INTRACAROTID INJECTION OF PAPAVERINE IN CASES OF CEREBROVASCULAR THROMBOSIS*

PRELIMINARY REPORT

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It is the purpose of this paper to report our clinical observations on the effect of injection of a known vasodilating agent directly into the common carotid artery in cases of thrombosis of cerebral blood vessels and ischemic cerebral infarction. This constitutes a preliminary report of a study concerned with the effect of intracarotid administration of vasodilating drugs upon the cerebral circulation in man.

The literature concerned with the treatment of patients with ischemic cerebral infarction has been replete with paradoxical statements and contradictions. Such basic considerations as the anatomic and physiologic arrangement of terminal vessels, the occurrence or nonoccurrence of angiospasm of intracranial blood vessels, the role of the autonomic nervous system in regulation of caliber of intracranial arteries and arterioles, the objective results of stellate ganglion block in the treatment of cerebrovascular disease, and the clinical effect of vasodilating drugs on the cerebral circulation of man are not yet clearly understood nor has agreement among authorities been reached on any of these issues. One of the most lucid essays on this subject is that of Schmidt. He says that while the possibility of cerebral angiospasm from sympathetic impulses in man can be neither affirmed nor denied, at present the preponderance of the evidence is against it. Our own clinical experience with stellate ganglion block in cases of cerebral vasoconstriction has thus far borne out this statement. Moreover, Schmidt has pointed out that the physiologic basis for failure of the commonly employed vasodilating agents to be clinically effective in increasing cerebral circulation is the apparent lesser sensitivity of intracranial vessels to vasodilator agents as compared with the sensitivity of the extracranial vessels. Hence a vasodilator agent, such as papaverine, when administered orally or parenterally in sufficient concentration to act all over the body, may bring about a redistribution of blood at the expense of the brain, plus a decrease in peripheral blood pressure and an actual decrease rather than the desired increase in cerebral blood flow.

Our investigation is ultimately concerned with several questions that bear upon the treatment of ischemic infarction of the brain. These questions are: (1) How can selective vasodilatation of the intracranial arteries and

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arterioles in man be best accomplished? (2) Under what conditions is such vasodilatation accompanied by increased cerebral blood flow? (3) What consideration must be given to the changes in the peripheral blood pressure, cardiac rate and output, and respiratory rate which are side effects produced by certain vasodilating agents? (4) If cerebral vasodilatation and increased cerebral blood flow can be accomplished in cases of ischemic brain infarction, will it prove to be clinically beneficial, or will reactive edema, increased intracranial pressure, and later angiospasm mitigate any possible benefits?

The phase of this study with which we are concerned in this preliminary report is the effort to produce selective dilatation of intracranial vessels. The basis for attempting to accomplish this by the intracarotid injection of papaverine is simply the rationale of delivering a vasodilating agent directly into the vessels to be dilated. Mufson\(^9\) has based his treatment of peripheral obliterative arterial disease on the same rationale. We wish to report certain of our clinical observations following the intracarotid injection of papaverine in 6 patients with complete hemiplegia caused by ischemic infarction of the brain, and in 10 additional patients in whom injection was carried out for its vasodilating effect during cerebral angiography. An evaluation of these early observations will not be attempted by us in this preliminary report, and only unequivocal objective findings will be reported.

Single and multiple intracarotid injections of papaverine, in dosage varying from 0.5 to 1.5 grains, were made in 6 patients demonstrating complete hemiplegia. In each patient the hemiplegia had been present for 72 hours or more. In each case a clinical diagnosis of cerebrovascular thrombosis with ischemic infarction of the brain had been arrived at independently by several examiners on the basis of mode of onset and development of the hemiplegia, neurologic examination, and absence of red blood cells from the cerebrospinal fluid. Each injection was made into the common carotid artery that was contralateral to the hemiplegic extremities. In 2 cases a single injection was made, in 2 cases two injections were made, and in 2 cases three injections were made. Four of the patients demonstrated an objective change in the paralyzed extremities within 60 seconds after the initial injection. Two demonstrated no observable change. Brief summaries of these clinical investigative procedures follow.

**CASE REPORTS**

**Case 1.** A.S., a 52-year-old white male, a known hypertensive, noted onset of weakness of the right extremities. This progressed to complete right hemiplegia within 24 hours. Neurologic examination revealed complete flaccid paralysis of the right extremities, sensory type aphasia, deviation of eyes to the right, and a positive response to the Babinski test on the right. The pupils were equal and reacted well to light.

On the second day after admission 0.5 gr. of papaverine was injected into the left common carotid artery.

Two days later another injection of 0.5 gr. of papaverine was made. During the next 10 minutes the patient moved his right arm spontaneously and on command.
No change occurred in the right lower extremity. All movements of the right extremities, including withdrawal from painful stimuli, disappeared 10 minutes after the second injection. The following day, a single dose of 1 gr. of papaverine was injected into the left common carotid artery. No change in the neurologic status of the patient ensued. He died 24 hours later, following a slowly progressive worsening of his clinical status.

