Vascular Complications With Use of Methysergide

CHARLES E. RACKLEY, MD; CHARLES E. MENGEL, MD; MARVIN POMERANTZ, MD; AND HENRY D. McINTOSH, MD, DURHAM, NC

VASCULAR headaches are thought to result from a disturbance in vasomotor tone. The pain of migraine has been attributed to vasodilatation of the temporal arteries. Therefore, therapy has been directed toward augmenting vascular tone. The demonstration of the vasomotor effects of serotonin suggested the possibility of this hormone being causally related to migraine. Subsequent studies failed to demonstrate an elevation of the blood level of serotonin in patients with migraine, nor did the administration of the agent produce the syndrome.[1] Despite these negative findings, methysergide (Sansert), a serotonin antagonist, was tried empirically in patients with migraine and led to significant clinical improvement. Since these initial observations, methysergide has been used extensively in patients with vascular headaches. As serotonin affects vessels throughout the body, the antagonist methysergide might be expected to have equally widespread vascular effects. This report describes unusual vasoconstrictor reactions in two patients resulting from the use of methysergide.

Report of Cases

CASE 1.—This 49-year-old white woman has experienced migraine headaches since the age of 14 years. The syndrome was characterized by one or two days of irritability followed by burning of the left ear and scotoma. The headaches were intense and lasted until the patient could go to sleep. She had rheumatic heart disease with mitral stenosis which was treated by a closed valvulotomy. In addition, during the last five years, she had had numerous hospital admissions for pneumonia, pleurisy, thrombophlebitis, pulmonary infarctions, and on one occasion, septicemia. The headaches complicated the therapy of these conditions and on many occasions meperidine hydrochloride was necessary for relief. Methysergide maleate 2 mg three times daily was prescribed and taken intermittently for several weeks with questionable results. The patient's present admission was for evaluation of pleuritic chest pain, sinus tenderness, and fever.

Her temperature was 38.8 C (101.8 F), pulse 102 beats per minute, blood pressure 160/60 mm Hg, and she was in acute respiratory distress. There was no cyanosis, and the neck veins were not distended. Purulent material was seen in the left nostril. Diffuse fine rales were heard below the right scapular. There was egophony at the right lower base. The heart was enlarged 1 cm beyond the mid clavicular line. There was a grade 3 apical holosystolic murmur which radiated into the axilla. A grade 2 pulmonic systolic ejection murmur and a diastolic blow were heard along the left sternal border. A ventricular gallop was audible at the apex. Pedal pulses were palpable, and no bruits were heard over the femorals. There was 2+ pitting edema of the lower extremities. Results of neurologic examination were within normal limits.

Accessory clinical findings included hemoglobin 10.9 gm/100 cc and white blood cell count (WBC) 20,850/cu mm with 89% polymorphonuclear cells, 1% stabs, 1% eosinophils, 8% small lymphs and 1% monocytes. Urinalysis revealed a specific gravity of 1.015, trace of protein, negative for sugar, and 4 WBC per high-power field in the sediment. The stool guaiac was negative. Blood urea nitrogen (BUN) was 13 mg/100 cc and the urine culture negative. Electrocardiogram (ECG) demonstrated digitalis effects. The chest x-ray film revealed a pneumonic process in the right middle lobe. Sputum smear was loaded with staphylococci, and the patient was treated with sodium methicillin (Staphcillin) and kanamycin sulface (Kantrex).

Three days following admission the patient developed a severe migraine headache and was given methysergide maleate, 4 mg each day in a long-acting preparation. The next day the patient experienced a sudden episode of squeezing left anterior chest pain which radiated into the left arm. She described parasthesias in the lower extremities. Examination was unremarkable, and the ECG did not indicate myocardial injury or ischemia.

The second day after methysergide administration, the femoral pulses were noted to be diminished and bilateral bruits were heard. No pulses were detectable in the feet. The diagnostic possibilities considered were myocardial infarction, dissecting aneurysm of the aorta, and saddle embolus from the damaged mitral valve. The patient had several more bouts of chest pain with radiation into the neck that day, and one episode was im-

Received for publication Aug 2, 1965; accepted Sept 20.

From the departments of medicine and surgery, Duke University Medical Center, Durham.

Reprint requests to Duke University Medical Center, Durham, NC 27706 (Dr. Rackley).

mediately terminated with carotid massage. Other bouts of chest pain were relieved with nitroglycerin. The methysergide was discontinued with relief of symptoms, return of pulses to the feet, and disappearance of the femoral bruits.

