We studied the effects of nifedipine, chlorpromazine, reserpine, furosemide, and thiopental on the mean arterial blood pressure, mean intracranial pressure, and cerebral perfusion pressure in 38 patients with increased intracranial pressure resulting from either hemorrhagic cerebrovascular disease or systemic hypertension. These agents are widely used in neurosurgical practice for the treatment of systemic hypertension. Patients were assigned to two groups on the basis of their mean intracranial pressure. Group I comprised 20 patients with a mean intracranial pressure of 20–40 mm Hg (moderately increased ICP group), and Group II consisted of 18 patients with a mean intracranial pressure of >40 mm Hg (severely increased ICP group). Nifedipine, chlorpromazine, and reserpine reduced mean arterial blood pressure by 18–20% in both groups (p<0.05 in each). In Group I these agents raised mean intracranial pressure by 10–35% and decreased cerebral perfusion pressure by 20–32% (p<0.05 for both), but in Group II these changes were more marked: mean intracranial pressure increased 38–64% and cerebral perfusion pressure decreased 40–54% (p<0.01 for both). Furosemide did not significantly reduce mean arterial blood pressure but slightly reduced mean intracranial pressure in each group. Thiopental reduced both mean arterial blood pressure and intracranial pressure in both groups. The effect on intracranial pressure was pronounced in Group II, in which mean arterial blood pressure fell by 18% (p<0.05) and mean intracranial pressure decreased 50% (p<0.01), whereas in Group I mean arterial blood pressure was reduced by 16% and mean intracranial pressure dropped 23% (p<0.05 in each). Our results suggest that barbiturates are preferable in the treatment of systemic hypertension in patients with increased, especially severely increased, intracranial pressure to agents that act as calcium channel blockers or α-adrenergic blockers. (Stroke 1988;19:314–321)

Systemic hypertension is frequently observed in patients with cerebrovascular diseases such as hypertensive intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction. These conditions are often associated with intracranial hypertension due to intracerebral hematoma, subarachnoid hematoma, hydrocephalus, or cerebral edema. Continuing systemic hypertension might not only augment the risk of rebleeding in hemorrhagic cerebrovascular diseases but might also increase the blood flow and blood volume in the damaged brain, resulting in more marked cerebral edema and intracranial hypertension. Thus, the management of systemic hypertension in patients with stroke is of great importance.

There have been reports that some hypotensive agents such as sodium nitroprusside and nitroglycerine can produce an increase in intracranial pressure (ICP) when intracranial compliance is decreased. We examined the effects of some hypotensive agents that are commonly used in neurosurgical practice on mean ICP, cerebral perfusion pressure (CPP), and mean arterial blood pressure (ABP) in patients with increased ICP resulting from both intracranial hemorrhage and systemic hypertension, and we attempted to clarify the risks and benefits of these agents when used in patients with raised ICP.

Subjects and Methods
There were 38 patients in the study: 22 with hypertensive intracerebral hemorrhage (15 thalamic and seven putaminal hemorrhages) and 16 with subarachnoid hemorrhage due to rupture of an intracranial aneurysm. The ruptured intracranial aneurysms were associated with the anterior communicating artery in eight cases, with the internal carotid artery in six, and with the basilar artery in two. Eighteen patients were men and 20 were women; their ages ranged from 43 to 72, with a mean age of 59 years. Their preoperative and/or postoperative ICP and ABP were continuously monitored as a guide to appropriate therapy, and the recordings showed both increased ICP (mean ICP >20 mm Hg) and systemic hypertension (systolic pressure >150 mm Hg, diastolic pressure >90 mm Hg, mean ABP >110 mm Hg). Written informed consent was obtained from each patient and/or family before the study.