Necropsy revealed multiple infarctions of the left cerebral hemisphere. Thrombi could not be demonstrated in any of the major cerebral vessels or their branches.

Case 2. Mrs. B.J., a 67-year-old housewife, was admitted to Bellevue Hospital with a complete left hemiplegia which had developed gradually over the previous 72 hours. She had not lost consciousness and was mentally lucid. There was no aphasia. Neurologic study led to a diagnosis of cerebrovascular thrombosis and/or ischemic cerebral infarction. She failed to show any sign of improvement during the ensuing 2 weeks.

Therefore on the 15th day after admission, 0.5 gr. of papaverine was injected into the right common carotid artery. Within 1 minute the patient could voluntarily move the left lower extremity and could lift this extremity from the bed. No change was noted in the left upper extremity. During the next 30 minutes the left lower extremity became progressively weaker and at the end of that time voluntary motion of the left lower extremity was impossible. Four hours later a second right intracarotid injection of 0.5 gr. of papaverine was carried out. No neurologic change was noted. A third injection of 0.5 gr. of papaverine was made into the right common carotid artery the following day. No neurologic change was noted. This patient died 4 weeks after following this study and permission for necropsy could not be obtained.

Case 3. F.C., a 56-year-old female, was admitted to our service with a complete right hemiplegia and a sensory-type aphasia. The hemiplegia had been gradual in onset, occurring over the course of 18 hours, and had been complete for 3 days prior to admission. Following complete neurologic evaluation the diagnosis of ischemic infarction of the left cerebral hemisphere was made and a trial of intracarotid papaverine was decided upon.

Therefore, 4 days following the onset of hemiplegia 0.5 gr. of papaverine was injected into the left common carotid artery. No objective neurologic change was noted during the next 30 minutes. A second 0.5 gr. of papaverine was injected into the left common carotid artery at the end of this 30-minute period and again no objective neurologic change could be noted. No further injections were made.

Case 4. B.J., a 65-year-old colored male, was admitted with a right hemiplegia of 3 hours’ duration. The hemiplegia had occurred suddenly and was accompanied by giddiness and severe left-sided headache, but was not accompanied by loss of consciousness. Hemiplegia had been complete since the time of onset. Following complete neurologic and medical evaluation, the diagnosis of ischemic cerebral infarction in the left cerebral hemisphere, secondary to embolism from a cardiac mural thrombus, was made.

Forty-eight hours after onset of hemiplegia, 1 gr. of papaverine was injected in the left common carotid artery. Immediately upon completion of this injection painful stimuli applied to either the right arm or right leg resulted in withdrawal of these extremities. Withdrawal from painful stimuli had not been present previous to this injection nor at any time during the previous 2 hours that the patient had
been on our service. This withdrawal from painful stimuli persisted for the following 30 minutes but no further neurologic improvement was noted. Therefore, an additional 0.5 gr. of papaverine was injected into the left common carotid artery. No neurologic improvement was noted. No further injections were made. This patient was followed by us for the ensuing 2 weeks, during which he showed evidence of neurologic improvement including some return of voluntary motion to the right lower extremity and moderate improvement in his speech difficulty.

Case 5. R.Y., a 47-year-old white male, was first seen 48 hours after development of a right hemiplegia accompanied by motor-type aphasia. The hemiplegia had occurred gradually during the course of the previous 14 hours. Complete neurologic study led to a tentative diagnosis of ischemic cerebral infarction of the left cerebrum, secondary to cerebral vascular thrombosis.

On the second day after admission, 4 days after onset of hemiplegia, 1 gr. of papaverine was injected into the left common carotid artery. Upon completion of this injection, the patient withdrew the previously paralyzed extremities from painful stimuli and could weakly voluntarily move the right lower extremity. He could not voluntarily use the upper extremity. There was no change in reflexes. The voluntary motion of the right lower extremity lasted approximately 45 minutes. Withdrawal from painful stimuli of both extremities lasted approximately 2 hours. Further intracarotid injection was refused. The patient was followed for a period of 2 weeks and during this time no appreciable improvement was noted.

Case 6. A.R., a 67-year-old white female, was first seen 1 week following onset of left hemiplegia. There was no speech involvement. Neurologic evaluation led to a diagnosis of ischemic cerebral infarction probably on the basis of cerebral vascular thrombosis.

On the day after admission, 8 days following onset of hemiplegia, 1 gr. of papaverine was injected into the right common carotid artery. During a 2-hour period of observation following the injection no change in the neurologic status was noted. No further injections were made.

