 ml $100 \text{ g}^{-1} \text{ min}^{-1}$) compared with the control group (51, 5.7 ml reducing to 42, 11.5 ml $100 \text{ g}^{-1} \text{ min}^{-1}$). The reduction in rCBF was significant in the nimodipine group ($p < 0.01$, unpaired t test) but not in the vehicle group. The maximum reduction in rCBF in the ipsilateral frontal cortex of the nimodipine group occurred within 5 minutes following production of the intracerebral haemorrhage, while in the vehicle group maximum reduction in rCBF was not seen until 30 minutes. Following this period of maximum reduction, the rCBF on the ipsilateral side in both groups rose over the remainder of the experimental period but not significantly above resting values.

In the contralateral frontal cortex following a reduction in rCBF at the time of the intracerebral haemorrhage, the rCBF gradually rose again in both groups. At the end of the experimental period, rCBF in the contralateral frontal cortex was 63, 7.2 ml $100 \text{ g}^{-1} \text{ min}^{-1}$ in the nimodipine group and 56, 7.4 ml $100 \text{ g}^{-1} \text{ min}^{-1}$ in the vehicle group.

Measurement of BBB permeability from the $^{14}\text{C}\alpha$ AIB autoradiographs

Table 8 shows the values of the capillary transfer constant (K_1) for $^{14}\text{C}\alpha$ AIB measured at 17 discrete neuroanatomically determined loci. In general the K_1 values were higher in both contralateral and ipsilateral structures of the nimodipine group than in the vehicle group. The increase in K_1 was significant in the ipsilateral hippocampus of the nimodipine group ($7.5, 1.0 \text{ ml g}^{-1} \text{ min}^{-1} \times 10^3$) compared with the vehicle group ($3.6, 0.3 \text{ ml g}^{-1} \text{ min}^{-1} \times 10^3$), and

Table 6 Analysis of regional cerebral blood flow

21 areas measured bilaterally, $N = 12$: mean values, SEM, (ml $100 \text{ g}^{-1} \text{ min}^{-1}$)				
	Nimodipine		Vehicle	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Frontal cortex	166, 22.8	150, 31.5	121, 15.3	117, 29.0
Cingulate cortex	178, 38.4	146, 25.3*	131, 22.0	96, 12.0*
Caudate nucleus				
Anterior —High	148, 24.2	106, 25.0	135, 17.4	97, 16.0
—Low	126, 15.8	70, 17.6*	114, 13.7	41, 11.2*
Middle —High	141, 10.9	131, 29.3	137, 14.4	87, 20.1
—Low	117, 12.2	47, 8.9*	111, 17.0	32, 5.1*
Posterior —High	135, 16.9	122, 20.3	135, 15.5	88, 21.3
—Low	88, 10.2	60, 15.6	93, 15.4	42, 12.8*
Hypothalamus	114, 11.9	114, 10.3	107, 17.3	93, 16.7
Sensorimotor cortex	163, 25.8	149, 27.3	139, 16.8	122, 22.1
Parietal cortex	199, 45.0	209, 68.5	127, 20.8	127, 25.1
Lateral geniculate	154, 43.4	144, 35.0	124, 26.6	114, 24.3
Thalamus	141, 15.7	131, 19.6	128, 18.5	123, 19.9
Internal capsule	55, 7.1	55, 8.8	56, 8.3	51, 5.6
Corpus callosum	55, 20.5	61, 24.4	58, 7.6	51, 5.6
Hippocampus	141, 58.0	93, 16.6	106, 15.0	114, 20.1
Red nucleus	118, 13.0	115, 12.7	121, 22.5	118, 19.3
Superior colliculus	143, 19.3	147, 18.6	147, 14.6	132, 20.5
Visual cortex	171, 18.3	156, 29.9	157, 30.0	174, 44.7
Pons	98, 10.9	90, 9.3	85, 9.0	98, 12.8
Cerebellum	88, 7.7	92, 10.1	91, 7.2	86, 10.0

