 Temporary Hemiplegia from Cerebral Injection of Diodrast during Catheter Aortography

Report of Two Cases

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Brain damage manifested by convulsions, hemiplegia, or death may result whenever concentrated Diodrast is injected into the cerebral circulation. Reactions are fairly common following cerebral angiography but may follow contrast visualization of the thoracic aorta by any method. The greatest danger is in aortography when the maximum dye concentration is in the aortic arch. The reactions probably do not result from vascular spasm but from an alteration in the blood-brain barrier. It is possible to minimize the danger of reactions in aortography by observing certain simple precautions. Treatment of brain damage when it occurs, however, is not satisfactory.

Brain damage resulting from cerebral injection of Diodrast or related compounds is perhaps the most common complication of cerebral angiography but the fact that similar grave reactions may result from contrast visualization of the aorta and its major branches is not generally appreciated. There are very few reports of such complications in the literature and the reasons for their occurrence are poorly understood. Since aortography and related procedures are coming into more general use, two cases of temporary hemiplegia in a series of 19 thoracic aortograms employing Diodrast are reported in detail. The method of aortography employed has been described previously.

Case Reports

Case 1. A 35 year old white male administrator was admitted for evaluation of an aortic diastolic murmur noted on routine physical examination. No murmur had been noted on previous examinations and the patient had had no cardiovascular or other symptoms. There was no history of syphilis or rheumatic fever.

The physical examination was within normal limits except for a grade 2 soft blowing aortic diastolic murmur and a grade 1 apical systolic murmur. The blood pressure was 140/80.

Serologic tests for syphilis on blood and spinal fluid were negative. Hemogram, urinalysis and electrocardiogram were within normal limits. A chest roentgenogram was normal except for aortic dilatation. Fluoroscopy revealed overactive aortic pulsations. Serial blood cultures showed no growth.

It was considered that the patient probably had aortic insufficiency but the possibility of an atypical aortic coarctation or other anomaly was also entertained. Consequently, aortography by the percutaneous femoral route was carried out.

Following premedication with 15 mg. morphine sulphate and local xylocaine a polyethylene catheter was inserted into the left femoral artery and passed under brief fluoroscopic control into the ascending aorta. There was no reaction to the intraarterial Diodrast used for positioning the catheter which was shown at the level of the aortic valve (fig. 1a). It was withdrawn about 4 cm. and with the patient performing a Valsalva maneuver, 20 cc. of 70 per cent Diodrast were injected in three to four seconds and a film taken. The ascending aorta was uniformly dilated. The aortic valves showed definite regurgitation of Diodrast (fig. 1b). A second film was made with the patient repositioned. There was no reaction following these injections. To visualize the descending aorta better the catheter was withdrawn about 8 cm. and a third film was taken.

The patient experienced marked discomfort in the left head, neck, and arm but soon said he felt all right. There was a visible flush in the left face and in the area of distribution of the left internal mammary artery. The film showed the injection to be in the mid arch with the left common carotid and left subclavian arteries densely opacified. There was no

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demonstrable abnormality (fig. 1c). The patient helped himself from the table but 15 minutes later a right hemiplegia developed. Fifty cubic centimeters of 50 per cent glucose were given in about 10 minutes after which the patient moved his arm but did not talk. Within 15 minutes he could move all four extremities, perform requests, and answer simple questions. Thirty minutes later there was a relapse with aphasia and almost complete right paresis. The patient made no effort to speak and would not follow simple commands. Fifty cubic centimeters of 50 per cent glucose caused no definite improvement. The temperature rose, reaching a peak of 101.2 F.

Improvement was progressive and in four days the patient appeared normal but felt that his speech was slow. It was learned that he was left handed.

No etiologic diagnosis could be made for the aortic dilatation and regurgitation but because the findings were similar to those of syphilitic aortitis a total course of 10,000,000 units of penicillin was given. Subsequently he returned to a very responsible job without difficulty and has shown no residual cerebral dysfunction.