The patient was again given methysergide maleate, 2 mg twice daily. The pulses in the lower extremities became strikingly diminished, and the femoral buits were again audible. Oscillometrics confirmed the marked diminution of the pulsations in the legs. The patient had no further episodes of chest pain. Methysergide was again discontinued and the pulses in the lower extremities returned to normal within two days.

Two months later the patient was readmitted for additional studies following administration of methysergide. The physical examination remained unchanged except for a grade 2 bruit over the right femoral and a grade 1 bruit over the left femoral. Pulses were palpable in the feet. Daily oscillometric readings were taken in both legs as well as auscultation over the femoral areas. The patient was administered methysergide maleate, 2 mg three times each day, and the results are indicated in the Figure. During each of the study phases, levels of blood serotonin, blood histamine, urinary 5-hydroxyindolacetic acid, and other urinary aromatic amines were determined.[2-7] No significant deviations from normal were noted in any of these parameters during either the control or special study periods. Following discharge, the patient continued to have severe migraine headaches frequently requiring the use of narcotics. No further episodes of chest pain occurred.

COMMENT: This 49-year-old white woman had the migraine syndrome since age 14. During the past five years she underwent a valvotomy for mitral stenosis and experienced recurrent thrombophlebitis and pulmonary emboli. Recently she was treated with methysergide maleate, 2 mg three times daily for her migraine. She developed chest pain which was relieved with carotid massage and nitroglycerin, and also experienced parasthesias of the lower extremities with femoral bruits and absent pulses in the feet. Methysergide was discontinued with disappearance of chest pain and return of pulses in the lower extremities. The patient was given methysergide, and diminished oscillometrics in the legs confirmed the vasospasm in the lower extremities. Histamine and serotonin studies were normal during control and studies with methysergide.

CASE 2.—This 29-year-old white woman was admitted with the typical symptoms of claudication. Two weeks prior to admission she developed bilateral calf pain with walking but experienced prompt relief when resting. One week before admission the patient noticed that both feet were cool, and the pain became almost constant in the left leg.

The findings on physical examination were limited to the lower extremities. Bilaterally weak femoral pulses were palpated, but no pulsations could be felt below the femorals. Both feet were cool, the left being cooler than the right. Results of routine laboratory studies were within normal limits.

The day following admission, bilateral femoral arteriograms were performed. The left femoral artery could not be entered percutaneously and a cutdown was necessary in order to perform the arteriogram. The vessels were diffusely diminished in caliber, but no definite occlusions were demonstrated. There was no evidence of any atherosclerotic process on the arteriograms. Following this procedure, the information was obtained that the patient had migraine headaches and three days before the first attack of calf pain had been placed on methysergide. While in the hospital the patient had gradual improvement of her symptoms, and palpable pulses returned to the lower extremities. The discharge diagnosis was arterial insufficiency secondary to the drug methysergide.

One month later the patient was seen in the outpatient clinic. She had remained completely asymptomatic in the interval. Oscilliometric values were normal in both legs. Arrangements were made to again administer methysergide, but the patient was lost to followup.

COMMENT: This 29-year-old white woman had the sudden onset of typical claudication two weeks before admission. Examination revealed faint femoral pulsations and no pulses in the feet. Bilateral femoral arteriograms were performed and the left femoral artery required a cutdown due to diminution of vessel size. Both femoral arteries were markedly reduced in caliber without evidence of an artherosclerotic process. Following the procedure a history of migraine headache was obtained from the patient, and she had been placed on a regimen of methysergide several days prior to the onset of claudication. Symptoms of claudication disappeared and pulses in the lower extremities returned to normal after discontinuation of the methysergide.

Comment

Wolff has demonstrated that the painful attacks of vascular headache are associated with dilatation of the intracranial and extracranial small blood vessel.[8-10] However, induced dilatation of these vessels by other

means is not generally painful nor is it accompanied by the other features of migraine. Such observations suggested that a localized inflammation of the vessels might be produced by a substance that affected capillary permeability or lowered pain threshold. Chapman et al have demonstrated that neurokinin, a polypeptide, and a neurokenin-forming proteolytic enzyme could be recovered from the tender region of the head during vascular headache.[11] Methysergide, an antagonist of the hormone serotonin was reported to be effective in the prophylaxis of vascular headaches. Studies were undertaken to investigate the role of serotonin in the pathophysiology of vascular headache.