*significant side-to side difference between structures in the same group
 $p < 0.05$ Unpaired t test

Fig 5 Percentage of caudate nucleus, cerebral hemisphere, and cerebral cortex having an rCBF within the stated limits. Flows are in $\text{ml } 100 \text{ g}^{-1} \text{ min}^{-1}$ in flow ranges of $10 \text{ ml } 100 \text{ g}^{-1} \text{ min}^{-1}$. Open bars represent vehicle treated animals, while black bars represent nimodipine treated animals.

also in the contralateral hippocampus of the nimodipine group ($6.9, 1.4 \text{ ml g}^{-1} \text{ min}^{-1} \times 10^3$) compared with the vehicle group ($3.5, 0.2 \text{ ml gm}^{-1} \text{ min}^{-1} \times 10^3$) ($p < 0.01$, Scheffe test).

Discussion

Animals in this experimental series were pre-treated with either nimodipine ($1 \mu\text{g kg}^{-1} \text{ min}^{-1}$) or vehicle prior to the production of the intracerebral haemorrhage. Although the relevance of pre-treatment may be questioned, we believe that there are clinical situations in which pre-treatment is possible. Evidence from several animal models of cerebral ischaemia suggests that the residual cerebral blood flow following the onset of ischaemia is important in determining the degree of ischaemic damage.²⁸⁻³² Increasing the rCBF after the onset of ischaemia may

therefore prevent the development of further ischaemic damage in the penumbra zone. Several authors have reported that nimodipine is capable of maintaining rCBF following cerebrovascular occlusion and of preventing the occurrence of delayed hypoperfusion.^{15 33 34} Steen^{35 36} in a canine model reported a significant increase in cerebral blood flow in animals treated with nimodipine either before or immediately following 10 minutes of complete cerebral ischaemia, when compared with controls. Following restoration of the cerebral circulation, repeated measurements of cerebral blood flow were made for up to 2 hours. Cerebral blood flow in the animals receiving nimodipine remained significantly higher than in the controls. Assessment of the dogs neurologically 48 hours following the ischaemic episode revealed a significant improvement in the neurological outcome in the group pre-treated with

Table 7 Regional cerebral blood flow in frontal cortex measured using H^+ clearance ($N = 12$: mean values, SEM ($ml\ 100\ g^{-1}\ min^{-1}$))

	Vehicle		Nimodipine	
	Contra-lateral	Ipsi-lateral	Contra-lateral	Ipsi-lateral
Resting	56, 6.6	66, 9.1	54, 3.4	55, 4.9
30 min infusion	66, 6.5*	69, 3.6*	49, 3.8	51, 5.7
5 min post haematoma	57, 2.5	35, 5.6†	36, 7.2	42, 11.5
30 min	56, 7.4	39, 5.0	40, 7.2	33, 2.7
60 min	65, 9.2	46, 8.4	43, 7.2	40, 7.6
90 min	59, 6.9	47, 4.2	46, 7.5	46, 12.8
120 min	62, 5.9	51, 4.6	47, 6.8	51, 14.4
150 min	57, 6.7	50, 3.9	50, 8.5	46, 7.5
180 min	61, 5.1	53, 3.9	50, 6.7	51, 10.9
210 min	61, 5.4	47, 3.1	59, 7.6	56, 9.5
240 min	63, 7.2	54, 3.3	56, 7.4	53, 6.0

†Significant difference when compared with the corresponding previous value in the same side, same group.

p < 0.01 (unpaired t test)

*Significant difference between the groups.

p < 0.05 (unpaired t test)

nimodipine when compared to the control group. However, in the group given nimodipine in the post-ischaemic period the results were equivocal.³⁶ A further series of experiments using a primate model of complete cerebral ischaemia³⁷ showed that nimodipine initiated in the post-ischaemic period significantly improved neurological outcome at 96 hours when compared with a control group.

