Recurrent Ergotism: A Case Report

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A patient was seen with absent pulses and vague symptoms. History and clinical findings supported a diagnosis of ergotism due to heavy use of ergotamine suppositories. The patient continued to use ergotamine despite warnings and was seen on two additional occasions with ergotism. Previously a heavy user of ergotamine, she became sensitive to small doses, demonstrating marked vasospasm after only one suppository. This phenomenon, not previously reported, is postulated secondarily to drug interaction. The patient is presented with a review of the pharmacology, toxicity, and treatment of ergotamine-induced ergotism. Alerted to the possibility of drug interactions, physicians may safely use ergotamine in the treatment of migraine headache with careful monitoring for signs and symptoms of early toxicity.

Ergot is the sclerotium of the fungus Claviceps purpurea, a pharmacologic "Pandora's Box" containing the ergot alkaloids and a number of unrelated compounds. C purpurea occasionally infects rye and other grains used in making bread, and ergotism may result from ingestion of the contaminated grain. Ergotism also occurs as a toxic effect of ergot derivatives used medically, designated iatrogenic ergotism.

Epidemics of ergotism were common occurrences in the Middle Ages. After the discovery in 1676 that ergot-contaminated rye caused ergotism, the frequency and severity of epidemics gradually declined.[1] The last epidemic occurred in France in 1951 when a baker made bread with contaminated bootleg flour to avoid paying a grain tax. Over 200 people developed ergotism with four resulting deaths.[2]

The medicinal use of ergot in the western world dates back to 1582 when it was found useful as a uterine muscle stimulant. In 1820, ergot was added to the US Pharmacopoeia for obstetrical use. The earliest reference to the use of ergot for the treatment of migraine headache appeared in 1883. The purified substance ergotamine was isolated in 1918 from crude ergot and subsequently obtained widespread use in the treatment of migraine.[3]

Contrasted with the diminishing frequency of epidemic ergotism, reports of iatrogenic ergotism are increasing. Most reports emphasize the difficulty of early diagnosis due to the insidious and varied nature of presenting symptoms. Frequently the diagnosis is suspected only after arteriography reveals arterial spasm. A patient was recently encountered in whom the diagnosis was made clinically on three separate occasions. This case is reported with a literature review to increase physician awareness of the clinical behavior and pharmacologic basis of ergotism.

Case Report

A 44-year-old white female was admitted for the first time to the Family Practice Service in Alachua General Hospital on January 20, 1977, with a four-week history of progressive weakness, generalized lassitude, nausea, vomiting, and inability to walk more than 15 feet. She complained of

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tingling and numbness in her left arm, coldness of all her extremities, and a dry mouth for four days. She denied chest pain, syncope, shortness of breath, hematemesis, hemoptysis, or melena. She had had intermittent migraine headaches for 20 years. Initially she denied taking any medication in the recent past. After a review of old records revealed her to be taking Cafergot P-B Suppositories, she admitted using these for more than one year, averaging about 50 to 60 suppositories per month with a maximum of three to four per day. Past medical history revealed that she had been treated for addiction to meperidine and pentazocine ten years previously.

On physical examination her temperature was 98.6 F, and pulse was 52 beats per minute. Her blood pressure was unobtainable and respirations were 20 per minute. Positive findings included absent radial, brachial, femoral, dorsalis pedis, and posterior tibial pulses. Carotid pulses were barely palpable. Her extremities were cold and cyanotic with decreased capillary filling and blanching. Neurological examination was negative except for ataxia.

Laboratory values included a sedimentation rate of 12 mm/hr, white blood cell count of 9,800 with normal differential, and a hematocrit of 48 percent. SMA-6, SMA-12, free thyroxine index, and serum cortisol were normal. An electrocardiogram revealed sinus bradycardia with incomplete right bundle branch block.

A diagnosis of probable ergotism was made and Cafergot was withheld. Within 72 hours all her pulses were palpable. Due to the persistant complaints of headache, a trial on methysergide was initiated and the patient was discharged much improved.

Seven weeks after her first admission she was readmitted complaining of substernal chest pain, nausea, vomiting, generalized weakness, a severe burning which was worse in the extremities and aggravated by the slightest touch, and coldness of her hands and feet. Since methysergide had not relieved her headaches, she had been taking Cafergot P-B Suppositories, one daily for two weeks.

Her blood pressure was unobtainable. The physical findings were again noteworthy for the absence of all peripheral pulses.

Routine laboratory data, skull series, and brain scan were normal. Computerized axial tomography revealed mild atrophy of the right frontal area. An electroencephalogram showed nonspecific findings which subsequently resolved. An electrocardiogram was unchanged from previous tracings. As before, she was treated expectantly and within 48 hours all her pulses were palpable. She continued to have intermittent migraine headaches. On the advice of a neurology consultant a therapeutic trial on propranolol was begun for her migraine headaches. Amitryptyline was also started after increasing evidence of depression was noted. On this regimen, the patient had no headaches during the 72 hours prior to discharge.