Brody described in 1900 the presence of a vasoconstrictor substance in the blood,[12] which was later identified by Rappaport and colleagues as 5-hydroxytryptamine (serotonin).[13] Serotonin was subsequently demonstrated to play a complex role in the regulation of vasomotor tone. Various reports indicated a close similarity between the vascular changes accompanying Raynaud's phenomenon and those produced by serotonin.[14] These results, however, were at variance with the clinical picture of the carcinoid syndrome. Patients with metastatic carcinoid who produce excessive amounts of serotonin suffer profound vascular effects including flushing, cyanosis and pulmonary vasoconstriction, but these patients do not generally complain of migraine headache. Serotonin failed to produce headaches when injected into susceptible migrainous patients.[1] The bioassay of subcutaneous fluid obtained from regions of the head during migraine attacks failed to reveal the presence of a serotonin-like material.[15]

If serotonin is operative in the production of migraine, the site of action in the peripheral vessels or the central vasomotor center is uncertain. Serotonin participates significantly in allergy phenomena, and Rowley and Benditt have shown that injection of serotonin in the rat's paw produced edema similar to that following histamine injection. Lysergic acid diethylamide is a known antiserotonin agent.[16] Doepfner and Cerletti tested many lysergic acid derivatives in regard to inhibitory qualities against histamine-induced edema in experimental animals.[17] In their studies the injection 1μg of serotonin per paw produced more edema than did a 200 times greater dose of histamine. Two derivatives of lysergic acid diethylamide proved to be definitely stronger antiserotonin compounds than did that substance itself, and the more potent compound was methysergide. In these experiments the edema-producing agent and the antagonist were injected subcutaneously in the animal's paw. This would indicate that antiserotonin action of methysergide is a peripheral process.

STUDY DAYS		1	2	3	4	5	6	7
OSCILLOMETRICS	R. Leg	3+	1+	1+	1/2+	3+	3+	4+
	L. Leg	3+	1 1/4+	1 1/2+	3/4+	3 1/2+	5+	4+
METHYSERGIDE ADMINISTRATION			▨	▨	▨			

▨ 2 mgm - 3 times per day

Observations on patient 1 illustrate diminution in arterial pulsations of lower extremities during administration of methysergide. Blood serotonin, blood histamine, urinary 5-hydroxyindolacetic acid, and other urinary aromatic amines showed normal levels during the entire study.

However, the failure to demonstrate elevated blood levels of serotonin and the absence of a serotonin-like material in the subcutaneous fluid obtained from tender extracranial area in patients with migraine suggest that the serotonin in the brain may influence vasomotor control. Bhargave and Tangri have shown that the injection of serotonin into the cerebral ventricles of dogs caused inhibition of the pressor response associated with occlusion of the carotid artery and inhibition of the depressor response evoked by stimulation of the central end of the cut vagus.[18] It is thus postulated that lysergic acid derivatives might obtain some of their pharmocologic activity through the combination with serotonin receptor sites. This would conceivably alter neural function by changing the requirements for stimulation. Thus, there are experimental data that indicate both a central and peripheral mechanism in the antiserotonin activity of methysergide.

Since the precise mechanism of methysergide antagonism to serotonin is not known, the investigation of histamine and serotonin substances in the blood and urine during methysergide administration was undertaken. In patient 1 the study of blood and

urinary histamine and serotonin substances and breakdown products indicated no detectable abnormality during or after methysergide therapy. The results of one large series of patients treated with methysergide suggested that side effects were greater in those patients taking more than 8 mg/day.[19] However, a number of patients with malignant carcinoid have been treated with 8 to 24 mg of methysergide maleate per day without apparent side effects.[20] Therefore in the first patient of this report we could not demonstrate detectable abnormalities in histamine or serotonin metabolism while on a regimen of methysergide nor did the vascular complications appear dose-related.

Methysergide has been used in several extensive studies for the evaluation of the amelioration of migraine headache.[19,21-24] Favorable responses to methysergide have been reported both in migraine and in cluster-type headaches. A large study at the Mayo Clinic which involved 132 patients with various vasomotor dilating headaches indicated a favorable response in 80% following the use of methysergide.[21] However, this study reported side effects in 10% of the patients which necessitated termination of the drug. Side effects included nausea, dizziness, weakness, nervousness, and dreamy state. Three patients reported claudication, and one patient was reported as having had a "heart attack," though confirmatory evidence was lacking. Several other isolated reports have described acute ischemia in limbs following methysergide treatment for headaches (25-27). Another study described not only peripheral vascular insufficiency in a 14-year-old whose vascular-type headaches had been treated with methysergide, but also an abnormal ECG reading with T-wave inversion across the precordium which reverted to normal following termination of methysergide treatment.[24]

The two patients described in this report demonstrate several problems warranting additional comment. Previous reports in the literature attributing acute ischemia of the limbs to methysergide therapy have occurred in men. In the series of Rooke et al two of the three cases of claudication were in men 36 and 37 years old.[4] The third patient's age and sex were not mentioned. Graham reported 21 patients with symptoms of claudication and 14 more with symptoms and pulse changes.[19] The two reports of claudication in the literature were also men. The patients in this report were women, ages 49 and 29 respectively.