This patient was in vigorous health and without cerebral disease. A total dose of 20

![Fig. 1. Case 1. (a) Catheter positioning film, right posterior oblique position. The tip is at about the level of the aortic valve. Catheter I.D. 0.062 inch, O.D. 0.082 inch. (b) First aortogram, right posterior oblique position with 20 cc. of 70 per cent Diodrast. The catheter tip is at some distance from the aortic valves. The ascending aorta is uniformly dilated. The aortic valves are well outlined and there is definite reflux of Diodrast into the left ventricle. No other abnormality is seen. (c) Third aortogram, left posterior oblique position, with 20 cc. of 70 per cent Diodrast. The catheter has been withdrawn so that the tip lies in the distal aortic arch. The left common carotid and left subclavian arteries are densely opacified but the arch and proximal descending aorta also contain a considerable density of Diodrast. There are no demonstrable abnormalities.](image-url)

in six hours and falling to normal after several days. Eight hours after the accident, lumbar punc-ture revealed a pressure of 220 mm. and a count of 1 lymphocyte and 12 red blood cells per cubic millimeter. A left stellate ganglion block was performed and the patient placed on papaverine and Dicumarol. By the following morning the patient was able to move his right side and could answer yes and no to questions, usually appropriately. Twelve hours later his right grip was near normal and he could say brief sentences. Speaking was a great effort and there was nominal apraxia, the patient being unable to say his name without prompting. He could read but could not understand much of what he read. A second stellate ganglion block was carried out.

cc. of 70 per cent Diodrast was injected into the aortic arch and the distribution of dye in the roentgenogram indicates that not over 5 cc., somewhat diluted, could have entered the cerebral circulation. The most important contributing factor was certainly the concurrent Valsalva maneuver. This may have caused sufficient circulatory slowing to predispose the brain to damage. A reasonable pathologic interpretation of the reaction is that immediately there was an increased capillary permeability with secondary cerebral edema involving the dis-
tribution of the middle cerebral artery. Possibly the use of 50 per cent glucose decreased the edema for a time. At any rate the reaction became more severe and certainly went on to some type of mild hemorrhage as shown by the spinal fluid. Whether stellate blocks, papaverine, or Dicumarol exerted a beneficial effect cannot be deduced from the record.

Case 2. A 54 year old Negro man was referred to the Tumor Service by the Veterans Administration in connection with a pension application because of roentgen findings of a mediastinal mass. About 20

months before admission there had been a gradual onset of exertional dyspnea and chest pain. Seven months before admission he was treated for severe cardiac decompensation in the dispensary of the Johns Hopkins Hospital with digitalis, mercurial diuretics, and a low salt diet. Diagnoses of syphilitic aortitis, aneurysm of aorta due to syphilis, and arteriosclerotic heart disease were made and he was given a course of 6,000,000 units of penicillin. Following this the patient was essentially symptom free on decreased activity. There was a history of an untreated penile lesion at the age of 17. The remainder of the history was essentially noncontributory.

Physical examination revealed evidence of recent weight loss. The blood pressure was 144/65 and equal in the two arms. Pupils reacted normally to light and accommodation. The trachea was in the midline but there was a distinct tug. Dilated veins were present over the upper chest. The heart was grossly enlarged and the area of retromammary dulness was increased. There was a grade 2 blowing aortic systolic murmur. No diastolic murmur was heard. Peripheral arteries were thickened. The remaining physical findings were noncontributory.

Routine laboratory studies were within normal limits except for a quantitative Kahn test of 32 units. Multiple films of the chest showed a deformity of the barium-filled esophagus produced by a sharply demarcated mediastinal density (fig. 2a). Fluoroscopic study revealed pulsation of the mediastinal mass. An electrocardiogram showed left axis devia-

Fig. 2. Case 2. (a) Roentgenogram of the chest, postero-anterior projection. There is a sharply demarcated mediastinal density extending as high as the right clavicle and measuring 13 cm. in transverse diameter.

(b) Arteriogram, postero-anterior projection using 25 cc. of 70 per cent Diodrast, showing dense opacification of the innominate artery and its branches including the right common carotid artery. There is marked deformity of the origin of the innominate artery. The catheter pursues a grossly abnormal course. Catheter I.D. 0.053 inch, O.D. 0.085 inch.

