Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use.

Cerebral Vasodilators

Vasodilator drugs cause the smooth muscle of the blood vessel walls to relax. The site of action of vasodilators given by mouth is not confined to one organ of the body and no selective cerebral vasodilator exists. Many of these drugs cause postural hypotension and are of little or no practical value in increasing intracranial blood flow unless given by intracarotid injection. Nevertheless, vasodilators may be of therapeutic value in two circumstances that affect the cerebral circulation: firstly, when arterial spasm occurs in otherwise healthy vessels; and, secondly, when the cerebral blood flow is reduced without vasospasm.

Cerebral Arterial Spasm

Arterial spasm is usually caused by blood in the cerebrospinal fluid[1] but neurogenic factors may also be responsible. The cerebral arteries of the pia mater are supplied with nerves,[2] and adrenergic fibres are present in the cerebral arteries of many species.[3 4] Though the functional significance of this innervation is not known, the long-acting α-adrenergic blocking agent phenoxybenzamine (Dibenylin) has been used successfully to prevent spasm after operation on cerebral aneurysms.[5]

Spasm of the cerebral arteries occurs in subarachnoid haemorrhage, and both intracranial and carotid artery spasm sometimes follows injury of the head and neck.[6-8] Spasm can also be caused by mechanical stimulation of cerebral arteries at operation,[9] and is thought to occur in hypertensive encephalopathy and during the prodromal phase of an attack of migraine.[10] It has also been implicated in the aetiology of transient ischaemic attacks, but most of these are due to atheroma of the cerebral vessels.[11] The presence of spasm after subarachnoid haemorrhage is accompanied by a high degree of morbidity,[12] and there is no clear evidence that spasm is protective against further bleeding. Thus at present the use of vasodilators is limited to preventing spasm, and the possible value of reversal of spasm needs to be established.

Reduced Cerebral Blood Flow

Cerebral blood flow is reduced in many vascular disorders as well as in coma, drug overdosage, and diffuse brain diseases.[13 16] Cerebral vasodilators have in particular been used in vascular disorders, which include transient ischaemic attacks,[17 18] progressive and established strokes due to thromboembolism,[19] and cerebral arteriosclerosis.[20 21] The rationale for using vasodilators in cerebral arteriosclerosis is that ischaemic damage to the nervous system may be prevented by an increased oxygen supply accompanying arterial dilation. It is not known how far function improves with arterial dilation once anoxic damage has occurred. Many factors control cerebral blood flow, including systemic blood pressure and changes in P_{CO_2},[22 23] and, while some vasodilator drugs usually increase cerebral blood flow, this increase is not always found.[24]

Difficulties in Evaluating Response

The course of cerebrovascular disease is variable and may be unpredictable. Many factors—including age and the type and severity of neurological disability—affect the prognosis in cerebral infarction and, though the probable course among a large number of patients can be predicted, it is difficult to predict accurately the rate or degree of recovery in an individual patient.[25] Similarly the likely outcome following a transient ischaemic attack cannot be forecast,[26] and it is difficult to be certain of the value of any method of treatment in a particular patient.

Cerebral arteriosclerosis is difficult to diagnose with certainty and may be confused with other causes of senile dementia, psychosis, or impairment of memory. The assessment of mental changes in the elderly is difficult and time consuming, and considerable fluctuations in the course of cerebral arteriosclerosis are a distinctive feature of the disease. Further confusion is caused by the use of the term "chronic brain syndrome" in some reports, which makes it impossible to know what symptom or indeed what disease is under discussion. Cerebral blood flow declines with age,[27] and the degree to which impaired mental function in elderly patients with cerebral arteriosclerosis can be attributed to reduced blood flow is uncertain. Hence assessment of the efficacy of a vasodilator drug in cerebral arteriosclerosis is one of the most difficult problems in therapeutics.

Dangers of Cerebral Vasodilators

The fall in systemic blood pressure caused by some vasodilator drugs may lead to cerebral ischaemia, and symptoms of this have occurred in elderly patients after the inhalation of glyceryl trinitrite to relieve angina.[28] Areas of the brain around a recent infarct are hyperaemic, and the autoregulation of the blood flow in response to changes in the blood pressure changes is abolished. Hyperaemia probably aids repair, and vasodilation produced by drugs may redistribute the distribution of blood, to the detriment of the most compromised areas.[29] Similarly, arteriosclerosis will reduce (but not abolish) the ability of the cerebrovascular blood vessels to dilate, and so the regional areas most in need of an increased supply of oxygen are further deprived by generalized cerebral vasodilatation.[30]

