TRANSIENT HEMIPLEGIA ASSOCIATED WITH CEREBRAL ANGIOGRAPHY (DIODRAST)*

J. G. CHUSID, M.D., FRANKLIN ROBINSON, M.D.,
AND M. P. MARGULES-LAVERGNE, M.D.

The Neurological Division, St. Vincent’s Hospital, New York City

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Since the introduction of cerebral angiography by Egas Moniz, repeated efforts have been made toward the simplification of the technique as well as the reduction in hazard for the patient undergoing the diagnostic procedure. The wider adoption of the percutaneous injection method of the carotid system and the use of serigraphic devices have overcome some of the difficulties formerly encountered. However, the development of an inert substance, ideal for radiographic visualization, is still forthcoming. Thorotrast is considered by some investigators superior to diodrast because of its relatively greater radiopacity and less frequent immediate systemic reactions. Nevertheless, because of the potentially dangerous radioactivity of thorotrast, other workers have employed diodrast as the contrast medium of choice.

Recently, the authors have observed the occurrence of transient hemiplegia in patients as an immediate complication of diodrast cerebral angiography. A review of the literature failed to disclose reports of such transitory hemiplegic phenomena with the use of diodrast in concentration of 35 per cent. These cases are presented, therefore, together with a brief résumé of the pharmacological action of diodrast and the clinical experience of others with its use.

Case 1. M. C., a 49-year-old white male, was admitted to St. Vincent’s Hospital on 25 Oct. 1948, 10 hours following the onset of severe supraorbital headache, vertigo, nausea and projectile vomiting. Neurological findings were normal except for moderate stiffness of the neck. The patient was right-handed. Blood pressure was 140/100 and temperature, pulse and respiration were normal. Lumbar puncture disclosed grossly bloody fluid with an initial pressure of 290 mm. By the 12th day the CSF was no longer bloody and the initial pressure was 156 mm. Gradual symptomatic improvement occurred during the next 2 weeks. Laboratory studies including complete blood count, bleeding and coagulation time, blood and spinal fluid serology, visual fields and skull x-rays were within normal limits. An EEG (Fig. 1) on the 17th day was borderline. The patient denied any personal or familial allergic reactions to food, pollen or bacteria. An ocular test for diodrast sensitivity was negative.

On the 32nd day right percutaneous cerebral angiography was performed under local anesthesia, using a No. 18 needle. Premedication consisted of nembutal 0.10

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gm. and codeine phosphate 0.06 gm. The right common carotid artery was entered without difficulty and a right lateral projection arteriogram and venogram was obtained with 20 cc. of 35 per cent diodrast. There was incomplete detail in the course of the right anterior cerebral artery and a repeat injection was performed using an equal amount of diodrast. Thirty seconds following the injection the patient lost consciousness and remained unresponsive for approximately 2 minutes. No convulsive movements were observed. A complete left flaccid hemiplegia with weakness of the left lower facial musculature was evident within 3 minutes. The deep reflexes on the left side were increased slightly, the left plantar response was extensor, and there was left ankle clonus. The blood pressure was recorded at 160/100 and pulse rate 76. The patient was given 300 mg. of tetraethylammonium chloride intravenously approximately 10 minutes later with immediate fall in blood pressure to 106/90 and rise in pulse rate to 96. The patient remained lethargic and moderately dysphasic, but return in motor function of the extremities of the left side occurred within 1½ hours after onset of the episode. At that time, the deep reflexes were equal and active bilaterally and the left plantar response was flexor. Another intravenous injection of 200 mg. of tetraethylammonium chloride was given. Approximately 2½ hours after onset of the reaction, the patient was alert, orientated, and there was no evidence of speech disturbance.

On the 37th day left cerebral angiography was performed using the same technique. The procedure was tolerated well and there was no discomfort. A small aneurysmal dilation of the left anterior cerebral artery just distal to the anterior communicating artery was disclosed. The remainder of the patient’s course was uneventful and he was discharged on the 44th hospital day. He remained asympto-
matic and neurological findings on 8 Mar. 1949 were within normal limits. An EEG tracing (Fig. 2) made on 20 Jan. 1949 had a normal pattern.

Case 2. W. T., a 49-year-old white married carpenter, was admitted to St. Vincent's Hospital on 4 Jan. 1949 for study. He had had an episode of severe left-sided headache associated with nausea and vomiting a year ago with apparent complete recovery. He remained well until the morning of 7 Dec. 1948, when, while bending over, severe generalized headache developed, radiating into the back of the neck. The headache persisted, and on the following day he was admitted to a hospital. Initial lumbar puncture revealed grossly bloody fluid under 180 mm. pressure. There was nystagmus on right lateral gaze with absence of right abdominal reflexes. Subsequent punctures revealed progressive clearing of the CSF with diminishing pressure, and he was asymptomatic on discharge. Neurological findings on admission to St. Vincent's Hospital were within normal limits. The patient was right-handed. Studies, including skull x-ray, EEG (Fig. 3), complete blood count, urinalysis, blood urea nitrogen, fasting blood sugar and blood Kahn, were not remarkable. The patient and his family denied sensitivity to food, pollen or bacteria. An ocular test for diodrast sensitivity was negative.