Three weeks later she was admitted with sharp, constant, left flank pain associated with nausea, vomiting, ataxia, coldness, and pallor of her extremities. The previously noted burning pain in her hands and feet had reappeared. She admitted taking one Cafergot P-B Suppository about 72 hours prior to admission.

Physical findings were unchanged from earlier admissions. All pulses were again absent except for the carotids.

Routine laboratory data were normal. An intravenous pyelogram was normal. Her pulses returned to normal in about 48 hours without specific therapy.

On the sixth hospital day the patient was given one Cafergot P-B Suppository after obtaining her informed consent. In two hours she developed profound weakness, nausea, vomiting, coldness of her extremities, and pallor with decreased capillary filling. Her blood pressure was unobtainable and her dorsalis pedis and radial pulses were absent. In four hours her brachial pulses were absent and in ten hours all her pulses except the carotids were absent. In 24 hours, the patient had regained all of her pulses.

She was discharged on a regimen of propranolol and amitryptyline as the frequency of her headaches had been significantly less on these drugs. She was strongly advised to avoid ergot preparations.

Pharmacology

Ergot contains a variety of substances divided by Barger into two main groups: (1) the ergot alkaloids, and (2) a heterogeneous collection of compounds including histamine, tyramine, acetylcholine, and others. The ergot alkaloids can be

Table 1. Products Containing Ergotamine

Brand Name	Method of Administration	Dose of Ergotamine	Other Ingredients
Bellergal	tablets	0.3 mg	Phenobarbital 20 mg, belladonna alkaloids 0.1 mg
Cafergot	tablets	1 mg	Caffeine 100 mg
Cafergot	suppositories	2 mg	Caffeine 100 mg, tartaric acid, theobroma oil
Cafergot P-B	tablets	1 mg	Caffeine 100 mg, pentobarbital 30 mg, Bellafoline .125 mg
Cafergot P-B	suppositories	2 mg	Caffeine 100 mg, pentobarbital 60 mg, Bellafoline .25 mg
Dolatrin	tablets	1 mg	Phenobarbital 20 mg, belladonna extract 8 mg
Ergomar	sublingual	2 mg	—
Ergostat	sublingual	2 mg	—
Gynergen	tablets	1 mg	—
Gynergen	injection	0.5/cc	—
Medihaler/Ergotamine	inhalation	0.36 mg/inhalation	—
Migral	tablets	1 mg	Caffeine 50 mg, cyclizine hydrochloride 25 mg
Oxoids	tablets	0.3 mg	Phenobarbital 20 mg, belladonna extract 8 mg
Wigraine	tablets and suppositories	1 mg	Caffeine 100 mg, belladonna alkaloids 0.1 mg, Phenacetin 130 mg

subdivided into the amine alkaloids, lysergic acid, and amino acid alkaloids.[4] Ergotamine, one of several alkaloids from the latter group, has been in clinical use since 1921. Commercially available products containing ergotamine are listed in Table 1.[4,5]

The pharmacologic actions of ergotamine are complex, intense vasoconstriction in large arteries, arterioles, and veins being a principle action. Vasoconstriction is probably due to stimulation of alpha adrenergic receptors in vessel walls, although direct stimulation of vascular smooth muscle also occurs. At doses much larger than those used in man, alpha adrenergic blockade occurs, suggesting that ergotamine acts as a partial agonist on alpha adrenergic receptors causing stimulation in low concentrations and antagonism in high concentrations. Ergotamine potentiates serotonin and stimulates serotonin receptors. The therapeutic benefit of ergotamine in migraine probably relates to both its vasoconstrictive action and its interaction with serotonin.[6] In addition, ergotamine induces generalized stimulation of smooth muscle, most evident clinically by its oxytoxic effect on uterine smooth muscle. In cases of toxicity, damage of capillary endothelium occurs leading to vascular stasis, thrombosis, and gangrene. Whether this is a direct effect of the drug on the capillary endothelium or secondary to the ischemia of vasoconstriction remains unclear.[3]

Ergotamine tartrate is irregularly absorbed from the gastrointestinal tract, better absorption occurring with sublingual and suppository administration.[4] The drug is metabolized by the liver with a half life for plasma elimination of 6.6 hours. Metabolic degradation products, however, are eliminated from the body at a much slower rate with a half life of 34.3 hours.[7]

Table 2. Recommended Dosage for Ergotamine

Route	Single Dose	Maximum per Attack	Maximum per Week
Oral	1-2 mg	6 mg	12 mg
Sublingual	2 mg	6 mg	12 mg
Rectal	2 mg	4 mg	8 mg
Inhalation	0.36 mg (1 inhalation)	2.16 mg (6 inhalations)	12 mg (33 inhalations)
Parenteral	0.25-0.5 mg	0.5 mg	1.0 mg

