BRIEF REPORT

ARTHRITIS AND CARPAL TUNNEL SYNDROME ASSOCIATED WITH DISULFIRAM (ANTABUSE) THERAPY

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Disulfiram (tetraethylthiuram disulfide; Antabuse) was first used in the rubber industry, and later was introduced as a scabicide and vermicide. It was accidentally discovered that drinking alcohol after taking disulfiram causes an unpleasant reaction (1). The drug has subsequently been used both orally and by subcutaneous implantation to treat alcoholism. In addition, the chelating activity of a metabolite of disulfiram has led to its use in the treatment of nickel dermatitis (2). Various adverse effects of disulfiram have been observed, even in the absence of alcohol. Myalgia has been observed in patients taking disulfiram, but arthritis is not a recognized complication. Two cases are reported here in which a symmetric arthritis of large and small joints was reproducibly associated with courses of disulfiram.

CASE REPORTS

Patient 1. KW is a 49-year-old white man with chronic alcoholism. He had a 9-month history of painful swelling of the wrists and knees. His joint symptoms began 2 months after oral disulfiram, 250 mg/day, was started. The patient also complained of numbness in the fingers. There was no history of rash or Raynaud's phenomenon. He had drunk no alcohol while on disulfiram. The patient had tried ibuprofen (Motrin), without significant relief. His only other medication was clorazepate dipotassium (Tranxene) on occasion.

On physical examination, the patient was normotensive. The sclerae were clear. There was a soft systolic ejection murmur. The lungs and abdomen were normal. The right wrist and left knee were mildly swollen. Light percussion over the volar aspect of the right wrist produced paresthesias in a median nerve distribution. There was hypesthesia to pinprick in the right second fingertip.

Arthrocentesis of the left knee yielded clear, yellow, viscous fluid with a white cell count (WBC) of 320/mm^3 (80% lymphocytes, 20% monocytes), and a total protein level of 2.5 gm/dl. No crystals were seen, and the cultures were negative. The hematocrit was 41%, WBC 7,200/mm^3 (1% eosinophils), erythrocyte sedimentation rate (ESR) 13 mm/hour Westergren, and serum uric acid 5.4 mg/dl. Results of the fluorescent test for antinuclear antibody, latex fixation test for rheumatoid factor, and thyroid and liver function tests were all normal or negative. Roentgenograms of the knee showed only a patellar spur. Left wrist roentgenograms showed no abnormalities. Electromyography confirmed the presence of carpal tunnel syndrome.

The disulfiram was discontinued. Six weeks later, the patient reported marked improvement, with minimal numbness in the hand, and mild, intermittent aching in the right knee. On examination, he had no soft tissue swelling or effusions. Three months after stopping disulfiram, he was totally asymptomatic. At that point, to investigate the relationship between the arthritis and disulfiram, the drug was restarted in the same dosage. Two to 3 weeks later, the patient's hands

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and knees became painful and mildly swollen, and the hand numbness returned. The patient continued the drug for another 2 weeks, then stopped. His joint symptoms subsequently improved, and 2 to 3 months after discontinuing disulfiram he was completely asymptomatic and had normal results on a joint examination. He has not been taking disulfiram or alcohol for a year and has remained symptom free.

Patient 2. GS is a 35-year-old white man, an alcoholic with no prior history of joint disease. About 6 weeks after starting oral disulfiram, he began complaining of pain in the shoulders, ankles, and the metacarpophalangeal joints of both hands. The patient's only other medication was Tranxene, which he took occasionally for insomnia. He had no joint swelling or subcutaneous nodules, and the results of general and neurologic examinations were normal. The hematocrit was 42%, WBC 7,200/mm^3 (1% eosinophils), and ESR 3 mm/hour Westergren. The results of the fluorescent test for antinuclear antibody and the rheumatoid factor test were negative. The uric acid was 4.4 mg/dl, and the results of liver function tests were normal. The patient was treated with Motrin without relief.

Four months after starting disulfiram, the drug was stopped; the patient's joint symptoms abated. Four months after stopping disulfiram his only symptom was mild aching in the left shoulder. A month later, the patient was challenged with disulfiram in the same dose (250 mg/day). Ten days later, he developed pain in the metacarpophalangeal joints of both hands, and in the shoulders and ankles. There was no joint swelling. The patient continued taking disulfiram for another week, then stopped the drug altogether. His joint pain subsided over the next 6 weeks; after that, he became asymptomatic. When last interviewed, 10 months later, he reported that he had had no recurrence of joint symptoms, and that he was taking neither disulfiram nor alcohol.

DISCUSSION

Disulfiram inhibits hepatic aldehyde dehydrogenase, and, when taken with alcohol, causes accumulation of acetaldehyde (3). The clinical manifestations of the disulfiram–ethanol reaction—flushing, dilatation of scleral vessels, tachycardia, nausea, vomiting, and headache—are thought to be caused by this excess acetaldehyde (1). Adverse reactions to disulfiram other than the disulfiram–ethanol one have also been reported. They include toxic hepatitis (4), peripheral neuropathy (5), lethargy, psychiatric complications, and convulsions (6,7). Carbon disulfide, a metabolite of disulfiram, has been linked to coronary artery disease (8).