Our choice of $1\ \mu g\ kg^{-1}\ min^{-1}$ is based on previous work in this laboratory¹² indicating that this was the optimum dosage to reduce ischaemic damage, in a rat model, of focal cerebral ischaemia. Mohamed *et al*¹² showed that higher dosages of nimodipine led to an elevated plasma glucose and fall in the mean arterial blood pressure (MABP), and would therefore be

unlikely to give additional benefits by virtue of increased cerebral blood flow. The transient fall in the MABP following infusion of nimodipine, in the present study, was of similar degree to that reported by other authors^{12 14 38} as was the rise in the plasma arterial concentration of glucose.

Although we used a constant volume of blood (100 μl), introduced at a standard pressure (100 mmHg), there was some variability in the configuration of the resulting haematomas. The size and extent of the lesions were similar to those reported by Nath *et al*, using 100 μl of blood in a similar model.⁷ The variation in configuration of the haematomas may have been responsible for the variability in rCBF values measured in the different loci from animal to animal. Nevertheless, measurement of rCBF from the ¹⁴C IAP autoradiographs 4 hours after the insult showed a distinct trend for animals pre-treated with nimodipine to have higher rCBF values ipsilaterally and contralaterally than those receiving vehicle. The difference in rCBF between the two groups was most marked in the ipsilateral caudate nucleus in areas of low flow, although rCBF was reduced in both groups ipsilaterally compared with the contralateral side. The reduction in rCBF was attenuated in those animals receiving nimodipine compared with those receiving vehicle. These findings are in keeping with those of other authors³³⁻³⁶ who reported that the occurrence of delayed hypoperfusion following various periods of ischaemia in animal models was either reduced in severity or abolished following the administration of nimodipine. This reduction of delayed hypoperfusion may be due to the direct effect of nimodipine on the cerebral blood vessels, as was suggested by Haws.³⁹

Table 8 Analysis of capillary transfer constant (K_1) for 14C- AIB areas measured bilaterally ($N = 12$: mean values, SEM ($ml\ g^{-1}\ min^{-1} \times 10^3$))

Brain region	Nimodipine		Vehicle	
	Contralateral	Ipsilateral	Contralateral	Ipsilateral
Frontal cortex	4.5, 0.3	4.7, 0.6	3.4, 0.2	3.9, 0.2
Cingulate cortex	4.0, 0.6	4.1, 0.5	3.7, 0.3	3.8, 0.2
Caudate nucleus				
Anterior				
—High	3.3, 0.4	5.0, 0.8	3.4, 0.2	5.0, 0.5
—Low	3.3, 0.5	4.0, 0.5	3.4, 0.2	3.7, 0.2
Middle				
—High	3.6, 0.4	5.9, 1.2	3.1, 0.1	5.0, 0.4
—Low	3.5, 0.4	4.5, 0.9	3.2, 0.2	4.3, 0.4
Posterior				
—High	3.2, 0.4	5.3, 0.8	3.2, 0.2	4.6, 0.5
—Low	3.3, 0.4	3.5, 0.3	3.1, 0.1	4.2, 0.4
Hypothalamus	4.0, 0.4	3.9, 0.5	3.4, 0.2	4.8, 1.1
Sensorimotor cortex	4.0, 0.2	3.9, 0.3	3.4, 0.2	3.8, 0.3
Parietal cortex	4.2, 0.3	3.9, 0.4	8.6, 4.7	8.8, 4.2
Thalamus	3.6, 0.4	3.5, 0.4	3.4, 0.2	3.8, 0.5
Hippocampus	6.9, 1.4†	7.5, 1.0†	3.5, 0.2	3.6, 0.3
Superior colliculus	6.7, 2.2	5.0, 1.6	3.6, 0.2	3.5, 0.1
Visual cortex	4.1, 0.2	3.8, 0.4	3.4, 0.2	3.6, 0.3
Pons	3.9, 0.6	3.9, 0.4	3.3, 0.2	3.5, 0.2
Cerebellum	3.4, 0.4	3.5, 0.4	3.4, 0.2	3.4, 0.2

†p < 0.01 (Scheffe test).