Toxicity

The maximum recommended dosage for ergotamine is listed in Table 2.[4,5] Tolerated dosage is extremely variable. Toxicity resulting in amputation of both legs and one hand occurred in one patient after taking only 7 mg by mouth—1 mg orally three times a day for seven doses.[2] Another patient took 18 mg parenterally, daily, for more than ten days with no evidence of toxicity.[8] Conditions which increase sensitivity to ergotamine include sepsis, febrile states, malnutrition, thyrotoxicosis, pregnancy, hepatic disease, renal disease, hypertension, coronary artery disease, avitaminosis, and peripheral vascular disease. Oral contraceptives and smoking may also potentiate the effects of ergotamine.[9]

Following the ingestion of whole ergot as described in many epidemics, toxic symptoms occur in two distinct clinical syndromes: (1) "Gangrenous Ergotism" with primarily vascular sequelae, or (2) "Convulsive Ergotism" with predominately neurologic signs and symptoms. Ergotamine toxicity produces a clinical syndrome with features of both entities, though more closely resembling "Gangrenous Ergotism."

Symptoms of ergotism suggesting vascular insufficiency include chest pain, abdominal pain, limb pain, joint pain, claudication, coldness, and formication of extremities. Neurologic manifestations include vertigo, dizziness, twitching, depression, confusion, peripheral nerve palsies, psychosis, syncope, convulsions, and coma. Other symptoms reported with ergotism are nausea, vomiting, diarrhea, headache, weakness, thirst, and amblyopia.[1]

Recent reports emphasize the vascular sequelae of "iatrogenic ergotism." Severe arteriospasm has been reported in most major arteries with resultant ischemia or infarction. The spasm may be focal and irregular mimicking atherosclerosis, or more commonly, generalized and symmetrical.[10] Vessels most commonly involved include aortoiliac or brachial arterial systems and peripheral arteries. The lower extremities are involved in 60 to 70 percent of cases.[11] Carotid involvement may produce unusual central nervous system symptoms.[12]

Acute myocardial infarction reported with ergotism suggests coronary spasm may occur and exacerbation of angina is not uncommon.[3,13] Renal artery spasm with diminished renal function has been documented by arteriography.[14] Intestinal infarction has occurred secondary to mesenteric vasospasm, and ophthalmic artery vasospasm may cause transient or permanent blindness.[3]

Treatment

There is no specific antidote for toxicity from ergot or its derivatives. Nonspecific measures recommended are vigorous intravenous hydration and prophylatic anticoagulation with heparin. With impending infarction of tissue, however, treatment becomes more urgent. Modalities previously attempted are sympathetic blockade with conduction anthesthesia techniques, regional sympathectomy, periarterial stripping, hyperbaric oxygen, low molecular dextran, and various vasodilators. Among drugs from the latter group, amyl nitrite, scopolamine, theophylline, Hyder-

gine, phentolamine, papaverine, procaine, and lidocaine have not proven useful. Niacin and tolazoline appear beneficial in some reports and ineffective in others. Recently sodium nitroprusside was employed in three cases with convincing benefit and would be our drug choice in patients with frank ischemia and impending infarction of tissue.[15,16]

Discussion

The condition of the patient whose case is presented in this paper was diagnosed clinically as ergotism on three separate occasions. In the review of the literature this is the first report of multiple recurrences of ergotism in a single patient. The diagnosis was suspected from the typical history and physical findings, and confirmed when she admitted using large doses of ergotamine. With the early diagnosis and withdrawal of ergot, the more serious complications of infarction and gangrene were avoided. Unfortunately, the patient continued to use ergotamine despite warnings of the potential dangers involved. Her history of drug abuse supported the postulate that she was habituated to the pentobarbital component of Cafergot P-B. Alternate explanations include true addiction to ergotamine, which to our knowledge has never been reported, or that the suffering from migraine headaches was so intense that she felt obtaining relief with ergotamine warranted risking the side effects.

This patient used large doses of ergotamine for months without ill effects, yet in a controlled hospital environment, one 2 mg suppository caused marked arterial vasoconstriction. She had none of the disorders known to increase sensitivity to ergotamine. Since acquired hypersensitivity has not been previously described, a search was made for another explanation, and drug interaction seems a likely possibility. This patient was taking propranolol and amytriptyline at the time one suppository administered under supervision produced severe arteriospasm. Both these drugs affect sympathetic vascular tone and conceivably, either singly or in combination, could increase vascular reactivity to ergotamine. Unfortunately, it was not possible to test this hypothesis and no reports were found in the literature on similar drug interactions with ergotamine.

It is hoped that this report will increase physician awareness of iatrogenic ergotism and possible drug interactions with ergotamine. The therapeutic value of ergotamine is uncontested and the incidence of serious side effects very small, estimated on the order of .01 percent.[8,17] The authors do not discourage the use of ergotamine in treating migraine headaches, but rather encourage careful attention to dosage, contraindications, possible drug interactions, and clinical follow-up of patients taking the drug.

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