ACUTE VASCULAR INSUFFICIENCY IN THE LOWER EXTREMITIES ASSOCIATED WITH METHYSERGIDE THERAPY FOR MIGRAINE

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Migraine, a common and disabling type of vascular headache, has long been a troublesome problem in prevention and treatment. According to Friedman and Losin,[1] 400 different methods of treatment have been reported, thus testifying to their inadequacy. In spite of numerous investigations during the past two decades, the basic aetiology remains obscure.[2] In 1937 Graham and Wolff (Graham[3]) demonstrated that the pain of the migraine attack is associated with dilatation of branches of the cranial vessels, and since then ergot alkaloids have been the principal drugs used in the symptomatic management. Although vasodilatation accompanies the attack, it is not considered to be the sole cause of symptoms and certain chemical agents produced locally, among them histamine, bradykinin, acetylocholine, neurokinin and serotonin, have been implicated in the production of the pain.[4]

Since the introduction of a powerful serotonin antagonist, methysergide (I-methyl-D-lysergic acid butanolamide, or UML-491 or 'deseril'), numerous reports on its use in the treatment of migraine and other vascular headaches have appeared. Initially, Sicuteri[5] and then Graham[3] and Friedman[6] drew attention to the benefit obtained, and others (Friedman and Losin,[1] Hale and Reed,[2] Rooke *et al.*,[7] Ekbom,[8] Dalessio *et al.*,[9] Leigh,[10] and McGregor[11]) have reported encouraging results.

The incidence of side-effects is as high as 39% in some reported series, but they are usually mild and transient. They include gastro-intestinal symptoms, with nausea and vomiting being the most common, as well as neurological and mental disturbances. In his initial report Sicuteri[5] stated that there was an absence of vasoconstrictor action, but since then 2 cases of severe arterial insufficiency in the extremities have been reported by Friedman and Losin[1] and Dalessio *et al.*,[9] and intermittent claudication has also been observed.[3] The purpose of this paper is to report another case of severe, acute arterial insufficiency of the lower extremities developing in a patient treated for migraine with methysergide.

CASE REPORT

A schoolgirl of 15 years was admitted to hospital on 13 November 1962 for pain and coldness of the feet. She suffered from migraine for 5 years and for this she took 'migryl' occasionally (a preparation containing ergotamine tartrate). Apart from migraine, the past history was essentially normal. Before the school examinations at the end of term, the attacks increased in frequency and she found that 'migryl' was ineffective. Her doctor then prescribed methysergide ('deseril' tabs. 2 mg. *t.d.s.*). Three days later she felt pain in both calves on walking, which was relieved by rest. That night she noticed tingling in both her feet and her toes, which recurred in bed 8 hours later. Claudication developed again 2 days later while dancing, and late that night she experienced paraesthesiae in her feet—being woken by severe pain and coldness felt more in the outer border of the left foot.

Examination on the following morning showed a well-looking adolescent girl. The temperature was 98°F, the pulse rate 80/min. and regular, and the blood pressure was 104/60 mm.Hg in both arms. No abnormalities were found in the head and neck, apart from the left pupil, which was slightly larger than the right, nor in the heart, chest or abdomen.

Both her legs and feet were cold and pale with the presence of mottled cyanosis. On elevation of the feet, the pallor increased and in dependency, there was persistent cyanosis. The femoral pulses were barely palpable and the popliteal and ankle pulses were absent. Oscillometry (G. Boullite Model) revealed half a deflection at both calves and a barely perceptible flicker at the ankles. No murmurs were audible over the aorta, iliac or femoral arteries. The deep reflexes in the lower extremities were physiological; movement was normal, but sensation to light touch was impaired over the toes. In the upper extremities and in the head and neck all the usual major pulses were present and normal.

In view of the severe degree of ischaemia in the lower extremities, the drug was discontinued at this stage, and a bilateral sympathetic nerve block of lumbar ganglia 2 and 3 was done. There was an immediate slight improvement in the colour of the feet, followed shortly by an increase in skin temperature. Reflex vasodilatation was then carried out by warming the trunk with an electric blanket. A dose of heparin (5,000 units) was then given intravenously, followed by 2,000 units 2-hourly, through a Gordh needle, maintaining the whole-blood clotting time between 15 and 20 minutes. Weak ankle pulses returned on both sides 14 hours later and after 48 hours they were considered to be normal. The heparin was discontinued after 4 days, when she was discharged, complaining only of occasional numbness in the little toe of the left foot, and there was mild pallor of the toes of this foot on elevation. When seen two weeks later, there were no symptoms or signs of vascular insufficiency.