DISCUSSION

In summarizing our experiences, we found that in 4 of these 6 cases, immediately following intracarotid injection of papaverine, there was some objective neurologic change which could be interpreted as neurologic improvement. In 2 cases this was evidenced by voluntary motion of the previously paralyzed extremities. In the other 2 cases this was evidenced by withdrawal of the previously paralyzed extremities from painful stimuli. Subjective sensations were not recorded during this phase of the investigation and are not herein reported. In those cases in which objective improvement was noted, the improvement was transient in every instance.

During the early phase of our investigation one sobering experience occurred which deserves mention in a study such as this concerned with treatment of cerebral ischemic infarction. We were called to see a patient who had a hemiplegia of 24 hours' duration. The patient had been examined previously by the medical resident and the attending medical staff and by our neurosurgical resident, and each examiner had found the patient to be completely
hemiplegic on the right side and each had reached the diagnosis of cerebral vascular thrombosis. We examined this patient and found the same objective findings and reached the same clinical diagnosis. Therefore, the patient was prepared for intracarotid injection. Following sterile preparation of the cervical region for injection, the patient was asked to lift the right paralyzed extremity before the carotid puncture was carried out. This request was purely a theatrical one to demonstrate to observers of this procedure the paralyzed condition of this extremity. However, the patient promptly obliged by lifting the right extremity which previously had been completely paralyzed and which had demonstrated no voluntary motion or withdrawal from painful stimuli. This case is cited merely to demonstrate the dangers in evaluating results of therapy in this type of investigation and explains our reluctance to attempt to draw any conclusion from early findings in this study.

Several miscellaneous observations may be mentioned at this time. In 10 consecutive cases of cerebral arteriography in which diodrast was used as the contrast medium cerebral arteriograms were made before and after the intracarotid injection of 1 gr. of papaverine. In 6 of these cases there was objective evidence of dilatation of the medium-sized intracranial arteries in arteriograms after intracarotid papaverine as compared with control arteriograms. Uihlein\textsuperscript{12} had previously noted similar effects of intracarotid papaverine on the caliber of intracranial vessels during arteriography. We have observed other phenomena that deserve further investigation. In 2 epileptic patients, the intracarotid injection of papaverine produced immediate onset of generalized convulsions. In 6 patients, the injection caused a sudden marked increase of peripheral systolic and diastolic blood pressure which lasted approximately 2 minutes. This is in marked contradistinction to the fall in blood pressure that usually accompanies intravenous administration of this drug. This rise in blood pressure cannot be ascribed to activation of the carotid sinus reflex since it was observed to occur in atropinized subjects. Whether it is secondary to dilatation of intracranial blood vessels, increased intracranial blood flow, increased intracranial pressure, direct effect of the drug upon vasomotor centers or other causes cannot be stated at this time. Similar changes in peripheral blood pressure have not been observed by us following intracarotid injection of 5 per cent glucose or of 35 per cent diodrast.

Many patients in whom intracarotid papaverine injection was carried out under local anesthesia complained of sudden severe burning of the ipsilateral side of the face and head, similar to, but apparently not as severe as, that occurring with intracarotid diodrast. One patient complained of burning in the face and contralateral fingers and became momentarily disoriented. In several instances marked flushing and cutaneous vasodilatation of the ipsilateral face followed intracarotid papaverine injection.

Obviously, conclusions are not warranted in a preliminary report of this type regarding therapeutic possibilities of intracarotid injection of
vasodilating substances. Certain factors can be pointed out, however, which indicate that further investigation in this regard may be fruitful. Despite the unquestioned action of papaverine as a vasodilating agent, its oral or parenteral use has not been attended by objective evidence of increased cerebral blood flow. On the other hand Henderson, Shipley and Chen\(^6\) have shown that intra-arterial coronary artery injection of papaverine or its analogue paveril is attended not only by vasodilatation but also by marked increased blood flow in the dilated arteries. Mufson\(^3\) has demonstrated the clinical efficacy and feasibility of intra-arterial administration of vasodilating agents in cases of peripheral obliterator arterial disease. The suggestive transient clinical improvement observed in 4 of our 6 cases, the enlarged caliber of cerebral arteries noted by arteriography following intracarotid papaverine, and the rationale of delivering such an agent directly into the vessels one wishes to dilate indicate that further exploration of this technique may prove fruitful. We are currently evaluating the use of a prolonged intracarotid drip of a solution containing papaverine as a means of producing a more prolonged vasodilating effect than single injections can provide.

**SUMMARY**

This constitutes a preliminary report of an investigation into the intracarotid injection of a known vasodilating agent. Objective neurologic improvement of a transient nature followed intracarotid injection of papaverine in 4 out of 6 patients with hemiplegia caused by ischemic cerebral infarction. The rationale of intracarotid administration of vasodilating agents has been outlined and possible avenues of further investigation in this regard have been indicated.

**REFERENCES**


12. Uhlein, A. Personal communication.