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General Review

Ergotism: A Change of Persepective

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Clinical ergotism is a rare disorder, and clinical and therapeutic implications have continued to attract attention. The Holy Fire or St. Anthony's Fire was the primary vascular manifestation, causing burning pain and gangrene in the feet and hands related to the arterial spasm properties of ergot.The chronic use of ergotamine and migraine has also been associated with ergotism. Severe vasospasm and acute peripheral ischemia of the extremities can develop. However, in modern times, the spectrum of poisoning by alkaloids has broadened to include antiviral therapies in patients with HIV and abuse of stimulants.These changes have made taking an accurate medical history and conducting an accurate detailed differential diagnosis more essential. The purpose of this review is to highlight the importance of ergotism as a cause of peripheral vascular ischemia and analyze changes associated with this poisoning.

INTRODUCTION

From the times of medieval Europe, ergotism has been related to peripheral vascular ischemia of the limbs. While ergotism is not currently common, the literature of medieval Europe included reports of thousands of people perishing or being crippled or maimed,[1–3] and the characteristic manifestations reported in ergotism are now documented in cases of poisoning by ergot derivatives.

Going by the name of Holy Fire or St. Anthony's Fire, the characteristic vascular manifestation was burning and gangrene in the feet and hands caused by the spasmodic properties of ergot. Peripheral vasoconstriction induced by ergotamine is one of the most common manifestations, and is more or less caused by eating rye contaminated with the fungus *Claviceps purpurea*. Still, its incidence is low.[4,5] Acting as a serotonin agonist, ergot produces vasoconstriction through mechanisms mediated by these receptors. Its pharmacologic effects include stimulation of smooth muscle, central sympatholytic activity, and peripheral alpha adrenergic blockade.[3–6] Patients may experience peripheral vasoconstriction causing coldness and tingling in the fingers and toes, and overuse can cause intermittent claudication, severe spasm, acral cyanosis, or even digital necrosis.[7] The symptoms may affect various systems, including the splanchnic or renal systems. Coronary vasoconstriction may manifest as angina pectoris. While in general the lower extremities are often affected the most, the upper extremities can also be compromised and, at times, be the only affected extremities.[8,9] These processes are usually symmetrical, but unilateral cases have been reported. Convulsive ergotism has not been reported with the use of pure compounds of ergotamine. However, the environment in which ergotism is expressed and identified has changed over the centuries. In modern times, the consumption of contaminated bread would clearly not be the immediate and direct cause of mortality; while most of the cases reported today are related to the overuse of ergotamine tartrate in the treatment of migraine and postpartum hemorrhage (PPH), epidemiologic variables and new drug interactions caused by various forms of existing treatments have helped to change the spectrum related to ergot.

In this specific case, these changes from the epidemiologic point of view make the importance of accurate differential diagnosis more relevant. This

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synergism with vasoconstrictor properties and subsequent risk of producing excessive vasoconstriction should be analyzed first. The presence in the current era of immunodeficiency syndromes such as HIV and the respective treatments with multiple antiviral drugs and the abuse of drugs such as cocaine are closely linked to cardiovascular disorders associated with ergotamine.

Indeed, between 2007 and 2010, our National Administration of Drugs, Food and Medical Technology National Pharmacovigilance System received 8 reports of adverse reactions caused by medicinal preparations containing ergotamine and its corresponding association with antimigraine therapeutic and antiviral protease inhibitor therapy.[10]

However, the use of ergot derivatives in antimigraine therapy is not new. Chronic migraine is a highly disabling disorder that dramatically affects quality of life. Ergotamine was recommended in 1868 by Woakes.[11] The sympathetic hyperactivity associated with the etiology of migraine allowed the further development of dihydroergotamine in 1943.[12] Somehow, the use of ergot derivatives contributed to support the vascular theory.[13]

Despite the advent of calcium channel blockers and beta-adrenergic antagonists, ergotamine is still being used and its use is widely spread throughout the world. However, the problems associated with intolerance, poor oral bioavailability, and the modest improvements with intranasal forms means that its clinical use has been limited.

From this point of view (and for many years), the association of ergot and migraine has been about peripheral vascular ischemia of iatrogenic origin. Even though it is currently rare, its incidence is estimated at 0.001−0.002% of patients treated for headaches. While the use of new therapeutic developments including triptans and other analgesics has partially offset the use of ergot, ergotism still remains a major clinical problem and, although rare, it should be included in the differential diagnosis of patients with a history of headache, migraine, and drug overdose.[7,14,15] Ergotamine is not recommended for the treatment of acute migraines,[16] but will be considered in the treatment of select patients who present with moderate to severe chronic migraines.[12]

The use of ergot in obstetrics to accelerate labors was common in Europe from the 16th century. Although there were dangers associated with its use (i.e., prolonged uterine contraction before delivery and uterine ruptures), ergot was recognized by obstetricians and recommended for PPH.[2−17] Introduced by John Stearns in 1822, the ''John Stearns effect'' was associated with pronounced and vigorous uterine contractions that incorporated the use of these uterotonic stimulants to treat postpartum bleeding.[18] That substance was later isolated and called ''ergometrine'' byDudley and Moir[19] who, alongside the Americans, called their preparation ''ergonovine.''