(c) Aortogram, postero-anterior projection using 20 cc. of 70 per cent Diodrast. There is marked opacification of the left common carotid artery which is narrowed at its mouth. The aortic arch shadow is widened and distorted.
while the patient performed a Valsalva maneuver. Since the catheter tip was in the innominate artery (fig. 2b), it was then withdrawn in stages to about the center of the arch. A film showed the opaque medium largely in the left carotid. After further withdrawal a fourth film was made which also showed filling of the left common carotid artery. A total of about 110 cc. of 70 per cent Diodrast had been injected over a 90-minute period. Films revealed findings consistent with syphilitic aortitis and aneurysm of the aortic arch (fig. 2c). Approximately one hour after the completion of arteriography there was a sudden onset of left hemiplegia accompanied by marked apprehension and subjective numbness of the left side. Fifty cubic centimeters of 50 per cent glucose were started intravenously without delay. Some function had reappeared in the left leg just prior to glucose administration and during the infusion motor function began to return in the left arm. There was no change in vital signs or electrocardiographic findings. Thirty minutes later there was only slight left sided weakness and the following morning the patient showed no residual neurological disturbance. Diagnoses at discharge were the same as those made at Johns Hopkins Hospital and the patient was referred to that institution to be followed.

The tendency of the catheter repeatedly to enter aortic arch branches indicates gross deformity of the arch region and is strongly suggestive in itself of aneurysm. Special care must be taken when the anatomic relations are so distorted in order to prevent injection of contrast material directly into a branch of the aortic arch. Although this patient had rather advanced cardiovascular disease, there was no gross evidence of cerebral involvement and the reaction is reasonably ascribable only to the Diodrast injection. There was no evidence of Diodrast sensitivity but there was ample opportunity for concentrated Diodrast to reach the right hemisphere at a time when the circulation was slowed by the Valsalva maneuver, since at least 50 cc. were injected directly into the innominate artery. There was also obvious chance for Diodrast to reach the left hemisphere under similar circumstances but this appears to have caused no trouble. It is likely that the cerebral reaction consisted only of edema. It was, however, in the right or more silent hemisphere and no spinal fluid examination was carried out to exclude hemorrhage.

**DISCUSSION**

Cerebral arteriography as originally reported by Egas Moniz in 1927 employed 25 per cent sodium iodide as a contrast medium. There were frequent reactions and an appreciable mortality. For this reason Thorotrast was introduced but has not been widely used, at least in this country, because of the reported late incidence of sarcoma and radiation injury. It was not until the use of dilute Diodrast was popularized that this procedure became generally accepted.*

Diodrast and similar compounds are used in hypertonic solutions, 35 per cent Diodrast having roughly twice the osmotic pressure of blood. In clinical amounts there is a brief blood pressure drop, while large doses may produce prolonged hypotension, and respiratory stimulation followed by depression. Rats tolerate 3.5 Gm. per kilogram while 4.5 Gm. is a lethal dose. This compares with 3.75 Gm. and 5 Gm. respectively in mice. Dogs show no toxic effects with 1.5 Gm. per kilogram while 4 Gm. per kilogram gives a mortality of about 20 per cent. The lethal dose in man is not known. Generally it is considered permissible to give single injections of about 0.5 to 1.0 Gm. per kilogram in adults which may be repeated after an interval. Such large doses are commonly used, however, only in angiocardiography.

Important human reactions appear to be related to hypersensitivity, cardiac arrhythmias, and cerebral damage. In a survey of reactions following Diodrast injection, mainly in urology, Pendergrass and his co-workers in 1942 reported 26 deaths in 661,800 cases. Ten of these were immediate and appeared to be on an anaphylactoid basis. The causes of the remainder were not clear. It has recently been shown that angiocardiography may bring about important electrocardiographic changes.

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* Diodrast is a trade name for the diethanolamine salt of 3.5 diiodo-4-pyridone-N-acetic acid. Other names include Umbradil, Dijodon, Perabrodil, Diodone, Pyelosil, and Pylumbrin. Umbradil forte is a 50 per cent solution of Umbradil with diethylamine added. Umbradil-methyl-glucamine is the methyl-glucamine salt while Ioduron is the morpholine salt. All are made up by weight volume and contain about 50 per cent iodine in firm combination.
and this toxic cardiac action may account for a few of the deaths from this procedure. In this regard Helmsworth, McGuire, and Fel- son reported an arrhythmia and sudden death following coronary arteriography. 

