ACUTE INTERMITTENT PORPHYRIA — RELIEF OF SEVERE PAIN AFTER TREATMENT WITH CHLORPROMAZINE HYDROCHLORIDE

Report of a Case

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THE intense pain that accompanies acute intermittent porphyria is often so severe and incapacitating that its alleviation becomes a primary therapeutic objective. Melby, Street, and Watson,[1] and Melby and Watson[2] reported that chlorpromazine hydrochloride* was an effective agent in this regard. Lee and Lucas[3] stated that trifluoperazine dihydrochloride† (another phenothiazine) gave dramatic relief of pain in a patient having acute intermittent porphyria. The purpose of this paper is to report the efficacy of chlorpromazine in abolishing pain, after other agents were ineffective.

Report of a Case

A 26-year-old woman was admitted to the Cleveland Clinic Hospital on March 12, 1960, because of severe abdominal cramps, and pain in the back, in association with acute intermittent porphyria. She stated she had not felt well since the normal delivery of a healthy child in January, 1959. In October of that year she was thought to have mumps; one month later she experienced severe suprapubic colicky pain, low back pain, and first noted dark urine. Pertinent facts in her family history are: her father had had repeated episodes of abdominal pain but had received no specific treatment; her mother, five brothers, two sisters, and two sons were asymptomatic.

On November 20, 1959, she was admitted to another hospital where a diagnosis of acute porphyria was made. During that hospitalization she was disoriented, with intense abdominal pain, and had quadriplegia. Phenobarbital was taken in a dosage of 1½ gr., at bedtime, on eight consecutive nights. Prochlorperazine,‡ in a dosage of 10 mg. administered intramuscularly, when requested by the patient, did not relieve the pain. During a two-month hospitalization the quadriplegia improved somewhat. She was discharged on January 20, 1960. On February 27, 1960, she returned to the same hospital because of a recurrence of symptoms including severe abdominal colicky pain and back pain. Therapy with ethylenediaminetetraacetic acid (E.D.T.A.), tetraethylammonium chloride, dimercaprol (BAL), diphenylhydantoin sodium, and pentobarbital sodium was ineffective. During her entire illness she had lost 36 pounds in weight.

At the time of admission to the Cleveland Clinic Hospital her appearance and reactions were childlike. Physical examination revealed a weight of 86 pounds; temperature, 99 F., pulse rate, 144; and supine blood pressure, 110/80 mm. of Hg; standing blood pressure could not be obtained, and the patient could not tolerate standing or sitting except for intervals of a few minutes. There were generalized muscular weakness, hypoactive deep tendon reflexes except for active Achilles reflexes; bilateral radial and median nerve palsy; and ataxia of the lower

*Thorazine, Smith Kline & French Laboratories.
†Stelazine, Smith Kline & French Laboratories.
‡Compazine, Smith Kline & French Laboratories.

extremities and bilateral foot drop. The skin was diffusely pigmented with no areas of pigment concentration. The other results of the physical examination were not remarkable.

Blood hemoglobin content, white blood cell and differential cell counts, blood sugar and blood urea concentrations were normal, and serologic tests for syphilis, and lupus erythematosus tests were negative. A routine urinalysis, and levels of serum calcium, phosphorus, and alkaline phosphatase were normal. A sulfobromophthalein test was abnormal, showing 21 per cent retention of the dye after 45 minutes. The serum transaminase level, thymol turbidity, and cephalin-cholesterol flocculation tests were within normal limits. Total serum protein (6.12 gm. per 100 ml.) and serum albumin (3.78 gm. per 100 ml.) concentrations were slightly reduced, but the various fractions were normal. Examination of the spinal fluid revealed no abnormalities. Porphobilinogen content from numerous samples of urine ranged from 2+ to 4+. The porphyrin excretion per liter was as high as 5,080 μg. In one 24-hour specimen the coproporphyrin was 310 μg., and the uroporphyrin was 1,725 μg. Fecal excretion studies of the porphyrins were not done.

Because of the severe intermittent abdominal colicky pain, and low back pain, chlorpromazine was administered orally, 25 mg. every six hours, but without effect. When the dosage was increased to 50 mg. every six hours, prompt and complete relief of pain ensued. Administration of chlorpromazine was discontinued, and pain recurred. At various times, administration of adrenocorticotropin (ACTH); a serotonin antagonist; an amine oxidase inhibitor; meperidine hydrochloride; brought no relief of pain, but there was complete relief with chlorpromazine in the dosage previously effective.

