

GANGRENE INDUCED BY METHYSERGIDE AND ERGOTAMINE

A CASE REPORT

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Gangrene of both great toes after bilateral Keller's arthroplasty is reported in a patient who had been taking regular doses of ergotamine and methysergide for the prophylaxis of migraine. The effects of these drugs on the peripheral circulation, and the reversibility of vascular lesions induced by methysergide, are discussed.

Outbreaks of ergot poisoning (St Anthony's fire) have occurred in Europe for centuries, the most recent being in 1953. Ergot is the product of a parasitic fungus infecting grain, in particular rye, and has been recognised as the cause of St Anthony's fire since the Middle Ages. However, it was not until 1920 that the amino-acid alkaloid, ergotamine, was isolated by Stoll. Ergotamine can reproduce the peripheral vasoconstriction and gangrene which is a prominent feature of ergot poisoning; it is used therapeutically in cases of migraine to reduce the vasodilatation and excessive pulsation of the branches of the external carotid artery.

All the alkaloids of ergot are derivatives of lysergic acid, and several types of semisynthetic products have been produced, of which methysergide is one. It is a potent antagonist of 5-hydroxytryptamine, which has been incriminated in the aetiology of migraine. Although methysergide is of established value in the prophylaxis of migraine it has a number of side-effects, the most serious of which is inflammatory fibrosis of retroperitoneal and endocardial tissues.

CASE REPORT

A forty-eight-year-old woman was admitted to hospital for treatment of bilateral hallux valgus. Seventeen years earlier she had undergone bilateral triple arthrodeses, with levelling of exostoses on both first metatarsals. On admission her chest radiograph was normal, blood pressure 140/80 millimetres of mercury, and haemoglobin 12.8 grams per 100 millilitres. The patient smoked twenty cigarettes a day and gave a history of migrainous headaches for which she had been taking six tablets daily of Bellerгал (each tablet containing 0.1 milligram of alkaloids of belladonna, 0.3 milligram of ergotamine tartrate, and 20 milligrams of phenobarbitone) and six tablets daily of Deseril (each tablet containing 1 milligram of methysergide maleate).

Bilateral Keller's arthroplasties, with longitudinal toe wires to maintain the length of the great toes, were performed under pneumatic tourniquet with cuffs applied to both thighs. The cuffs were inflated one at a time and released before closure of the skin. The patient was discharged from hospital eight days after operation when the circulation in the toes was noted to be normal. She attended again on the fourteenth day after operation for removal of toe wires and sutures, when it was noted that the right hallux was a dusky blue colour and had apparently been so for four days, while the left hallux was

normal. She continued her medication for a further six days. At this stage the right hallux was blackened and the left had become a dusky blue. No pulses distal to the femoral were palpable on the right side while those on the left were normal. Intravenous heparin in a dose of 40 000 international units daily was started and the Bellerгал and Deseril discontinued. On the thirtieth day after operation the pulse of the right dorsalis pedis artery was again palpable and a femoral arteriogram was normal.

The right hallux was amputated through the metatarsophalangeal joint five weeks after the original operation and the wound healed by first intention. The left hallux recovered slowly without the need for operation. At review two years later, she was receiving no medication, the pulses in the lower limbs were normal and a painful prominence on the right first metatarsal head was trimmed without complication.

DISCUSSION

There have been several reports of vascular complications associated with methysergide. One early report (Graham 1960), a study of 113 patients, mentioned thrombosis and temporary insufficiency of the left brachial artery in one patient which disappeared on stopping the drug. A further study (Graham 1964) of 500 patients, who had taken the drug for three or more years, found that thirty-five patients had developed cold extremities or intermittent claudication, and fourteen had had an alteration in their peripheral pulses. Johnson (1966) reported the case of a patient who had received methysergide for severe headaches some five days after removal of an exostosis from the first metatarsal head; on the tenth day after operation she had complained of numbness of the foot but was nevertheless allowed to go home. The left foot became painful and the whole limb cyanosed; the popliteal and femoral vessels were explored and the limb recovered with considerable loss of calf muscle bulk. All pulses had returned to normal when this patient was examined two years later.

