Experimental Evaluation of Potential Spasmolytic Drugs*

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Neither the parenteral nor topical use of drugs has been effective in the relief of spasm in cerebral arteries. In 1956, Cooper noted spasm of the internal carotid artery and its branches by arteriography following surgical occlusion of an anterior choroidal artery. He subsequently modified his technique to include continuous intravenous infusion of papaverine during and after the surgical procedure. He reported that, since he instituted this modification, he had seen no further neurological evidence of spasm following anterior choroidal artery occlusion. He had no arteriographic evidence, however. Pribram recently studied by arteriography the effect of intra-arterial papaverine, dibenzylene, chlorpromazine, and inhalation of 7% CO₂ in a limited number of patients. He observed no relief of spasm with any of these materials.

There have been no controlled studies of the effects of cervical sympathectomy or sympathetic blocking on spasm. This form of therapy has been tried sporadically by various neurosurgeons without apparent benefit.

We have previously described a laboratory model for the study of cerebral arterial spasm, and confirmed the effectiveness of the topical application of autogenous blood as a spasmogenic agent. This report concerns our evaluation of several systematically administered potential spasmytic drugs when tested against blood-induced spasm in this model.

Method

Preparation. Adult cats were anesthetized with intraperitoneal pentobarbital, 30 mg/kg body weight. A tracheostomy was performed, and a Harvard respirator was used for controlled respiration. A polyethylene catheter was placed in a femoral artery and attached to a Sanborn transducer for continuous monitoring of arterial pressure. A polyethylene catheter was placed in the femoral vein for drug administration. The basilar artery was exposed transorally, and continuous irrigation of the exposed artery and brain stem with mammalian Ringer's solution at body temperature was instituted.

Photographic Technique. Photographs of the exposed vessel were made using Kodak EHB-135 color film in a 35 mm camera attached to the operative microscope. Photographs were made before and at specified intervals after induction of spasm or administration of drugs. The photographs were projected, and the diameter of the basilar artery was measured with a millimeter ruler. The results were expressed as per cent change in vessel diameter relative to control diameter immediately prior to induction of spasm or drug administration. When segmental constriction occurred in the photographed area of the vessel, the area of maximum constriction was selected for measurement.

Production of Spasm. Spasm was produced by allowing fresh autogenous blood to come into contact with the exposed basilar artery. The continuous irrigation was stopped for 2½ min to allow a clot to form around the artery and to allow time for bleeding to stop. A sufficient portion of the clot was then removed by suction so that the walls of the artery were visible. During removal of the clot, care was taken to avoid mechanical stimulation of the wall of the artery.

Controls. In six control animals, the basilar artery constricted to 52% of its original diameter when exposed to autogenous blood. After an initial relaxation phase, which averaged 18% during the first 15 min, the mean vessel diameter did not change more than ± 4% during any subsequent 5-min observation period (Fig. 1).

Administration of Drugs. Usually, drugs were administered starting at least 15 min after spasm was induced, during the late or

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stable phase of spasm, by rapid injection in to the femoral vein via a polyethylene catheter. In specified cases, a drug was given during the first 15 min of spasm, or injection was accomplished via a catheter in the left vertebral artery rather than in a femoral vein. Carbon dioxide was administered via the respirator in a closed, nonrebreathing system. Photographs of the artery were made immediately before administration and immediately afterward with at least one photograph per min taken for 5 min after drug administration.

Selection of Drugs. Some drugs were selected because they are commonly used as dilators of cerebral or other peripheral arteries, others because they are believed to inhibit specific receptor sites. In general, dosage was calculated from recommended human dosage.

The number of studies of each drug varied. Preliminary studies of each drug were done on one or two animals. If the drug appeared to be effective in relieving arterial spasm, additional studies were done. If no change in vessel diameter, or additional constriction, was observed after drug administration, and the dosage was adequate to produce the expected blood pressure response, the drug was not tested further.

Results

Choline.* The constricted basilar artery was dilated an average of 60% when choline was given more than 15 min after production of spasm. Figure 2 shows an average of corresponding points for the five animals in this group. There was an initial rapid dilatation of the vessel, which reached a maximum in 2 min, associated with an early rise in arterial blood pressure, followed by a fall to subcontrol levels. Choline given within the first 15 min of induction of spasm was less effective and produced an average maximum dilatation of 45%.

In an attempt to determine if the spasmodic effects of choline chloride were due to its action as a parasympathomimetic or depolarizing blocking agent, acetylcholine and succinylcholine were tested. Succinylcholine, 10 mg intravenously, produced an average further constriction of the vessel of 15%. This was associated with an initial rise followed by slight fall in arterial blood pressure. Acetylcholine, 25 mg intravenously, produced a further constriction of 45% and severe hypotension. In an attempt to circumvent the hypotension, acetylcholine was given in doses of 25 to 50 µg directly into the vertebral artery. This produced a further constriction of 36% associated with a somewhat milder fall in blood pressure. These data are summarized in Table 1.

Other Drugs. Three other drugs with spasmodic properties were found, although none of these drugs was as effective as choline in relieving spasm. Magnesium sulfate increased the diameter of constricted vessels approximately 20% when given by intravenous infusion in doses of 250 to 300 mg/kg.

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*Choline purchased from Eastman Kodak Company, Rochester, New York.

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[Fig. 1. Blood-induced spasm. Average values for six controls.]

[Fig. 2. Effect of choline chloride on blood-induced spasm for six animals.]