Rheumatic complications of disulfiram therapy have been infrequently reported. Christensen found the incidence of myalgia among patients taking disulfiram to be twice that of patients taking placebo (6). Ekvärn and associates reported degeneration of myocardial and skeletal muscle fibers in rats given disulfiram (9). Black described a hypersensitivity reaction to a disulfiram implant in a 35-year-old man. The patient had rash, facial swelling, and painful swelling of the joints of the hands (10).

Two cases of polyarteritis nodosa have been reported in association with disulfiram therapy. In 1 case, a 27-year-old man developed fever, migratory pains in the extremities, and a sensorimotor neuropathy 1 month after implantation of disulfiram (11). The patient had histologic evidence of polyarteritis nodosa, and eventually died, with widespread vasculitis. In the second case, a 36-year-old man developed fever and recurrent abdominal pain a few weeks after starting an iodine-containing compound and oral disulfiram. Over the next few months, renal failure, hypertension, coma, and finally death ensued. Autopsy showed evidence of widespread polyarteritis nodosa (12). The authors suggested that the disulfiram might have caused the polyarteritis, but could not rule out iodine-induced disease.

In the 2 cases presented in this report, joint pain developed several weeks after starting oral disulfiram. That the drug was causally related to the patients' articular symptoms is suggested by the reproduction of the joint symptoms upon challenging with disulfiram, and by the long symptom-free period following final cessation of disulfiram therapy.

In the first case, the joint pain and swelling were accompanied by carpal tunnel syndrome. Peripheral neuropathy is a well-known complication of disulfiram therapy. It is a sensorimotor neuropathy that tends to be more severe distally and occurs more commonly in the legs (5). Histologically, there is axonal degeneration and segmental demyelination (13). The neurotoxicity is thought to be caused by carbon disulfide, a metabolite of disulfiram (14). In the first case presented here, however, the presence of wrist swelling made compression neuropathy seem more likely.

Excretion of disulfiram is known to be slow (15). This might account for the fairly long interval

observed between the cessation of therapy and complete resolution of symptoms.

It appears that disulfiram can cause a benign, reversible arthropathy. How disulfiram induces joint pain and swelling is unknown.

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REFERENCES

1. Hald J, Jacobsen E: A drug sensitising the organism to ethyl alcohol. Lancet 2:1001–1004, 1948
2. Menne T, Kaaber K, Tjell JC: Treatment of nickel dermatitis. Ann Clin Lab Sci 10:160–164, 1980
3. Eneanya DI, Bianchine JR, Duran DO, Andresen BD: The actions and metabolic fate of disulfiram. Annu Rev Pharmacol Toxicol 21:575–596, 1981
4. Eisen HJ, Ginsberg AL: Disulfiram hepatotoxicity (letter). Ann Intern Med 83:673–675, 1975
5. Mokri B, Ohnishi A, Dyck PJ: Disulfiram neuropathy. Neurology (NY) 31:730–735, 1981
6. Christensen JK: Bivirkninger efter disulfiram. Ugeskr Laeger 135:1457–1459, 1973
7. Weddington WW, Marks RC, Verghese JP: Disulfiram encephalopathy as a cause of the catatonia syndrome. Am J Psychiatry 137:1217–1219, 1980
8. Hernberg S, Tolonen M, Nurminen M: Eight-year follow-up of viscose rayon workers exposed to carbon disulfide. Scand J Work Environ Health 2:27–30, 1976
9. Ekvärn S, Jönsson M, Lindquist NG, Holmberg B, Kronevi T: Disulfiram-induced myocardial and skeletal-muscle degeneration in rats (letter). Lancet 2:770–771, 1977
10. Black D: An allergic reaction to disulfiram implant. Br J Addict 74:88–90, 1979
11. Telerman–Toppet N, Vanaise A, Six R, Vanherweghem JL, Sternon J, Coers C: A propos d'un cas de periarterite noueuse après implantation de disulfiram. Acta Clin Belg 30:101–107, 1975
12. Zanini S, Porciello PI: Considerazioni su un caso di panarterite nodosa possibile azione patogena dell'Antabuse. Frascatoro 63:117–127, 1970
13. Nukada H, Pollock M: Disulfiram neuropathy—a morphometric study of sural nerve. J Neurol Sci 51:51–67, 1981
14. Rainey JM: Disulfiram toxicity and carbon disulfide poisoning. Am J Psychiatry 134:371–378, 1977
15. Eldjarn L: The metabolism of tetraethyl thiuramdisulphide (Antabus, Aversan) in man, investigated by means of radioactive sulphur. Scand J Clin Lab Invest 2:202–208, 1950