Left percutaneous cerebral angiography was performed under local anesthesia on the 2nd hospital day. Two injections of 35 per cent diodrast were made, using a total of 35 cc. of solution for the arterial and venous phases in the left lateral projection with no untoward effect. A moderately large saccular aneurysm of the intracranial portion of the left internal carotid artery was seen. A 3rd injection of 15 cc. of 35 per cent diodrast was made in order to obtain an A-P projection. Promptly following this injection he became confused and dysphasic. A right flaccid hemiparesis with inactive right plantar response was evident. The blood pressure
HEMIPLEGIA ASSOCIATED WITH ANGIOGRAPHY

was 108/60. The patient received an infusion of 500 cc. of saline containing 500 mg. of tetraethylammonium chloride and appeared less confused. Two hours later full power of the right lower extremity was regained and the right plantar response was flexor. Flaccid paralysis of the right upper extremity and the lower right side of the face persisted. Lumbar puncture, 3 hours after onset of the reaction, yielded clear fluid under initial pressure of 110 mm., with 6 cells / c.mm., total protein 38 mg. per cent, and colloidal gold of 11 \times 10^4. Motor power in the right upper extremity continued to improve and 4 days later, motor function and speech were normal.

On the 22nd hospital day left carotid compression, starting with a 5-minute period, was begun without ill effect. By the 27th day, the patient tolerated 20 minutes of carotid compression quite well. On 1 Feb. 1949, the 28th hospital day, the left common carotid was exposed and ligated under local anesthesia, with uneventful postoperative course. On the 6th postoperative day right cerebral angiography was performed under local anesthesia. A total of 40 cc. of 35 per cent diodrast was used without side effect. The vascular pattern appeared normal and the aneurysm of the left side did not fill. The patient was discharged on the 9th postoperative day.

The initial EEG (Fig. 3) taken on 5 Jan. 1949 was normal. The 2nd EEG (Fig. 4) 7 Jan. 1949, taken 1 day following the right hemiplegia, indicated an abnormal record with evidence of severe dysfunction over the left cerebral hemisphere. Subsequent records taken on the 8th, 13th and 20th day following the angiographic reaction (14, 19 and 26 Jan. 1949 respectively) showed considerable improvement, but there was consistent left frontal focal abnormality in the form of 2 to 4/sec. waves with amplitude up to 100 microvolts. On the 25th day following the angiographic reaction (51 Jan. 1949) a record (Fig. 5) was run during a 20-minute period of digital occlusion of the left common carotid without change in the EEG.

Fig. 8. Normal EEG present on admission (Case 2).
or EKG, either during occlusion or immediately thereafter. On 1 Feb. 1949 a record run during and immediately after left common carotid ligation failed to show any further difference between the two cerebral hemispheres.

Fig. 5. EEG made on 25th day after onset of transient right hemiplegia showing focal left frontal slowing (Case 2).
HEMIPLEGIA ASSOCIATED WITH ANGIOGRAPHY

PHARMACOLOGICAL ACTION OF AND CLINICAL EXPERIENCE WITH DIODRAST

The chemical name of diodrast is 3,5-diiodo-pyridone-N-acetic acid and diethanolamine. Diodrast is known as well by the trade names of diodone, pyelosin, pylumbrin, perabrodil, and umbradil.\textsuperscript{14,16,21} The substance contains 49.8 per cent iodine in firm combination as an organic iodide. It is sterilized by autoclaving and can be resterilized by boiling. According to Marshall\textsuperscript{19} the intravenous lethal dose of a 70 per cent solution for the mouse is 5 gm. and for the rat 4.5 gm./kg. of body weight. Further, the tolerated dose for the mouse is 3.75 gm. and for the rat 3.5 gm./kg. of body weight. Doses ranging from the dose tolerated by man to 10 times that amount have been borne well by dogs.\textsuperscript{19} Heathcote and Gardner\textsuperscript{11} have determined “one equivalent human dose” (1 HD) as 100 mg. of the solid per kg. of body weight. However, these investigators\textsuperscript{11} found no toxic effects in dogs following the intravenous administration of 1.5 gm. of perabrodil per kg. of body weight. Perfusion of the isolated rabbit heart produced increased amplitude of contraction with associated increase in coronary flow when solutions of 1:250 strength were used. Similarly, increase in tone of the isolated intestine was observed which was unaffected by atropine. Intravenous doses of 0.75 gm./kg. in the dog caused transient fall in blood pressure and stimulation of respiration. With larger doses, the duration of the blood pressure effect was longer and the initial respiratory stimulation was followed by depression, which, in the fatal cases, was considered the cause of death. In clinical studies, Edwards and Biguria\textsuperscript{5} found that the intravenous administration of diodrast, 20 cc. of 35 per cent solution, produced routine fall in blood pressure within 1 minute and reached maximum fall in 5 minutes, with recovery to the original level after 15 minutes. The systolic fall was of the order of 15–20 mm. Hg. and the diastolic fall was 8–10 mm. Hg. They reported one episode of vasospasm with subsequent albuminuria following femoral arteriography with 35 per cent diodrast.