ICP was recorded with an indwelling ventricular catheter placed in the frontal horn of the lateral ventricle, preferably on the right side, and connected to a pressure transducer. This method was based on that
described by Lundberg. ABP was recorded simultaneously through an intra-arterial catheter placed in the femoral artery or the dorsalis pedis artery. ICP and ABP were continuously monitored on a two-channel paper-chart recorder for between 6 and 72 (mean 28) hours. There were no complications (such as intracerebral hematoma or infection) attributable to the indwelling ventricular catheter. Increased ICP was usually treated by hyperventilation and/or osmotic agents except during the period of drug administration. If these treatments were ineffective in reducing ICP, continuous ventricular drainage was carried out. The ICP level for drainage was set at between 20 and 30 mm Hg.

Mean ABP was calculated as the diastolic pressure plus one-third the pulse pressure, and mean ICP was calculated the same way. CPP was determined as the difference between mean ABP and mean ICP.

The study protocol is shown in Table 1. Patients were assigned to two groups based on mean ICP. Group I comprised 20 patients with a mean ICP of 20–40 mm Hg (moderately increased ICP group). In Group II there were 18 patients with a mean ICP of >40 mm Hg (severely increased ICP group). The following hypotensive agents were administered during the course of the recordings, and their effect on mean ICP and CPP, as well as on mean ABP, were studied: 20 mg nifedipine administered sublingually, 20 mg chlorpromazine and 2 mg reserpine administered intramuscularly, and 20 mg furosemide and 20 mg/kg thiopental administered intravenously.

The results, expressed as mean±SEM, of mean ABP, mean ICP, and CPP in both groups in each study were calculated before drug administration and at 20, 40, 60, 80, 100, 120, 140, 160, and 180 minutes after drug administration. Analysis of variance was used for intergroup and intragroup comparisons. The differences were then subjected to the modified t-test according to the methods of Bonferroni. A value of p<0.05 was considered significant.

**Results**

The effects of nifedipine on mean ABP, mean ICP, and CPP in Groups I and II are shown in Figure 1. In both groups mean ABP began to decrease 20 minutes after nifedipine administration and persisted until 80 minutes. In Group I the greatest decrease of mean ABP was observed at 40 minutes, reaching 15% of the control level (p<0.05) and in Group II, 18% of the...
control \((p<0.05)\). The changes in mean ABP were nearly identical for Groups I and II. In both groups mean ICP began to increase 20 minutes after nifedipine administration and persisted until 80–120 minutes. In Group I the greatest effect was seen at 40 minutes, at which time mean ICP was increased by 14% of the control \((p<0.05)\); in Group II the effect was greatest at 60 minutes, showing an increase of 36% of the control.

**Figure 2.** Arterial blood pressure (ABP) and intracranial pressure (ICP) after nifedipine administration in a Group II patient. p.o., per os (sublingually).

**Figure 3.** Mean arterial blood pressure (MABP), mean intracranial pressure (MICP), and cerebral perfusion pressure (CPP) after chlorpromazine administration in Groups I and II. Ordinate: mean changes in MABP, MICP, and CPP compared with preadministration values, expressed as percent. Vertical bars represent ±SEM. I.M., intramuscularly. *\(p<0.05\), †\(p<0.01\), compared with preadministration values.
FIGURE 4. Arterial blood pressure (ABP) and intracranial pressure (ICP) after chlorpromazine administration in a Group II patient. I.M., intramuscularly.

FIGURE 5. Mean arterial blood pressure (MABP), mean intracranial pressure (MICP), and cerebral perfusion pressure (CPP) after reserpine administration in Groups I and II. Ordinate: mean changes in MABP, MICP, and CPP compared with preadministration values, expressed as percent. Vertical bars represent ±SEM. I.M., intramuscularly. *p<0.05, †p<0.01, compared with preadministration values.
value ($p < 0.01$). Thus, mean ICP increases were more pronounced in Group II than in Group I. CPP decreased in both groups, paralleling the decrease in mean ABP and the increase in mean ICP. In Group I the effect was maximal at 40 minutes, at which time CPP decreased by 20% of the control ($p < 0.05$); in Group II the effect was greatest at 60 minutes, with a CPP decrease of 40% of the control ($p < 0.01$). Figure 2 shows the ABP curve...
and the marked increase in ICP of a Group II patient after nifedipine administration.

