Clinical ergotism with severe bilateral upper limb ischaemia precipitated by an erythromycin – ergotamine drug interaction

Ergotamine and related compounds have been used widely for many years in the management of migraine. Reports of ergotism (St Anthony's fire) are widespread and usually occur as a result of chronic ingestion exceeding the recommended maximum dose. Additionally, a little appreciated cause of ergotism is the interaction of ergot compounds with several commonly prescribed drugs. We report a case of ergotism with bilateral marked upper limb ischaemia precipitated by co-ingestion of ergotamine (Migral) with erythromycin (Eryc).

A 58-year-old man presented to the Emergency Department with a 24-hour history of severe pain in both hands and clinical features consistent with ergotism. The background history included paroxysmal atrial fibrillation and migraines. The patient had suffered from migraines since age 15 with an average of two to three episodes occurring per month. The episodes were suggestive of classical migraine with aura, scintillating scotoma and nausea and vomiting as components of each attack. Verapamil, propranolol and sumatriptan had been ineffective in reducing the severity or frequency of attacks. Migral (ergotamine tartrate 2 mg, cyclizine hydrochloride 50 mg, caffeine hydrate 100 mg) had been used in the preceding eight years to abort acute attacks. The use of Migral had been irregular depending on the frequency of symptoms but was estimated at approximately three tablets every two weeks. Of particular note, the patient had a 30 pack/year history of smoking.

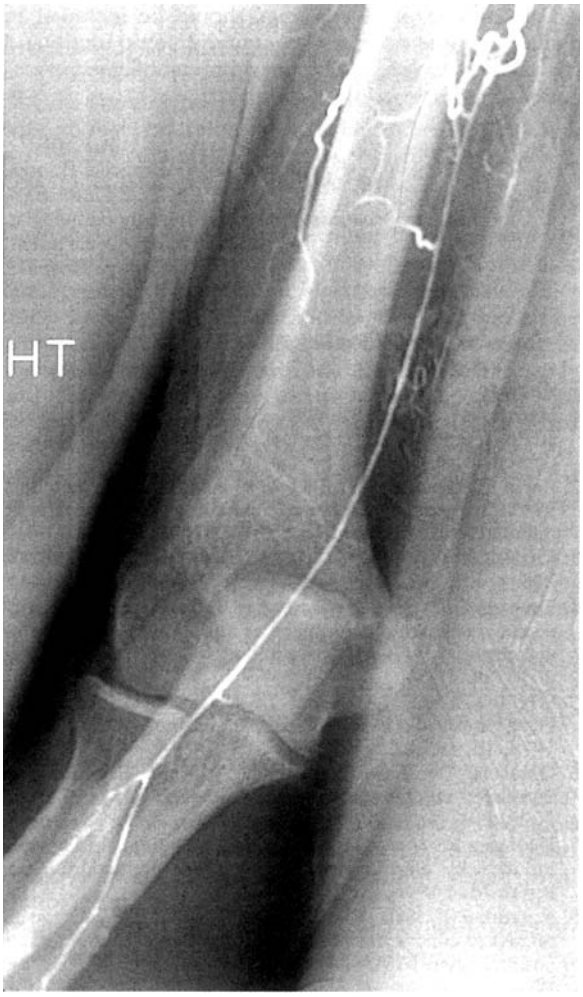

Figure 1a: Angiogram® upper limb performed on admission.

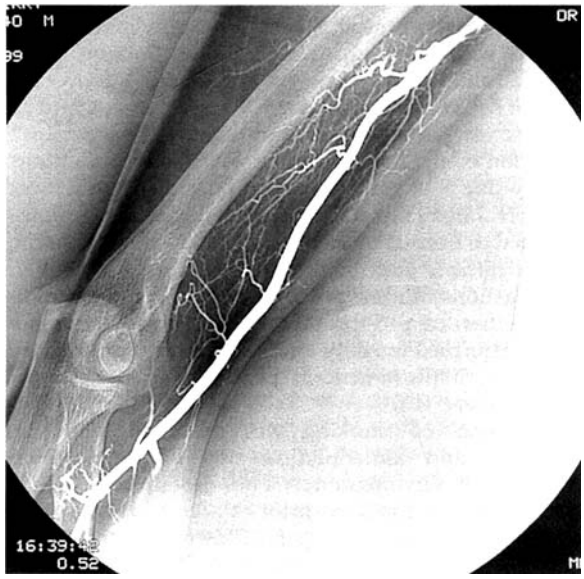

Figure 1b: Angiogram® upper limb performed ten days after admission.