Today, uterotonic drugs are used for a variety of preventions and treatments, including PPH, induction and augmentation of labor, management of inevitable or incomplete abortion, or elective medical abortion. However, the use of ergot derivatives has been criticized because of the serious and unpredictable side effects and the instability of the drugs. Because the use of ergometrine in these cases involves doses in short periods and for a short time, cases of severe ergotism associated with the treatment of PPH are documented individually and sporadically. Symptoms of postpartum psychosis and peripheral circulatory abnormalities have been reported.[20−23]

Oxytocin, synthetic oxytocin, misoprostol, and other prostaglandins are the current most widely used uterotonics.[24]

The drug combination of ergot derivatives in HIV-positive patients began to appear in those treated with protease inhibitors. The introduction of antiretroviral drugs in 1994 in combination with other nucleoside analogues for the treatment of adult patients infected with HIV-1 with progressive or advanced immunodeficiency brought a new form of interaction related to ergotrate. The inhibitors of cytochrome P450 (e.g., ritonavir) may alter the metabolism and increase the concentration to toxic levels, causing severe ergotism in certain circumstances, even in the presence of ergotamine alone or in low doses.[25] Ritonavir, which has been approved by the US Food and Drug Administration, acts as a selective inhibitor of HIV protease-1 and HIV-2. With hepatic metabolism, ritonavir has a high affinity for several cytochrome P450 forms, mainly by the isoenzyme CYP34.[26]

The consequences of this drug association have been reported and the incidence of ergotism among HIV-positive patients treated with these antiviral medications seems to be increasing. Although this association usually occurs as isolated cases, there are irreversible consequences in certain circumstances, including death.[9,15,27−34]

The abuse of stimulant drugs is also associated with ergot drug interactions. Cocaine has been a problem in the 20th century. This alkaloid has been and continues to be used widely for its psychoactive properties. The preferred routes for users of cocaine hydrochloride are nasal ingestion, intravenous use, and smoking (known as crack cocaine). Regarded as a potent vasoconstrictor, cocaine blocks

the uptake of catecholamines in adrenergic nerve terminals, acting as an agonist of serotonergic receptors, thereby producing an indirect sympathomimetic stimulation with vasoconstriction. The procudtion of cocaine generally tends to be associated with substances used as diluents (e.g., quinine, procaine, or amphetamines), which increase the synergistic toxicity of the alkaloid. The association of cocaine with other vasoconstrictor drugs, such as ergotamine, added simultaneously, can cause extreme vasospasm, mostly of the limbs. Cutaneous injuries can develop. The risk of severe vasoconstriction and presentation of Raynaud's type phenomenon has been linked in literature, in some circumstances with disabling sequelae.[35,36]

Despite the great advances of medicine in the 20th century, the ideal treatment of ergotism has not been identified. There is no convincing evidence that any treatment other than discontinuation of ergotamine is of benefit in the treatment of iatrogenic ergotism. The cessation of the medication is considered the most effective therapy. On the other hand, vasodilation therapy is fundamental for the improvement of the patient's clinical status. However, its standardization seems to be unified, and there is no evidence that a particular treatment is more beneficial than any another treatment.

This finding is probably related to the low incidence of ergotism, the corresponding presentation of sporadic cases as ''case reports,'' the logical difficulty of proper randomization, and the haste needed when implementing treatments in order to avoid complications or major and permanent consequences. This decision leads to the need to adopt >1 drug treatment in certain situations.[37] The intravenous administration of nitroprusside has been reported,[38] including an association with oral nifedipine.[39] Both nifedipine infusions of intra-arterial indwelling or prostaglandin E1 (PGE1)[14,40] and nitroglycerin have been used.[7,14,41,42] Even today, we use oral sildenafil in conjunction with PGE1. The effectiveness of sympathetic blockade is controversial, and induction drugs administered with epidural sympatholysis have also been mentioned, but many authors consider low performance, only for the relief of ischemic pain.[41,43–46] Invasive endovascular procedures have been reported.[47] Results have been associated with the disruption of the presumed arterial smooth muscle layer and the prevention of vasoconstriction. The use of heparin, dextrans, and/or antiplatelet agents seem to be recommended in the prevention of vessel thrombosis engaged by spasm.[43] Surgical treatment (i.e., marginal amputation or fasciotomy) is not frequent and must be indicated in cases of irreversible changes, gangrene, and limb loss.

CONCLUSION

Ergotism is a rare cause of peripheral ischemia. However, the danger of ergotism persists, and 0.01% of patients receiving ergot components show toxicity at some point. The spectrum where this pathology is associated has changed in recent years, and today the identification of adverse reactions or drug interactions is essential. This requires a high index of clinical suspicion where the importance of history is essential to avoid delays in diagnosis that may lead to irreversible consequences. The presentation in sporadic cases with extensive distribution means that ergot poisoning may not be detected by the clinical interview and physical examination. In certain circumstances, the classic association often cannot be obtained, and the cause of ischemia can be ignored. Ergotism should be suspected whenever there are perceived symptoms consistent with vasospasm and a history of drug ingestion in the absence of any thrombotic or vasculitic pathology. Patients with a history of migraine, HIV treatment, and probable drug abuse or drug interactions should be included by the vascular surgeon in the differential diagnosis.

While the cornerstone of therapy in ergot toxicity is to discontinue the use of caffeine, cigarettes, and all ergot-containing medications, the lack of precise pharmacologic algorithms requires an aggressive treatment modality, usually with varying results. Early recognition should be taken into account and multiple and variable therapies must be considered in order to avoid sequelae.

There has been no therapeutic consensus to date. No current therapy is associated with immediate effectiveness, and there is even less standardization. Because of the range of clinical responses to therapy, different treatments will, in some cases, become necessary.

In cases of interactions with retroviral agents, the degree of responsibility of the patient and the availability of over the counter medications should be taken into account when prescribing these drugs.

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