The effects of chlorpromazine on mean ABP, mean ICP, and CPP in Groups I and II are shown in Figure 3. In both groups mean ABP began to decrease 20 minutes after chlorpromazine administration and persisted until 120–160 minutes. The greatest effect was observed at 60 minutes in both groups, at which time mean ABP decreased by 18–19% of the control value (p<0.05 in both groups). Mean ABP changes were nearly the same for Groups I and II. Mean ICP began to increase in both groups 20 minutes after chlorpromazine administration and persisted until 140–180 minutes; the greatest effect was observed at 40 minutes in both groups, when mean ICP increased by 35% of the control in Group I (p<0.01) and by 64% in Group II (p<0.01). Thus, the effects on ICP after chlorpromazine administration were more marked in Group II than in Group I. CPP decreased in both groups proportionate to the decreases in mean ABP and the increases in mean ICP. In Group I the effect was maximal at 40 minutes, at which time CPP decreased by 32% of the control (p<0.01); in Group II it was greatest at 60 minutes, with a 54% decrease compared with the control level (p<0.01). Figure 4 shows the ABP and ICP curves after chlorpromazine administration in a Group II patient. A marked postadministration increase is seen in ICP.

The effects of reserpine on mean ABP, mean ICP, and CPP in Groups I and II are shown in Figure 5. In both groups mean ABP began to decrease 60–100 minutes after reserpine administration and persisted for 40–80 minutes, with the greatest effect being a mean ABP decrease of 16–18% of the control level (p<0.05). The changes in mean ABP were nearly identical in Groups I and II. In both groups mean ICP began to increase 20–40 minutes after reserpine administration and persisted for 60 minutes. The effect was greatest at 100 minutes in both groups, when mean ICP increased by 35% of the control in Group I (p<0.01) and by 48% in Group II (p<0.01). Thus, mean ICP increases were more pronounced in Group II than in Group I. CPP in both groups decreased with the decreases in mean ABP and increases in mean ICP. The effects were maximal at 100 minutes in both groups, at which time CPP decreased by 25% in Group I (p<0.01) and by 45% in Group II (p<0.01) compared with the control values.

The effects of furosemide on mean ABP, mean ICP, and CPP in Groups I and II are shown in Figure 6. Mean ABP was not significantly changed in either group. Moreover, mean ICP was slightly but significantly decreased (p<0.05 in both groups). CPP also was not significantly changed after furosemide administration.

The effects of thiopental on mean ABP, mean ICP, and CPP in Groups I and II are shown in Figure 7. In both groups mean ABP and mean ICP decreased. Mean ABP began to decrease in both groups 20 minutes after initiation of thiopental administration, and the greatest effects were at 20–40 minutes, the decreases in mean ABP at these times being 16–18% of the control (p<0.05). The changes in mean ABP were nearly the same for Groups I and II. In both groups mean ICP began to decrease 20 minutes after initiation of thiopental administration and persisted for 60–160 minutes. The greatest effect was noticed at 40 minutes in Group I, at which time mean ICP decreased by 23% of the control (p<0.01), but at 60–80 minutes in Group II, with a decrease of 50% (p<0.01). Thus, the effect of thiopental on ICP was more pronounced in Group II than in Group I. However, mean ICP was slightly but significantly decreased (p<0.05 in both groups). CPP also was not significantly changed after thiopental administration.

Figure 8 shows marked decreases in ABP and ICP after thiopental administration in a Group II patient. Marked respiratory depression was observed; therefore, intubation and ventilation were carried out in patients receiving thiopental. Figure 8 shows marked decreases in ABP and ICP after thiopental administration in a Group II patient.

**Discussion**

Lundberg et al classified the increase of ICP as 1–10 mm Hg, normal; 11–20 mm Hg, slightly increased; 21–40 mm Hg, moderately increased; and >40 mm
Hg, severely increased. We used this classification and selected patients with a mean ICP of 20–40 mm Hg as having moderately increased ICP (Group I) and a mean ICP of >40 mm Hg as having severely increased ICP (Group II).