At the end of January 1999 the frequency of headaches increased to five to six per month and the patient increased the frequency of Migral administration to approximately three tablets every seven days.

Four weeks following the increase in dosage of Migral, the patient developed an upper respiratory tract infection. Erythromycin (Eryc 250 mg formulation) was commenced at 500 mg tds and contained for a total of 14 days. Migral was continued at the dose stated with the last dose taken one day prior to presentation.

Three days following completion of the erythromycin

course, the patient presented with severe pain in both hands. On examination, there was evidence of bilateral ischaemia of both hands and absent radial and ulnar pulses. Lower limb pulses were reduced but present with no evidence of lower limb ischaemia. There was no clinical or ECG evidence of myocardial ischaemia. An urgent angiogram was performed (Figure 1a).

With the provisional diagnosis of ischaemia secondary to ergot poisoning, treatment included intravenous heparin, topical nitrates, and nifedipine 60 mg tds PO with cessation of ergotamine. Sodium nitroprusside and prostacyclin were considered, but over the next 24 hours there was a definite improvement with an increase in perfusion to both hands. The patient's condition continued to improve over the next 48 hours and by day 3 of the admission the radial pulses were palpable bilaterally. Circulation to the upper limbs returned to normal by day 6 and subcutaneous heparin, topical nitrates and nifedipine were ceased on day 7. Investigations did not reveal any evidence of vasculitis or an inherited pro-thrombotic tendency. The angiogram performed ten days after admission demonstrated a marked improvement in perfusion to both upper limbs (Figure 1b).

Cessation of smoking was achieved while an inpatient and amitriptyline was commenced as prophylaxis for migraine. The description of the headaches in the months prior to admission suggested a non-migrainous aetiology, possibly related to caffeine withdrawal with rebound headache.

Ergotamine tartrate has been recommended for the treatment of migraine since 1926 and has become a useful therapeutic agent for the treatment of acute attacks usually in preparations that combine ergotamine with caffeine[1] (e.g., Cafergot, Migral). Although the concurrent administration of caffeine improves both the rate and extent of absorption, the absorption of oral ergotamine is erratic and this is compounded by the gastric stasis induced by migraine. Additionally, the bioavailability of ergotamine is poor as the drug undergoes extensive first pass metabolism in the liver. Metabolism is via the CYP450 system with the CYP3A4 isoform most active,[2] and elimination is primarily as metabolites in the biliary system. The plasma half life is 0.5 to three hours but the clinical effects may last longer than 24 hours. The mechanism of action is complex involving antagonist/partial agonist activity at $5HT_1$ receptors and partial agonist effect at adrenoreceptors (blood vessels), with the overall clinical effect of potent construction of peripheral and cranial vessels. The recommended maximum dose is stated as not more than 6 mg in a 24 hour period and not more than 10 mg in a seven day period.[3]

Macrolide antibiotics are associated with a large number of clinically significant drug interactions and may be classified according to their affinity for CYP3A4.[4] Erythromycin has a high affinity for the isoenzyme and agents such as azithromycin have little or no affinity and thus are theoretically less likely to result in clinically important drug interactions.[5] Clinical ergotism has been reported following the co-administration of ergots and several drugs of the macrolide class including erythromycin[6] and clarithromycin.[7] The mechanism of toxicity relates to the inactivation of CYP450 3A4 isoenzymes, which are responsible for the metabolism of ergot compounds. Indeed, the hazards of combining erythromycin and ergot compounds are recorded in MIMS annual and supplement[8] but not in the product information package inserts of some of the common trade forms of erythromycin and ergotamine (e.g., Cafergot, Migral and Eryc). Finally, ergotism has also been reported with co-administration of other CYP450 inhibitors including indinavir[8] and ritonavir.[9]

This case highlights one of the serious complications arising from the inadvertent combination of two common drugs. The addition of erythromycin appears to have been the precipitant explaining the acute episode of ergotism with the chronic ingestion of ergotamine contributing to the overall clinical presentation.

This case demonstrates not only the potential for this life threatening drug interaction but also the reality that the use of ergot preparations is often unsupervised. Accordingly, explicit warnings should be included in package inserts for ergot containing compounds and for those macrolide antibiotics with a confirmed ergotamine drug interaction. ■

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