‡Significant difference between the same side in both groups

Fig 6 Typical appearance of an autoradiograph obtained using ^{14}C - α AIB. Naked eye appearances are similar in both the vehicle treated (a) and nimodipine (b).

In addition to measuring rCBF using autoradiographic techniques, it was possible using the H^+ clearance technique to obtain serial rCBF measurements from the overlying frontal cortex. The significant rise in rCBF seen following infusion of nimodipine is in keeping with the finding of other authors.^{10–12} Surprisingly, following production of the intracerebral haemorrhage there was a significant reduction in the rCBF in the ipsilateral frontal cortex of the nimodipine group ($p < 0.01$, unpaired t test) but not in the vehicle group. This may have been due to an “inserve steal” phenomenon^{38,40} in the nimodipine group, whereby rCBF in underperfused areas (that is the ipsilateral caudate nucleus) is preserved at the expense of rCBF in relatively normal areas where CBF was measured with H_2 clearance (in this case, the ipsilateral frontal cortex). Alternatively, the reduction in rCBF may appear greater in the nimodipine group because the rCBF prior to the production of the haematoma was higher than in the vehicle group.

Following the significant reduction in rCBF in the ipsilateral frontal cortex of the nimodipine group

(maximum at 5 minutes), rCBF rose rapidly compared to that of the vehicle group (maximum reduction at 30 minutes), suggesting that nimodipine prevented the occurrence of delayed hypoperfusion. Steen^{35,36} pointed out that the hypoperfusion state generally starts 15 to 30 minutes after the ischaemic episode. This would be supported by the maximum reduction in rCBF values in the vehicle group occurring 30 minutes following production of the haematoma.

The changes in intracranial pressure (ICP) following production of the intracerebral haemorrhage were of similar magnitude to those reported previously.⁶ Both Gaab⁴⁰ and Guggiani⁴¹ have previously suggested that nimodipine may elevate ICP by virtue of its capacity to increase rCBF. However, their studies were performed on patients who had sustained severe head injuries and the ICP was measured using epidural pressure transducers rather than directly from the lateral ventricle, as in our series. There was not a significant difference in the ICP between the two groups at any time during the course of the experiments.

The trend for the nimodipine animals to have higher rCBF values was complemented by a reduction in the volume of pathological ischaemic damage seen in the ipsilateral caudate nucleus (especially anteriorly) in the nimodipine group compared to the vehicle group. A similar reduction in the amount of pathological ischaemic damage has recently been reported by us using a 50 μl model of intracerebral haemorrhage.⁴² Nimodipine is thought to be capable of reducing the amount of ischaemic damage by acting in two ways: firstly, by relaxing the smooth muscle of the cerebral vasculature, vessel diameter is increased with a resulting increase in rCBF thereby preventing the occurrence of delayed hypoperfusion.^{10,12} The second possibility, a blockage of the entry of Ca^{2+} into ischaemic cells and hence the prevention of the metabolic cascade that would be initiated in areas of ischaemia, remains speculative.⁴³

There was not a significant difference in the brain specific gravity (SG) measurements between the two groups of animals. Most of the ischaemic damage and reduction in rCBF values were confined to the ipsilateral caudate nucleus, rCBF in other areas being above levels sufficient to cause ischaemia and hence oedema formation. The ipsilateral caudate nucleus was occupied mainly by the intracerebral haematoma, and tissue from this area may have been heavier due to extravasated protein from the haematoma,⁴⁴ thereby masking any reduction in specific gravity due to oedema formation.