There are several mechanisms that compensate for the increase in ICP in the cranial cavity, such as shifts of brain tissue, increased absorption of cerebrospinal fluid, and extrusion of blood from the cerebral vascular bed. If the limits of these compensatory mechanisms are exceeded, ICP begins to increase, first slowly (the period of spatial compensation), then more rapidly (the period of spatial decompensation) as the intracranial volume increases. This pressure-volume curve approximates an exponential function and is termed compliance. In our present study, the Group I patients were in the period of spatial compensation, and the Group II patients were in the spatial decompensation period. Thus, in patients with intracranial hypertension, especially in those with severely increased ICP, compliance in the cranial cavity may be greatly reduced and, as a result, changes in the intracranial dynamics that increase ICP may elicit an enhanced secondary rise in ICP.

Of the many hypotensive agents used in clinical practice, we studied nifedipine, chlorpromazine, reserpine, furosemide, and thiopental. Calcium channel blockers have vasodilating actions, resulting in a reduction in ABP in patients with systemic hypertension. Clinical and experimental studies have shown that calcium channel blockers are also potent cerebral artery dilators, resulting in an increase in ICP. In our present study, in patients with increased ICP nifedipine-induced hypotension produced an increase in ICP and a decrease in CPP, and this tendency was disproportionately larger in Group II than in Group I. Chlorpromazine is sometimes used for the treatment of systemic hypertension in patients with brain damage probably resulting from excessive sympathetic discharges, causing intensive sympathetic vasoconstriction, because of this agent’s vasodilatory effects and hypotensive action. Chlorpromazine can also block the α-adrenergic receptors, resulting in a widespread vasodilatation affecting the cerebrovascular system as well. Reserpine also possesses advantages over most ganglionic blocking or adrenergic blocking drugs. In our present study, both chlorpromazine- and reserpine-induced hypotension produced a larger ICP increase and a larger CPP decrease than was induced by the other agents, and the ICP increase and the CPP decrease in Group II were disproportionately greater than those in Group I. Bauer and Reams claimed that the drugs that dilate the cerebral vessels may cause a rise in ICP, augmenting preexisting increases in ICP, diminishing CPP, and creating the potential risk for cerebral herniation. Furosemide is a powerful diuretic used in the treatment of systemic hypertension. The antihypertensive effect of this agent is considered to be related solely to its effect on blood volume. Clinically, furosemide is known to have an ICP-lowering effect, which may result from systemic dehydration and decreased formation of cerebrospinal fluid, and some direct effect on astroglial metabolism. In our present study, furosemide produced no significant reduction in ABP but caused a slight reduction in ICP. Our results suggest that furosemide alone has no beneficial effects in the treatment of systemic hypertension in patients with elevated ICP.

Barbiturates can produce general depression of the central nervous system. It is also well recognized that barbiturates are cardiovascular depressants and reduce increased ICP. It has been suggested that the decrease in ICP is due to the reduction in cerebral blood volume caused by the direct vasoconstrictive effect of barbiturates and that the decreased neural metabolic rates caused by barbiturates lead to a decrease in cerebral blood flow, resulting in a reduction of increased ICP. We have suggested that the mechanism of barbiturate-induced ICP reduction may be the alleviation of cerebral vasomotor instability by depression of the medullary vasomotor center. In the clinical setting, high-dose barbiturate anesthesia is often used to reduce increased ICP. In our present study, administration of thiopental produced a reduction in both ABP and ICP, but CPP did not decrease. The effect on ICP was more pronounced in Group II patients. The troublesome issue associated with the use of relatively high-dose barbiturates, however, is respiratory depression. In our study, intubation and ventilation of the patients were required. Our results suggest that, in the treatment of systemic hypertension in patients with increased ICP, especially when the increase is severe, barbiturates are preferable to agents with calcium channel and α-adrenergic blocking actions, except for the problem of respiratory control.

References

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