NOTE

Clofibrate-Induced Myopathy in Patients with Diabetes Insipidus

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Abstract

Clofibrate has been considered to be a relatively safe antidiuretic in the treatment of diabetes insipidus. However, we have recently had four cases of clofibrate-induced myopathy in patients with diabetes insipidus due to hypothalamic lesions. Physicians should therefore be aware of its occurrence and carefully monitor serum levels of CPK, GOT and GPT during the treatment of diabetes insipidus with clofibrate, especially in patients with associated hypothyroidism, latent or overt, which possibly favors the development of myopathy.

Clofibrate, a hypolipidemic agent with relatively few side effects, has been used as a safe and effective antidiuretic in the treatment of diabetes insipidus (De Gennes et al., 1970; Moses et al., 1973). However, this drug has been reported to induce acute muscular syndrome when used for the treatment of hyperlipidemia (Langer and Levy, 1968; Bridgman et al., 1972; Sekowski and Samuel, 1972; Fabre et al., 1973; Pierides et al., 1975). Recently, similar muscular syndrome was also reported in two patients with diabetes insipidus treated with clofibrate (Smals et al., 1977; Abourizk et al., 1979). We report here four additional cases of clofibrate-induced muscle damage during the treatment of diabetes insipidus.

Report of Cases

Case 1. -A 15-year-old boy treated for idiopathic diabetes insipidus with clofibrate (750 mg/day) and chlorothiazide (1,500 mg/day) for two years with no side-effects was re-evaluated because of marked emaciation, and a diagnosis of slight hypopituitarism with diabetes insipidus due to a pinealoma was finally established. After a ventriculoperitoneal (V-P) shunt, the patient was treated for a pinealoma with radiation (5,000 rads) and for polyuria with the two oral antidiuretics at the same doses as prescribed before. On the 10th day of the treatment he noticed anorexia and weakness in the proximal muscles of the arms and legs without pain. Serum glutamic oxalacetic (GOT) and pyruvic (GPT) transaminase were 92 and 15 IU/l (normal, < 40) and serum creatine phosphokinase (CPK) was 947 U/l (normal, < 80). After clofibrate was discontinued, weakness disappeared and serum enzyme activity returned to normal in about ten days. Thereafter, he was treated with chlorothiazide and hydrocortisone without muscular symptoms.

Case 2. -A 13-year-old boy had headache, polyuria and polydipsia for two years and was found to have hypopituitarism with...
impaired ACTH reserve and diabetes insipidus due to a pinealoma. He was treated for the pinealoma with a V-P shunt and radiation (5,000 rads) and for diabetes insipidus with clofibrate (1,500 mg/day). After one week of the treatment, cramp-like pain and tenderness with weakness developed in the proximal muscles of the legs and arms along with low lumbar backache. The serum CPK was raised to 7,700 U/l, and GOT and GPT to 85 and 94 IU/l. Clofibrate was immediately stopped and trichlormethiazide (4 mg/day) given instead. In three weeks, muscular symptoms and increased enzyme activity resolved completely (Fig. 1). This patient was later given hydrocortisone for coexisting adrenal insufficiency.

Case 3. - A 47-year-old man who had acromegaly with elevated plasma GH levels due to a pituitary tumor underwent a transfrontal hypophysectomy. He was immediately started on 1,750 mg clofibrate daily because of polyuria occurring post-operatively. Two weeks later, serum CPK rose to 555 U/l and GOT and GPT to 74 and 52 IU/l without any muscular symptoms. After clofibrate was stopped, carbamazepine (600 mg/day) combined with trichlormethiazide (4 mg/day) was prescribed. Within two weeks, raised levels of the serum enzymes quickly returned to normal (Fig. 2).

Case 4. - A 13-year-old boy had polyuria, polydipsia and general malaise for two years and was finally shown to have diabetes insipidus caused by an ectopic pinealoma. He was treated for a pinealoma with a V-P shunt and radiation (5,000 rads) and for diabetes insipidus with clofibrate (2,250 mg/day). Twenty days later, although he was asymptomatic, serum CPK rose to 370 U/l and serum lactic dehydrogenase (LDH) to 1,440 U/l (normal, < 450) with serum GOT and GPT of 190 and 44 IU/l. After the dose of clofibrate was reduced to 1,500 mg/day because of these values, serum enzyme abnormality was resolved spontaneously. Two years later, the patient was also found to have developed mild hypothyroidism and adrenocortical insufficiency, which apparently masked polyuria and polydipsia in such a way that clofibrate therapy was not required at this time. Clofibrate (1,000 mg/day) was reintroduced when polyuria recurred after the start of replacement therapy with hydrocortisone (20 mg/day). On the fifth day of the treatment the patient complained of nausea and general malaise and serum CPK
rose to 1,521 U/l with serum GOT and GPT of 190 and 55 IU/l. Cessation of clofibrate and administration of desiccated thyroid powder (50 mg/day) for mild hypothyroidism resulted in a gradual alleviation of symptoms and serum enzyme abnormality.

Discussion

This observation shows that clofibrate-induced acute muscular syndromes and/or abnormal enzyme activity occur in patients with diabetes insipidus as reported previously (Smale et al., 1977; Abourizk et al., 1979) as well as in those treated for hyperlipidemia with the drug (Langer and Levy, 1968; Bridgman et al., 1972; Sekowski and Samuel, 1972; Fabre et al., 1975). None of the patients studied here had impaired renal function although both uremic and nephrotic patients were reportedly prone to clofibrate-induced myopathy, when treated with this drug, probably due to the high serum non-protein-bound drug levels caused by a significant delay in excretion of the drug and hypoalbuminemia in these patients (Bridgman et al., 1972; Pierides et al., 1975; Goldberg et al., 1977). However, it appears likely that hypothyroidism, coexisting often in patients with secondary diabetes insipidus, may precipitate the development of clofibrate-induced myopathy (Rumpf et al., 1977) since myopathy with increased serum CPK is not uncommon in hypothyroidism alone (Craig and Smith, 1965). Although the presence of overt hypothyroidism was confirmed in one (Case 4) among the four cases studied here, it is possible that some of the other patients also might have latent hypothyroidism due to the hypothalamic-pituitary lesions despite apparent euthyroidism with normal thyrotrophin secretion to intravenous thyrotrophin-releasing hormone (500 μg). Caution should therefore be exercised and serum levels of CPK, GOT and GPT should be carefully monitored when clofibrate, alone or combined with the other drugs, is used as an antidiuretic in the treatment of secondary diabetes insipidus, particularly in the possible coexistence of hypothyroidism, latent or overt.

References