The following were the results of the investigations that were carried out: Urine analysis was normal. The haemoglobin was 15 G/100 ml., haematocrit 46 vols.%, and the leukocyte count was 11,700 per cu.mm. The differential count was as follows: neutrophils 49·5%, eosinophils 4·5%, basophils 0·0%, monocytes 8·5%, lymphocytes 30·5%. Platelets were numerous. The erythrocyte sedimentation rate (Wintrobe) was 7 mm. in 1 hour. Stained white and red cells showed no abnormality. LE cells were not seen. The systemic lupus erythematosus slide test was negative. The total proteins were 7·8 G./100 ml., the albumin was 4·9 G./100 ml. and the globulin 2·9 G./100 ml. with the alpha 1, alpha 2, beta and gamma fractions within the normal range. Cryoglobulins were not detected. The cold agglutination titre was 1:16.

DISCUSSION

The nature of the occlusion in this case was not established. The benign course and temporary nature of the disorder strongly suggests that the clinical picture was caused by intense vasospasm. Since this patient was a young, healthy individual and there were no other predisposing factors, we feel that there was a definite causal relationship between the arterial insufficiency and the administration of methysergide. This contention is supported by the reports of Friedman and Losin[1] and Dalessio *et al.*,[9] in which the clinical features in their patients strongly resembled those presented here. In the case reported by Friedman and Losin, a female patient who received 14 mg. of methysergide over a period of 5 days, there were generalized muscle pains and cramps, excruciating pain in both feet and numbness in the hands and feet.

Pulses were not obtained in either leg up to the level of the femoral arteries, and it was difficult to determine the blood pressure in the arms. With conservative treatment, the pulses returned in both the hands and the feet, though some numbness remained in the little toe of the left foot at the time of her discharge. Dalessio *et al.*[9] reported severe peripheral vascular insufficiency in the lower extremities of a 14-year-old boy, who had vascular headaches of the migraine type and who was treated with methysergide. Five days after stopping the drug there was complete resolution of signs of vascular insufficiency, although the patient had residual claudication in both calves when walking about the hospital corridors. This patient also showed electrocardiographic changes similar to those found in myocardial ischaemia, which later returned to normal. In the same paper these authors also reported the development of cold, numb feet in a 70-year-old man who was taking 2 mg. of methysergide 7 times a day.

Of further significance in our case was the development of intermittent claudication. This symptom has been reported as one of the side-effects of the drug in several of the previously mentioned reports.

The similarity of the major vasoconstrictor effects of methysergide and ergotamine tartrate has been pointed out by Dalessio *et al.*[9] They remark that this is understandable, if the chemical similarity between lysergic acid and certain ergot alkaloids are considered. The exact mode of action of methysergide is not known, but they have suggested two possibilities. The first is that methysergide is changed in such a way in the body as to acquire ergot-like properties. This would explain the increased sensitivity of patients to additional ergot as has been observed. It should be noted that our patient had been on an ergot preparation sporadically for some time, but that the last dose was taken at least 2 weeks before she started taking methysergide. The second and more likely possibility suggested by these authors is that methysergide increases the individual sensitivity to both endogenous constrictor agents such as epinephrine and nor-epinephrine as well as exogenous constrictor agents.

CONCLUSIONS

We subscribe to the view of Graham[3] that although methysergide is by no means as active a vasoconstrictor as ergotamine tartrate, it should be used with caution in patients with arterial disease.

A case is reported of intense arterial vasoconstriction occurring in the lower extremities of a schoolgirl who had been taking methysergide for migraine. There was a complete resolution of symptoms and signs after stopping the drug and instituting conservative treatment.

Although there were no permanent sequelae in this patient and in those reported previously in the literature, patients receiving methysergide should be warned against the possible occurrence of side-effects indicating peripheral vascular impairment and instructed to report immediately to their practitioner if such symptoms do occur. They should also be instructed to discontinue therapy with methysergide at once on the occurrence of such symptoms.

We are grateful to Dr. P. G. Stein of Sandoz Pharmaceutical Department, Johannesburg, for his assistance in placing at our disposal some of the pertinent literature.

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