PRELIMINARY COMMUNICATIONS

Intracarotid Phenoxybenzamine for Cerebral Arterial Spasm

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British Medical Journal, 1971, 1, 382–383

Summary

Phenoxybenzamine was injected into the carotid artery of 23 patients after operations on their cerebral arterial aneurysms. Rapid improvement was seen in three cases with pronounced neurological disability. The other 20 were treated prophylactically in an attempt to prevent the onset of spasm. These results would appear to indicate that intracarotid phenoxybenzamine may be of value in the treatment of cerebral arterial spasm, provided that it is given before irreversible infarction of the brain has occurred. Until more is known about its action it would be best to give the drug only after operation.

Introduction

Modern operative techniques and anaesthetic methods have made the surgery of intracranial aneurysms relatively safe, but the results of a satisfactory clipping of a cerebral arterial aneurysm are often marred by delayed and prolonged arterial spasm. This spasm is seen on carotid angiography as a narrowing of the lumen of the large cerebral arteries. Spasm may be localized or it may involve the whole internal carotid arterial tree on both sides. It is often associated with progressive deterioration of consciousness, leading to coma and death, or with the development of major neurological deficit, such as hemiparesis and dysphasia. This may be permanent and disabling. There is evidence that the initial subarachnoid haemorrhage brings about spasm within a few days whether or not operation is carried out.

Much experimental work in animals has been performed with spasmogenic and spasmolytic substances applied direct to the arterial wall, without any one substance or treatment being shown to be singularly effective. Blood and blood extracts applied to the artery are spasmogenic. Lende (1960) showed that while phentolamine, a short-acting α-adrenergic blocking agent, did not reverse established spasm well it did confer a protection against spasm if applied before the spasmogenic substance. Fraser *et al.* (1970) reported that α-adrenergic blockade of the cerebral vessels of monkeys by direct application could prevent cerebral arterial spasm induced by the application of blood.

Mchedlishvili (1964) showed adrenergic fibres histologically in the cerebral arteries of baboons, while Peerless and Yasargil (1969) described a rich adventitial collection of noradrenaline within the cerebral arterial walls in the rabbit. Using the electron microscope, Nelson and Rennels (1970) showed vesicles probably containing noradrenaline within the walls of the cerebral arteries associated with nerve filaments in cats. They also extensively reviewed the literature concerning cerebral arterial innervation.

Consequently it appeared that a long-acting α-adrenergic blocking agent might be effective in reducing cerebral arterial spasm in man. Phenoxybenzamine has been used systematically for some years for prolonged sympathetic blockade of the α-adrenergic receptors (Gump *et al.*, 1968). It has also been injected into the brachial artery, conferring arterial vasodilation lasting up to three days localized to that limb (Duff and Ginsburg, 1957). There is some evidence to suggest that the drug protects organs against ischaemia, as is seen in the experimental transplantation of the liver (Fonkalsrud *et al.*, 1969). Given intra-arterially in the human brachial artery it acts within 10 minutes of injection (Duff and Ginsburg, 1957).

Methods

Since March 1970 we have injected phenoxybenzamine into the carotid artery after operation in 23 cases. This route was chosen because of the selective action which can be achieved without generalized peripheral vasodilatation with consequent falls of blood pressure. In 20 cases we performed immediate postoperative carotid arteriograms under continued anaesthesia. Phenoxybenzamine 10 mg in 20 ml of normal saline was injected into the carotid artery over the course of 10 minutes after angiography. The blood pressure was monitored during and after the injection. A fall of 20 mm Hg in the systolic blood pressure was noted in two patients, both of whom were receiving halothane. This fall in blood pressure was reversed when halothane was discontinued. No adverse side effects were observed. Low molecular weight dextran was given postoperatively for three days in each case.

Case Reports

Case 1.—A 45-year-old active mother of 11 children was admitted to hospital on 3 March 1970 having had a spontaneous intracranial haemorrhage from an anterior communicating artery aneurysm on the previous day. Apart from stiffness of the neck there were no neurological abnormalities. She was alert and cerebral vascular spasm was not visible on the arteriograms. On the seventh day after the haemorrhage the aneurysm was clipped without incident via a left frontal craniotomy under moderate hypothermia (31°C). She made an immediate good recovery, being alert, co-operative, and without neurological signs 12 hours later. Her level of consciousness deteriorated 36 hours after operation. Intravenous mannitol and low molecular weight dextran were given without effect, and five hours later she was deeply unconscious, with fixed and dilated pupils. Left carotid arteriography showed diffuse arterial spasm. Phenoxybenzamine 5 mg diluted in 20 ml of saline was then injected direct into the left carotid artery at a rate of 1 mg/minute. There was no fall in systemic blood pressure. Within 30 minutes of the injection consciousness had returned accompanied by gross dysphasia, which had disappeared by the following day. Further recovery was uneventful and she was discharged home 11 days after operation. When seen at follow-up two months after operation she was quite well and managing her large family as usual.