Carbon Dioxide

Carbon dioxide in a concentration of 5-7% is a potent cerebral vasodilator, and its use may be accompanied by a rise rather than a fall in systemic blood pressure. Nevertheless, there is no evidence that the inhalation of carbon dioxide has any value in preventing the progression or speeding the recovery of a stroke due to thromboembolism, despite an increase in cerebral oxygenation.[31] Prolonged treatment is impracticable and repeated inhalations of carbon dioxide sometimes have no effect on arterial spasm.[32]

Papaverine

This drug relaxes smooth muscle throughout the body and causes a decrease in cerebral vascular resistance and an increase in cerebral blood flow.[33] Recovery from recent thromboembolism may be enhanced by papaverine given as an intravenous infusion

over several days, though further control studies are required to substantiate this.[19] It produces the unwanted effects of hypotension, drowsiness, and apprehension as well as thrombophlebitis at the site of injection. Papaverine has been used to prevent cerebral vasocontriction due to mechanical stimulation of blood vessels occurring at the time of operation,[31] but because of postural hypotension is of little value in increasing cerebral blood flow in ambulant patients.

Cyclandelate and Isoxsuprine

Cyclandelate (Cyclospasmol) is a smooth muscle relaxant like papaverine, though the former is less toxic and has greater spasmolytic action. Isoxsuprine (Duvadilan) is a synthetic vasodilator used to relax smooth muscle. Both drugs predominantly influence blood vessels in skeletal muscle, and have been used in many types of vascular disease.[35-38] They are used as cerebral vasodilators since they do not cause postural hypotension.

Though cyclandelate has no effect in patients who have had a definite stroke, the incidence of transient ischaemic attacks was found to be reduced in many patients during treatment. The significance of this reduction is doubtful since the patients were also treated with reserpine, ephedrine, and anticoagulants, and no untreated patients were studied.[17] In a group of patients given isoxsuprine headache, dizziness, and other transient symptoms attributed to vasospasm were improved. Nevertheless, the degree of improvement was not significant and neither the presence of vasospasm nor its reversal by isoxsuprine was demonstrated.[18]

Both isoxsuprine and cyclandelate are reported to be of value in the treatment of arteriosclerotic cerebrovascular disease.[20 21 39-44] It is uncertain whether improvement in mental function is associated with vasodilatation or is produced by some other mechanism. The onset of the effect of cyclandelate is delayed and a short initial deterioration sometimes occurs.[40] The pattern of improvement has been inconsistent in different trials, for, while mood and drive benefited in one,[41] there was no change in mood in another, though both orientation and communication improved;[40] the reaction times diminished in one trial,[42] yet the time taken to complete tests remained unchanged in another.[40] These differences reflect the difficulty in testing patients with cerebrovascular disease, but also suggest that any overall improvement is only slight. Patients and ward sisters may not be able to detect any difference between the effects of cyclandelate and a placebo preparation.[20] Many patients have been treated in their home surroundings with apparent benefit, but a placebo rather than specific drug effect has not been excluded.[43] The degree of mental impairment seldom relates to the degree of the reduction of blood flow, either before or after treatment.[44]

Side effects from cyclandelate (800-1,200 mg/day) and isoxsuprine (60 mg/day) are not common but include flushing, tingling, dizziness, headache, and sweating. Nevertheless, most patients tolerate these drugs well.

Various other drugs have been used as cerebral vasodilators including nicotinyl tartrate (Ronicol); and buphenine (Dilacol), which like cyclandelate and isoxsuprine predominantly affects blood vessels in skeletal muscle. Nicotinyl alcohol given intravenously is reported to be of value in both migraine and cerebral arteriosclerosis[45] and buphenine has been used in perceptive deafness with some improvement.[46] The absence of controls makes these claims difficult to substantiate.

Conclusion

The outlook in many forms of cerebrovascular disease is poor and though dramatic results sometimes follow carotid endarterectomy or anticoagulant treatment, most patients have a long-standing and disabling condition. Thus any further treatment of proved value is highly desirable. Nevertheless, despite the fact that some vasodilators will increase cerebral blood flow, there is no convincing evidence that they are of value for patients with focal transient ischaemic attacks or during the course of a stroke. The hazards of treatment may be greater than possible advantages.

The diagnosis of cerebral arteriosclerosis is difficult to establish, and the value of treatment may be hidden or exaggerated by natural variations in the disease. No consistent pattern of benefit from vasodilators has been shown, and slight improvement in some aspects of mental function has not always been related to an increase in cerebral blood flow. At present without long-term controlled trials involving many patients, the value of vasodilators in arteriosclerotic cerebrovascular disease must remain in doubt.

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