By far the most important group of reactions are those resulting from cerebral damage. Dotter and Steinberg report 23 deaths in a series of 6,824 angio- cardiograms collected by questionnaire. The majority of these occurred in patients with congenital heart disease with septal defects which probably permitted concentrated Diodrast to go more or less directly to the brain. Death was generally from respiratory failure. Minor cerebral reactions to Diodrast following angio- cardiography probably occur even more frequently. Gross reported two cases of jacksonian convulsions and one hemiplegia following the use of 70 per cent Diodrast in 10 patients but only one convulsion in 10 patients when 50 per cent Diodrast was employed for cerebral arteriography. Dyke reported a severe cerebral reaction follow- ing the use of 35 cc. of 70 per cent Diodrast for a cerebral arteriogram. During the past 10 years Diodrast has generally been employed in 35 per cent solution and there have been very few reports of complications. Important papers listing no major complications include: Ingraham and Cobb, 1947, 25 cases; Lindgren, 1947, 153 cases; Green and Arana, 1948, 107 cases; Torkildsen, 1949, 2,000 cases. In 1949, however, Chusid, Robinson, and Margules-Lavergne presented two cases of transient hemiplegia complicating cerebral arteriography at the New York Society of Neurosurgery and in the general discussion 21 additional similar complications following cerebral angiography with 35 per cent Diodrast were reported. Important electroencephalographic changes lasting up to 27 days occurred in Chusid's two cases. Dunsmore, Scoville, and Whitcomb in 1951 reported 11 cerebral complications in 147 carotid angiograms. These included three deaths, four nonfatal hemiplegias with residual dysfunc- tion, two transient hemiplegias, and three seizures. It is apparent that brain damage following cerebral Diodrast injection is more common than has been appreciated.

It has generally been assumed on the basis of Holm's work on arterial cinematography and the early paucity of findings in experimental animals that vasospasm plays the major role in the causation of complications. Although transient cerebral vasospasm does occur in animals under certain conditions after Diodrast injection it has not been proved that it occurs in humans or that it is of sufficient degree to cause symptoms. Demel and Sgalitzer reported that peripheral arteriography with 20 per cent Perabrodil (Diodrast) induced prolonged increase in the lumen of smaller arteries in animals. In actual practice visible vasodilatation with a flush resembling that of histamine is not infrequently observed in humans as in the two cases here reported. Certainly further investigation is necessary before it can be concluded that Diodrast causes cerebral arterial spasm in humans under clinical conditions and such studies are difficult because of the peculiarities of cerebral blood flow. The excellent work of Bromen and Olsson with intravascular injection of the vital dye trypan blue demonstrated very clearly that the probable cause of cerebral damage to Diodrast and related compounds was a disturbance of the blood brain barrier resulting in a pathologic sequence of events including increased vascular permeability, cerebral edema, punctate hemorrhages, stasis, and infarction. The stage of damage reached in animals depended primarily on the concentration of the contrast medium and the time that it was present in the cerebral arteries. Damage, however, was greatly augmented by repeated injections of Diodrast compounds, concomitant slowing of the cerebral circulation, or prior subclinical damage with unrelated substances. They also demonstrated that reactions were probably not due primarily to the increased osmotic pressure of the contrast substances alone as had been maintained earlier since it took concentrations of such substances as sodium chloride or glucose equivalent to much higher osmotic pressures to produce even minor pathological changes.

Contrast visualization of the proximal aorta and its great branches in adults requires the
use of 70 per cent Diodrast and under certain circumstances considerable amounts of injection material may enter the brain. Such procedures are being used with increasing frequency yet there are very few reports of cerebral complications. Freeman and associates, in 1949 reported one case of temporary hemiplegia and one case of prolonged brain stem and cerebellar damage resulting from retrograde aortography via the carotid artery. A case of left hemiplegia has been reported by Bierman and co-workers, following right carotid catheterization with injection of only 11 cc. of 35 per cent Diodrast into the internal carotid artery.3 In these cases complications may be ascribable to carotid manipulation or temporary compression as well as to the injection of Diodrast. Immediate convulsions with death after four hours occurred in a case of a 36 year old woman when an injection of 22 cc. of 70 per cent Diodrast was made into the mouth of an anomalous left innominate artery using the method of Radner.27, 28 As in the two cases reported in the present paper this reaction may reasonably be ascribed to cerebral damage from Diodrast alone.