Case 2.—A 38-year-old personnel manager was admitted to hospital on 1 March 1970 in a very drowsy state and with a left hemiparesis and hemianaesthesia, having had severe headache two days previously. Right carotid arteriography showed a large right frontoparietal intracerebral haematoma, with no obvious source of haemorrhage. The haematoma was evacuated and he made a fair recovery, with pronounced weakness and sensory loss in the left

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limbs. A repeat right carotid arteriogram showed a large middle cerebral aneurysm which had failed to fill on the previous examination. His recovery continued to a moderate weakness and sensory loss in the left limbs. Six weeks after admission the aneurysm was clipped under hypothermia (31°C). He was able to move his left limbs in response to stimulation immediately after operation, but on the following day had a complete left hemiplegia and was very drowsy. A further arteriogram, performed under local anaesthesia, showed occlusion of the aneurysm and very little spasm. Phenoxybenzamine 10 mg was injected as described above. Within 10 minutes of the injection he began to move his left arm spontaneously, and thereafter made a slow recovery of power in the left limbs. He was discharged home, able to walk, four weeks after operation. Five months later he was back at his former work, with good power in the left limbs and a very mild left-sided sensory loss.

Case 3.—A woman aged 46 years was admitted to hospital on 16 April 1970 four days after a subarachnoid haemorrhage. On admission she was severely dysphasic and had a mild right hemiparesis. Bilateral carotid arteriography showed a left middle cerebral aneurysm with no evidence of haematoma or spasm. On the day of admission the aneurysm was clipped at normal temperature, and immediately after the operation 10 mg of phenoxybenzamine was injected intra-arterially. She made an immediate good recovery and lost her right hemiparesis and most of her dysphasia. At discharge two weeks later she was well and normal except for a minimal expressive dysphasia. Six months after operation she was well and active, with no expressive dysphasia or neurological signs. She admitted to a minimal auditory verbal agnosia.

Case 4.—A 46-year-old housewife was admitted to hospital on 14 August 1970 having developed a sudden headache the same day. She was well orientated but had pronounced neck stiffness. There was a mild and fluctuating left hemiparesis. Carotid arteriography showed spasm locally around a small right middle cerebral aneurysm. Four days after admission she developed more weakness of the left limbs and became confused and incontinent. Further arteriography on that day showed more severe spasm, and 10 mg of phenoxybenzamine was injected into the carotid artery. She improved rapidly, became less drowsy, and was without limb weakness at the time of her operation seven days after admission. The aneurysm was clipped under hypothermia (31°C) and immediate postoperative arteriography showed spasm. A further 10 mg of phenoxybenzamine was injected into the cartoid artery. For the next 36 hours she was alert and moved her limbs normally, but then developed a fluctuating left hemiparesis which progressed to a left hemiplegia after a further 24 hours. Repeat arteriography carried out 24 hours after the hemiplegia became complete showed less spasm. Phenoxybenzamine 10 mg was injected into the carotid artery. The only noticeable improvement was the return of a withdrawal response to pain. Six weeks later she had a little voluntary movement in her left upper limb, but was able to move her left leg more freely. She was unable to walk but was alert and well orientated. This may be seen as a failure of phenoxybenzamine to confer protection beyond 36 hours.

Results

Following the initial cases we injected phenoxybenzamine prophylactically into the carotid artery in 21 patients at the time of the immediate postoperative arteriogram in an attempt to protect them against the development of spasm. Most were operated on within the first week after their haemorrhage, and 11 had some confusion or localized signs at the time of operation. In all cases no deterioration occurred during the first 36 hours after prophylactic injection, compared with the condition immediately on recovery from anaesthesia. One further case deteriorated at 48 hours but improved rapidly after a second injection of phenoxybenzamine. The second postoperative arteriogram showed spasm to be slightly worse than it had been immediately after operation. Two deaths occurred, spasm being incriminated in neither case.

Discussion

It must be made clear that spasm is by no means the only common cause of postoperative deterioration. Two patients developed severe communicating hydrocephalus requiring a ventriculoatrial shunt for its control within the first two weeks after operation. One patient in this small series developed intracerebral haematoma, one subdural haematoma, and one extradural haematoma, on each occasion being evacuated without delay. Half of these patients had severe meningism, drowsiness, and neurological signs at the time of operation, features which are normally associated with an operative mortality of the order of 40%. Despite this 18 of the 23 patients returned home, most with little or no disability.

We feel that we have observed clinical improvement which was probably due to the action of the drug, and on this ground it merits a properly controlled trial. No patient has been made worse as a result of taking the drug, and its use has been associated with an acceptably low mortality and morbidity in these severely ill patients. It is important in further assessment of the drug to note that its duration of action makes it unlikely that it will confer protection lasting longer than 36 hours. Similarly, it will be of little use in established infarction, and probably should be given at the first sign of deterioration if causes other than spasm can be excluded.

We have, in general, avoided giving the drug before the aneurysm has been safely clipped or wrapped at operation because of the risk that relaxation of vascular spasm might promote bleeding from the aneurysm.

We are grateful to Mr. D. G. Phillips and Mr. A. Hulme for allowing us to treat and report cases under their care, and to Dr. Outram, of Smith Kline and French Ltd., for supplies of Dibenyline and for helpful advice. We are also grateful to Dr. John Zorab for help and discussion.

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