Since claudication of the lower extremities in young women on an atherosclerotic basis is distinctly unusual, the differential diagnosis in each patient consisted of etiologies requiring surgical intervention. Patient 1 had known rheumatic heart disease with previous mitral-valve surgery, and the onset of paresthesias and diminished pulses in the feet suggested and embolus to the abdominal aorta. The occurrence of chest pain in this patient made a dissecting aneurysm a possibility. In patient 2 the sudden onset of pain and claudication in the legs again suggested an embolus from an unsuspected cardiac lesion. Indeed, surgery was necessary in the second patient in exposing the small left femoral artery for the purpose of an arteriogram.

Although the initial sudies with methysergide demonstrated an antiserotonin and an anti-edema action in experimental animals, methysergide was originally introduced and investigated as an agent for the prevention of vascular headache. It was felt that methysergide did not produce direct or immediate vasoconstriction. However, both patients in this report developed symptoms referable to vasoconstriction, within one to three days following methysergide ingestion. Patient 1 had a significant decrease in the pulsations in the legs as measured by the oscillometer the day following methysergide therapy. We may conclude from the experience in these two patients that the vasoconstrictor properties of methysergide can be rather prompt in onset.

Finally attention should be directed to the possibility of large vessel constriction by methysergide. Both patients had diminished femoral pulsations, and this was proved in patient 2 by surgical exposure of the vessel and arteriography. Perhaps even more alarming was the development of chest pain compatible with coronary insufficiency in patient 1. There were no associated ECG changes, but the chest pain did respond convincingly to carotid massage and nitroglycerin. Graham's experience in following up 500 patients with vascular headaches for a

period of three years treated with methysergide yielded only four patients with the onset or increase in existing anginal pains.[19] The author did not elucidate further the relationship of methysergide to the production of coronary insufficiency. Emphasis was made that patients with vascular disease or a disposition to vascular disease should not receive methysergide. In the report of Rooke et al a 50-year-old man was said to have had a heart attack while on methysergide but details were unavailable.[21] In Graham's series two patients had coronaries, but the relationship to methysergide was uncertain.

In conclusion, the two women in this report, ages 49 and 29, developed symptoms of severe arterial insufficiency while on methysergide therapy for migraine headache. The onset of vasoconstrictor phenomena was abrupt in both patients following the administration of the drug. Neither patient had evidence of arterial disease, although one patient had rheumatic heart disease with recurrent pulmonary emboli. Demonstrable abnormalities in histamine and serotonin metabolism could not be detected in one patient during administration of methysergide. Methysergide is still highly regarded for its therapeutic benefit in patients with vascular headaches, but patients must be carefully observed since severe arterial insufficiency may occur in patients without evidence of vascular disease.

Summary

Two patients who developed vascular complications while on methysergide for migraine headache are described. Both women developed arterial insufficiency of the lower extremities, and one patient had several bouts of chest pain compatible with coronary insufficiency. Biochemical studies were performed in one patient during methysergide administration, and no detectable changes were found in histamine or serotonin metabolism. The neurophysiological role of serotonin in the maintenance of vascular tone and the possible relationship to the production of migraine headache are discussed. The literature is reviewed with particular reference to previous vascular complications in patients with migraine on methysergide therapy. It is concluded that methysergide may produce vascular insufficiency in susceptible patients, and one must be alerted to this problem in patients with migraine headache receiving methysergide.

This work was supported in part by grants HE-07563, HE-5369, CA-06452, and MO1-FR30 from the National Institutes of Health.