The increase in K_1 of ^{14}C α AIB may indicate an increase in BBB permeability in the group receiving nimodipine, or may reflect the fact that the amount of

ischaemic damage was less in this group, a greater amount of functioning tissue being available to take up the ^{14}C AIB. The value of K_1 depends on several factors;⁴⁵ these include the permeability coefficient of ^{14}C AIB, the surface area of the brain capillaries, the distribution volume of the test material in the blood, and the velocity of blood flow. Under normal circumstances ^{14}C AIB exchanges slowly across capillaries and the BBB permeability can be equated to the K_1 in the following manner:⁴⁵

$$PS = -F \ln[1 - (K_1/F)]$$

where PS is the product of the permeability and surface area of the capillaries, and F is the blood flow. In our experiments K_1/F was small (<0.01) and therefore $PS = K_1$. Using this theoretical model with the range of rCBF values recorded in our experiments, analysis of the data showed that the increase in K_1 seen in the nimodipine group cannot be explained solely by the greater rCBF. Some other factor must be responsible, possibly increased uptake in the nimodipine group due to preservation of functioning tissue.

In conclusion, our experiments have shown that following an intracerebral haemorrhage pretreatment with nimodipine tended to attenuate the reduction in CBF that was seen at 4 hours, especially in the vicinity of the haematoma, and to reduce the amount of ischaemic damage. These findings suggest further experimental studies are indicated using nimodipine following the production of an intracerebral haemorrhage, particularly if the variability can be reduced. Nimodipine may also be of benefit following subarachnoid haemorrhage from ruptured intracranial aneurysms when it would be possible to effectively "pre-treat" the patient prior to the onset of delayed cerebral vasospasm, the aim being to maintain cerebral blood flow and thereby reduce the incidence of delayed cerebral ischaemia, as suggested previously from animal^{18,19} and human studies.^{16,17} Furthermore, such pretreatment may protect the brain if a further haemorrhage occurs before its cause can be treated surgically.

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Correction

In the article by Sinar E J, Mendelow A D, Graham D I, Teasdale G M. Experimental intracerebral haemorrhage: the effect of nimodipine pretreatment (*J Neurol Neurosurg Psychiatry* 1988;51:651-62) there were important errors in tables 2 and 6. Table 2 should have been as follows:

Table 2 *Physiological variables in the two groups (N = 48: mean values, SEM)*

	Arterial pH		Arterial PaO ₂ mmHg		Arterial PaCO ₂ mmHg	
	Nimodipine	Vehicle	Nimodipine	Vehicle	Nimodipine	Vehicle
Resting	7.424, 0.007	7.420, 0.022	145.9, 7.7	140.2, 12.2	38.9, 0.4	37.1, 0.9
Infusion for 30 minutes	7.428, 0.014	7.407, 0.035	148.5, 7.0	137.2, 9.2	37.7, 0.7	36.6, 1.1
5 min post haemorrhage	7.434, 0.009	7.462, 0.018	160.0, 5.6	151.6, 7.3	37.6, 0.8	37.6, 0.5
30 min	7.429, 0.009	7.448, 0.020	162.6, 6.1	144.7, 6.6	38.5, 0.5	37.7, 0.6
60 min	7.438, 0.012	7.438, 0.019	162.8, 5.2	141.0, 10.5	37.6, 0.6	38.0, 0.8
90 min	7.441, 0.013	7.436, 0.026	160.7, 4.2	145.9, 6.8	37.2, 0.7	37.9, 0.7
120 min	7.400, 0.020	7.436, 0.022	163.2, 4.9	147.5, 9.2	37.3, 0.8	36.8, 0.8
150 min	7.399, 0.021	7.459, 0.025	170.2, 5.9	146.7, 8.2	36.6, 0.4	36.6, 0.6
180 min	7.434, 0.013	7.463, 0.012	169.5, 7.4	148.0, 6.2	37.7, 0.5	36.9, 0.6
210 min	7.426, 0.009	7.457, 0.013	144.2, 8.2	140.6, 8.4	36.6, 0.5	36.8, 0.3
240 min	7.431, 0.014	7.440, 0.012	161.7, 8.6	145.4, 4.4	37.0, 0.3	37.6, 0.3