In 1937 Demel and Sgalitzer\textsuperscript{4} found evidence to indicate that peripheral arteriography with 20 per cent solution of perabrodil induced prolonged and increased size of the lumen of the finer arterial channels of the limbs of animals. Kristiansen and Cammermeyer\textsuperscript{18} could not demonstrate any immediate or delayed histological changes in the vessels or parenchyma of the rabbit brain that could be attributed to 35 per cent perabrodil cerebral angiography. Robb and Steinberg\textsuperscript{24} reported studies of angiocardiography with the use of 70 per cent diodrast. The individual dosage employed ranged from 17.5 to 31.5 gm. and 238 intravenous injections were carried out in 127 patients without serious effect. Transient venospasm with pain at the site of injection was noted in a few instances.

In this country diodrast was used initially in 70 per cent concentration for cerebral angiography by Gross,\textsuperscript{7,8} but, because of the danger of convulsions, he later recommended its use in the strength of 50 per cent.\textsuperscript{9,10} Other
workers\textsuperscript{6,13,22,23} have advocated 35 per cent diodrast which is used, perhaps, more widely at the present time.

With cinematographic technique, Holm\textsuperscript{13} in 1944, noted smaller calibre of the vessels with 35 per cent perabrodil cerebral angiography than with thorotrast. He interpreted this finding as indicative of increased vascular contraction. Therefore, Holm recommended selection of the contrast medium accordingly, employing thorotrast rather than perabrodil in patients past 50 years of age or when arteriosclerotic and angiospastic conditions were suspected. In 1947 Lindgren\textsuperscript{16} reported the use of 35 per cent umbradil (which is identical to perabrodil in composition according to that author) in 153 patients without a major reaction. Green and Arana\textsuperscript{6} in 1948, described their technique of cerebral angiography performed in 107 cases. These workers used a total of 60 cc. of 35 per cent diodrast (21 gm.) in order to obtain the desired vascular phases and projections without major reactions. Diodrast angiography using 35 per cent solution was performed by Ingraham and Cobb\textsuperscript{14} in a series of 25 patients with age range of 2 to 67 years without undesirable effects.

Diodrast has been employed extensively in intravenous urography. In 1942 Pendergrass, Chamberlin, Godfrey, and Burdick\textsuperscript{21} collected data on 661,800 urographic examinations performed at various centers with different contrast substances. Analysis of questionnaires revealed 26 deaths in addition to those already reported in the literature. There were 10 deaths classified as immediate, occurring within the first 24 hours, all in diodrast injections. In Case II of their report generalized convulsions occurred 8 minutes after intravenous diodrast injection and demise within 45 minutes. Death was attributed to spasm of the cerebral vessels, but no postmortem examination was obtained. Diodrast was not the offending agent in the 16 delayed deaths following urography. A detailed allergic history and use of sensitivity tests were recommended to forestall some of the untoward systemic reactions. Experience with sublingual,\textsuperscript{3} ocular,\textsuperscript{1} and skin tests\textsuperscript{25} for diodrast sensitivity have been reported. Although there is not complete correlation their use prior to diodrast injection appears indicated.

**COMMENT**

The cases presented followed similar patterns of reaction with complete recovery as determined by clinical neurological examination. In Case 1 no further disturbance of the electrical activity of the brain was present on the EEG taken 6 weeks after the angiographic reaction. In Case 2 there was residual left frontal focal abnormality on EEG 3 weeks later. The clinical manifestations may have been associated with induced vasospasm of the intracranial vessels. Tetraethylammonium chloride has been employed widely both as a diagnostic and therapeutic agent in the relief of certain vasospastic syndromes. This drug was used, therefore, to produce temporary autonomic blockade in the hope of influencing what was thought to be vaso-
spasm, but it is difficult to be certain of the exact role played by tetraethylammonium chloride in these cases.

Although the patients had negative ocular tests for diodrast sensitivity, complications occurred. In addition, these patients underwent subsequent angiographic study without incident. So it would seem that the phenomena were not due to diodrast sensitivity. According to the literature, the quantities of 35 per cent diodrast used, 14 and 17.5 gm. in Cases 1 and 2, respectively, do not seem inordinately large.

It is difficult to obtain information concerning the incidence of transitory hemiplegic phenomena with 35 per cent diodrast cerebral angiography since no reports have been found in a careful review of the literature. Since general anesthesia with endotracheal intubation is used in many clinics to perform cerebral angiography it is possible that the depth of anesthesia depresses vasospastic reflex activity and inhibits the onset of hemiplegia. Further, it is, perhaps, possible that transitory cerebrovascular spasm may occur but its clinical expression be masked during the period of recovery from anesthesia.

SUMMARY

Two cases of hemiplegia following 35 per cent diodrast cerebral angiography are reported. The patients manifested no sensitivity to diodrast by the ocular test. The condition is presumed to be due to cerebral vascular arterial spasm and the patients were treated with tetraethylammonium chloride with recovery. The pharmacological action of diodrast has been considered in the light of its clinical effects.

REFERENCES