Generic and Trade Names of Drugs

Methysergide maleate—*Sansert.*
Sodium methicillin—*Dimocillin RT, Staphcillin.*
Kanamycin sulfate—*Kantrex.*

REFERENCES

1. Kimball, R.W.; Friedman, A.P.; and Villejo, E.: Effect of Serotonin in Migraine Patients, *Neurol* **10**:107, 1960.
2. Shore, P.A.; Burkhalter, E.; and Cohn, V.H., Jr.: A Method for the Fluorometric Assay of Histamine in Tissues, *J Pharmacol Exp Ther* **127**:182, 1959.
3. Undenfriend, S.; Titus, E.; and Weissback, H.: The Identification of 5-hydroxy Indolacetic Acid in Normal Urine and a Method for its Assay, *J Biol Chem* **216**:499, 1955.
4. Dalgliesh, C.E.: Isolation and Examination of Urinary Metabolites Containing an Aromatic System, *J Clin Path* **8**: 73, 1955.
5. Dalgliesh, C.E.: Two Dimensional Paper Chromatography of Urinary Indoles and Related Substances, *Biochem J* **64**:481, 1956.
6. Mengel, C.E., and Kelly, M.G.: Biochemical and Morphologic Changes in a Mast Cell Neoplasm During Treatment With Cyclophosphamide, *Cancer Res* **21**:1545, 1961.
7. Mengel, C.E., et al: Clinical and Biochemical Effects of Cyclophosphamide in Patients With Malignant Carcinoid, *Amer J Med* **38**:396, 1965.
8. Graham, J.R., and Wolff, H.G.: Mechanism of Migraine Headache and Action of Ergotamine Tartrate, *Arch Neurol Psychiat* **39**:737-763 (April) 1938.
9. Wolff, H.G.: *Headache and Other Head Pain,* New York: Oxford University Press, 1948.
10. Wolff, H.G.: Headache Mechanisms, *Intern Arch Allergy* **7**:210, 1955.
11. Chapman, L.F., et al: A Humoral Agent Implicated in Vascular Headache of the Migraine Type, *Arch Neurol* **3**:223, 1960.
12. Brodie, T.G.: The Immediate Action of an Intravenous Injection of Blood Serum, *J Physiol* **26**:48, 1900.
13. Rapport, M.M., et al: Partial Purification of Vasoconstrictor in Beef Serum, *J Biol Chem* **174**:735, 1948.
14. Halpern, A., et al: Raynaud's Disease, Raynaud's Phenomenon and Serotonin, *Angiology* **11**:151, 1960.
15. Dalessio, D.J., et al: Studies on Headache: Relevance of Prophylactic Action of UML-491 in Vascular Headache of Migraine Type to Pathophysiology of Syndrome, *World Neurol* **3**:66, 1962.
16. Rowley, D.A., and Bendict, E.P.: 5-Hydroxytryptamine and Histamine as Mediators of the Vascular Injury Produced by Agents Which Damage Mast Cells in Rats, *J Exp Med* **103**:399, 1956.
17. Doepfner, W., and Cerletti, A.: Comparison of Lysergic Acid Derivatives and Antihistamines as Inhibitors of the Edema Provoked in the Rats Paw by Serotonin, *Intern Arch Allerg* **12**:89, 1958.
18. Bhargava, K.P., and Tangri, K.K.: Central Vasomotor Effects of 5-hydroxytryptamine, *Brit J Pharmacol* **14**: 411, 1959.
19. Graham, J.R.: Methysergide for Prevention of Headache, *New Eng J Med* **270**:67, 1965.
20. Mengel, C.E.: Therapy of Malignant Carcinoid, *Ann Intern Med* **62**:587, 1965.
21. Rooke, E.D., et al: Vasodilating Headaches: Suggested Classification and Results of Prophylactic Treatment With UML-491 (Methysergide), *Proc Staff Meet Mayo Clin* **37**: 433, 1962.
22. Friedman, A.P., and Fosin, S.: Evaluation of UML-491 in the Treatment of Vascular Headaches, *Arch Neurol* **4**:19, 1961.
23. Friedman, A.P., and Elkind, A.H.: Appraisal of Methysergide in Treatment of Vascular Headaches of Migraine Type, *JAMA* **184**:125, 1963.
24. Dalessio, D.J., et al: Studies on Headache, *Arch Neurol* **4**:235, 1961.
25. Graham, J.R.: Use of a New Compound UML-491 (1-methyl-D-lysergic acid butanolamide) in the Prevention of Various Types of Headache, *New Eng J Med* **263**:1273, 1960.
26. Ureles, A.L., and Rob, C.: Acute Ischemia of a Limb Complicating Methysergide Maleate Therapy, *JAMA* **183**: 1041, 1963.
27. Daniell, H.W.: Vasospastic Reaction to Methysergide Maleate Simulating Leriche Syndrome, *Ann Intern Med* **60**:881, 1964.