	Mean Arterial BPmmHg		Arterial Plasma Glucose mmol/l		Arterial Haematocrit %	
	Nimodipine	Vehicle	Nimodipine	Vehicle	Nimodipine	Vehicle
Resting	98.3, 1.4	95.8, 3.7	9.8, 0.4	9.8, 0.3	46, 1.0	44, 1.1
Infusion for 30 minutes	92.2, 3.5*	100.6, 4.2	11.6, 0.3†	9.1, 0.5	47, 1.1	45, 1.0
5 min post haemorrhage	93.6, 3.2*	101.8, 3.9	11.2, 0.4†	9.4, 0.4	45, 0.4	45, 1.3
30 min	101.5, 8.3	100.0, 1.9	11.4, 0.2†	9.1, 0.4	48, 0.7	46, 0.3
60 min	111.5, 6.3	99.3, 2.8	11.2, 0.6	9.3, 0.3	47, 1.0	45, 1.3
90 min	111.0, 5.7	97.5, 3.5	11.2, 0.5	9.7, 0.5	44, 1.2	44, 1.7
120 min	109.7, 4.0	102.5, 4.1	11.3, 0.6	8.9, 0.3	45, 1.1	44, 1.7
150 min	107.2, 2.0	105.2, 3.7	11.3, 0.5	9.2, 0.5	46, 1.4	46, 1.1
180 min	99.3, 2.0	103.8, 1.8	10.9, 0.5	9.6, 0.4	47, 0.9	46, 1.1
210 min	95.8, 1.7	97.7, 0.7	10.8, 0.4†	9.2, 0.2	50, 0.7	48, 0.8
240 mins	97.5, 1.3	94.5, 1.8	10.9, 0.4†	9.0, 0.2	49, 0.9	50, 1.1

*p < 0.05 (unpaired *t* test)

†p < 0.01 (unpaired *t* test)

*, †significant difference between the two groups

In table 6 the column headings Ipsilateral and Contralateral should be transposed.

Table 6 *Analysis of regional cerebral blood flow*

	21 areas measured bilaterally, N = 12: mean values, SEM, (ml 100 g ⁻¹ min ⁻¹)			
	Nimodipine		Vehicle	
	Contralateral	Ipsilateral	Contralateral	Ipsilateral
Frontal cortex	166, 22.8	150, 31.5	121, 15.3	117, 29.0
Cingulate cortex	178, 38.4	146, 25.3*	131, 22.0	96, 12.0*
Caudate nucleus				
Anterior —High	148, 24.2	106, 25.0	135, 17.4	97, 16.0
—Low	126, 15.8	70, 17.6*	114, 13.7	41, 11.2*
Middle —High	141, 10.9	131, 29.3	137, 14.4	87, 20.1
—Low	117, 12.2	47, 8.9*	111, 17.0	32, 5.1*
Posterior —High	135, 16.9	122, 20.3	135, 15.5	88, 21.3
—Low	88, 10.2	60, 15.6	93, 15.4	42, 12.8*
Hypothalamus	114, 11.9	114, 10.3	107, 17.3	93, 16.7
Sensorimotor cortex	163, 25.8	149, 27.3	139, 16.8	122, 22.1
Parietal cortex	199, 45.0	209, 68.5	127, 20.8	127, 25.1
Lateral geniculate	154, 43.4	144, 35.0	124, 26.6	114, 24.3
Thalamus	141, 15.7	131, 19.6	128, 18.5	123, 19.9
Internal capsule	55, 7.1	55, 8.8	56, 8.3	51, 5.6
Corpus callosum	55, 20.5	61, 24.4	58, 7.6	51, 5.6
Hippocampus	141, 58.0	93, 16.6	106, 15.0	114, 20.1
Red nucleus	118, 13.0	115, 12.7	121, 22.5	118, 19.3
Superior colliculus	143, 19.3	147, 18.6	147, 14.6	132, 20.5
Visual cortex	171, 18.3	156, 29.9	157, 30.0	174, 44.7
Pons	98, 10.9	90, 9.3	85, 9.0	98, 12.8
Cerebellum	88, 7.7	92, 10.1	91, 7.2	86, 10.0

*significant side-to-side difference between structures in the same group

p < 0.05 Unpaired *t* test