Several cases of abdominal angina or bowel infarct have been described in patients receiving methysergide (Buenger and Hunter 1966; Katz and Vogel 1967; Regan and Poletti 1968), and abnormal mesenteric angiograms have returned to normal when the drug has

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been discontinued. Severe claudication and coldness of the legs were reported in two patients receiving methysergide, in one after one month and in the other after two years (Ureles and Rob 1963; Conley, Boulanger and Mendeloff 1966). Absent peripheral pulses returned after the drug was stopped, and in the patient of Conley *et al.* (1966) a translumbar aortogram which showed partial obstruction of the aorta returned to normal when repeated two months later. The great variation in sensitivity of patients to the drug was mentioned by Graham (1964) with symptoms developing on daily doses of methysergide of from 1 milligram to 30 milligrams.

Imrie (1973) reported two cases of severe arterial insufficiency of the lower limbs in patients who had been taking ergotamine for several years but had recently increased their dosage. Lucas and Falkowski (1973) also reported on five patients who had increased their regular dosage of ergotamine and methysergide; one was taking 50 tablets weekly of Bellergal when signs of peripheral

vascular insufficiency developed in the fingers, with poor peripheral pulses. The symptoms resolved on withdrawal of the drug. Cameron and French (1960) described a patient who had developed peripheral ischaemia of both legs and the right thumb after only 7 milligrams of ergotamine tartrate had been administered over two days; amputation of both legs, the right thumb and the tip of the right index finger was required.

No previous case of gangrene of the great toes after Keller's arthroplasty has been reported, and in the patient here described it is presumed to be associated with ergotamine and methysergide therapy. The effects of ergot poisoning are well known but those of methysergide less so. It is apparent that there is extreme sensitivity to these drugs in some patients but in others the toxic effects might not be observed for months or years. Although ischaemia following methysergide therapy is potentially reversible it would seem unwise to embark on peripheral operations on the limbs in patients receiving either methysergide or ergotamine.

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REFERENCES

- Buenger, R. E., and Hunter, J. A.** (1966) Reversible mesenteric artery stenoses due to methysergide maleate. *Journal of the American Medical Association*, **198**, 558-560.
- Cameron, E. A., and French, E. B.** (1960) St Anthony's fire rekindled: gangrene due to therapeutic dose of ergotamine. *British Medical Journal*, **2**, 28-30.
- Conley, J. E., Boulanger, W. J., and Mendeloff, G. L.** (1966) Aortic obstruction associated with methysergide maleate therapy for headaches. *Journal of the American Medical Association*, **198**, 808-810.
- Graham, J. R.** (1960) Use of a new compound UML-491 (1-methyl-d-lysergic acid butanolamide), in the prevention of various types of headache. *New England Journal of Medicine*, **263**, 1273-1277.
- Graham, J. R.** (1964) Methysergide for prevention of headache. *New England Journal of Medicine*, **270**, 67-72.
- Imrie, C. W.** (1973) Arterial spasm associated with oral ergotamine therapy. *British Journal of Clinical Practice*, **27**, 457-460.
- Johnson, T. D.** (1966) Severe peripheral arterial constriction, acute ischemia of a lower extremity with use of methysergide and ergotamine. *Archives of Internal Medicine*, **117**, 237-241.
- Katz, J., and Vogel, R. M.** (1967) Abdominal angina as a complication of methysergide maleate therapy. *Journal of the American Medical Association*, **199**, 124-125.
- Lucas, R. N., and Falkowski, W.** (1973) Ergotamine and methysergide abuse in patients with migraine. *British Journal of Psychiatry*, **122**, 199-203.
- Regan, J. F., and Poletti, B. J.** (1968) Vascular adventitial fibrosis in a patient taking methysergide maleate. *Journal of the American Medical Association*, **203**, 1069-1071.
- Ureles, A. L., and Rob, C.** (1963) Acute ischemia of a limb complicating methysergide maleate therapy. *Journal of the American Medical Association*, **183**, 1041-1042.