It is thus clear that concentrated Diodrast injected into the aortic arch or directly into the innominate, carotid, or left subclavian arteries may gain access to the brain via the vertebral or carotid arteries. Ordinarily, the relatively small volumes of Diodrast are safely diluted before they reach the brain but there is always some danger and whenever there are repeated injections or where the cerebral circulation has been slowed as by the Valsalva maneuver there is grave danger of serious reaction. For these reasons, the following precautions are strongly recommended during thoracic arteriographic procedures:4 (1) Do not inject dye in such a manner that the maximum concentration is in the arch unless this is essential to the success of the procedure. (2) If a catheter is employed always ascertain where the tip is by a positioning film and do not have it in one of the aortic arch branches if 70 per cent Diodrast is to be used. (3) The Valsalva maneuver2 should not be employed whenever Diodrast may directly enter the cerebral circulation. (4) After a preliminary test, apply digital carotid pressure to prevent concentrated dye from reaching the brain if an injection is made directly into the aortic arch.3 This should probably be done also whenever a coarctation of the aorta is examined by a proximally inserted catheter as concentration of the dye in the arch region is favored by this anomaly. (5) The use of 35 per cent Diodrast is satisfactory in infants and small children and here 70 per cent Diodrast should be avoided. (6) With single film technics good pictures may frequently be obtained with as little as 10 cc. of 70 per cent Diodrast. If a rapid changer is available half of this dose may suffice. The smallest volume permitting adequate examination should be employed.

It would also appear desirable to avoid direct injection into the coronary ostia unless specific information about the coronary arteries is required. These precautions apply to all types of catheter arteriography,4, 13, 27 retrograde arteriography,2 and aortography by trocar29 or needle.30 In addition to the above measures suitable emergency drugs should be available to combat an anaphylactoid reaction, hypotension, or respiratory failure. It has been suggested also that barbiturate anesthesia41 provides some protection against brain damage. Antihistaminic drugs do not appear to protect against reactions.32

There is no generally advocated method of treatment should a cerebral Diodrast reaction occur. Most therapy has been aimed at combatting arterial spasm and for this purpose vasodilators such as papaverine and tetraethylammonium chloride as well as sympathetic blocking by means of serial stellate ganglion injections have been employed.1, 39 Procedures to combat cerebral edema, as the injection of hypertonic glucose, may be tried but their effectiveness is unknown. The use of anticoagulants would appear to have much the same rationale as their use in coronary occlusion. All methods of therapy, however, need careful evaluation in animals and a fruitful attack would appear to be by employing the vital dye technique of Bremen and Olson23 in statistically valid series of experimental cases. It is hoped that a truly satisfactory
inert contrast medium will eventually be forthcoming.\textsuperscript{33}

**SUMMARY**

Two cases of temporary hemiplegia immediately following thoracic aortography are reported. Seventy per cent Diodyrast was employed as a contrast medium. The literature on arteriography is reviewed for similar cases. Reactions of this type may result whenever concentrated Diodyrast enters the cerebral circulation and their occurrence is probably favored by repeated injections, slowing of the cerebral circulation, or preexisting pathological states. Evidence supports the contention that damage is due to alterations in the blood brain barrier rather than vascular spasm. Means of avoiding reactions and possible therapeutic measures are outlined.

**SUMARIO Español**

Daño cerebral manifestado por convulsiones, hemiplegia, o muerte puede resultar cuando Diodyrast concentrado es inyectado en la circulación cerebral. Reacciones son bastante comunes consiguiente a angiocardiografía cerebral y pueden también ser consiguientes a angiocardiografía de la aorta torácica por cualquier método. El peligro más grande es en la aortografía cuando la concentración máxima del tinte se encuentra en el arco aórtico. Las reacciones probablemente no resultan debido a espasmo vascular pero si a alteración producida mediante la barrera entre el cerebro y la sangre creada por el tinte. Es posible reducir al mínimo el peligro de reacciones en aortografías observando precauciones simples. El tratamiento para el daño cerebral cuando este ocurre no es satisfactorio.

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