During her hospitalization, periods of apnea and bulbar speech occurred; there was gradual improvement of these symptoms, and the orthostatic hypotension lessened, but sinus tachycardia persisted. She was discharged from the hospital on April 16, 1960, and was advised to take chlorpromazine, 25 mg. four times a day. At the last examination, one year later, on April 13, 1961, there was no evidence of autonomic imbalance; pulse rate was 72; blood pressure was 110/80 mm. of Hg, supine, and after standing for four minutes there was no appreciable change (105/80 mm. of Hg). The bulbar speech had disappeared; there was improvement in the peripheral neuropathy; she had regained strength in the lower extremities except for some weakness in the flexors of the toes of the right foot, and could walk briefly on the tips of her toes. All medication had been discontinued for four months. In August, 1961, she reported she was actively taking care of her two children; she occasionally had pain and passed dark urine, but required no medication and had had no severe flare-up of symptoms. She was free of muscular weakness and had gained 40 pounds.

Comment

No specific treatment for acute intermittent porphyria is known, but relief of pain is one of the most important initial steps to be taken in therapy. This patient was freed of pain by administration of chlorpromazine in 50-mg. doses taken six times daily. Forty-eight hours later the administration of chlorpromazine was stopped and a number of other agents were administered; there was then a prompt recurrence of the pain. All observers were impressed by the immediate and dramatic control of this symptom when the administration of chlorpromazine was resumed. The mode of action of chlorpromazine is not known. No effect on the paralyses, tachycardia, or porphyrin excretion occurred; this also has been the experience of Melby and Watson.[2] Broomfield[4] also noted immediate relief of pain by the use of chlorpromazine in a patient with acute intermittent porphyria; however, a subse-

quent relapse of the porphyria with pain occurred while chlorpromazine was still being given.

Peters, Woods, Eichman, and Reese[5] reported apparently undesirable effects of chlorpromazine. Their patient had acute intermittent porphyria with neurologic and psychiatric manifestations, and, after chlorpromazine therapy, exhibited nystagmus, aphasia, and general clinical deterioration. Whether this actually represented undesirable effects of the drug or a natural progress of the disease cannot be stated.

Other drugs have been reported to be effective in controlling the pain of acute intermittent porphyria. Peters, Eichman, and Reese[6] found that the chelating agents, BAL and E.D.T.A., produced favorable responses in 31 of 47 patients who had various types of porphyria. These agents must be used cautiously, since E.D.T.A. may cause renal damage, and BAL may precipitate an attack of porphyria. Ganglionoplegics, ACTH, and hydrocortisone have been reported to be effective in relief of pain in acute intermittent porphyria, but responses are unpredictable; in fact, ACTH has been reported[7] to worsen symptoms in some patients.

Episodes of acute intermittent porphyria can be precipitated by a number of agents: barbiturates, alcohol, sulfonamides, heavy metals, oil paints, and solvents, aureomycin, Doriden,* meprobamate, Placidyl,† Valmid,‡ chloroquine phosphate, acetanilid, Phanodorn,§ ergot preparations, progesterone, and Bal.|| Exposure to these substances or use of the drugs should be avoided. Paralyses are said to occur with greater frequency in such induced attacks. Other precipitating factors are menses, pregnancy,[8,9] infection, and emotional disturbances. The precipitating factor in the case reported here was not apparent.

An outstanding clinical manifestation of acute intermittent porphyria in this patient was the orthostatic hypotension, a symptom also observed by Schirger, Martin, Goldstein, and Huizenga.[10]

Summary

In one patient having severe acute intermittent porphyria, pain was relieved by chlorpromazine hydrochloride. The use of this agent was believed to be lifesaving by disrupting the pain cycle. No claim is made that chlorpromazine had an influence on the porphyria other than to relieve pain. The dosage should be increased sufficiently to control the pain in the absence of side effects. Barbiturates and certain other drugs are to be avoided because they may precipitate or may increase the severity of attacks in the patient with acute intermittent porphyria.

*Ciba Pharmaceutical Products Inc.
†Abbott Laboratories.
‡Eli Lilly and Company.
§Winthrop Laboratories.
||Hynson, Westcott, & Dunning, Inc.

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