Severe Alpha-2 Agonist Withdrawal Syndrome in Diabetes Mellitus

Although alpha-2 agonists are known to cause withdrawal syndrome after their discontinuation (1), the true incidence of severe alpha-2 agonist withdrawal syndrome has been considered to be low (2). Here we present three cases of diabetes mellitus, who developed severe withdrawal symptoms after discontinuation of the alpha-2 agonist, clonidine or guanabenz. The first case is a 49-year-old man, who had undergone hemodialysis because of diabetic nephropathy. The patient had taken clonidine (150 μg/day) for hypertension since several years ago. When the patient could not take clonidine because of gastric symptoms, he always developed severe symptoms, such as abdominal colicky pain, palpitation, nausea, vomiting, restlessness, and markedly high blood pressure (systolic pressure higher than 200 mmHg). Urinary catecholamine levels were measured, which showed no significant change during the withdrawal attacks. When clonidine was administered again, his symptoms gradually abated. Although tapering of clonidine has been tried, the patient has often developed withdrawal syndrome. He still needs a low dose of clonidine. The second case is a 42-year-old woman, who also underwent hemodialysis because of diabetic nephropathy for three years and had taken clonidine for hypertension. The patient developed symptoms similar to those of the first case when she did not take clonidine. Urinary catecholamine was unchanged during the attack. Morphine and FK 33-824 (Met5-enkephalin, an opiate analog) were administered, both of which achieved a partial improvement of her symptoms, but did not decrease her blood pressure. Clonidine was administered, which eliminated the symptoms and normalized the blood pressure. The third case is a 73-year-old woman, who had been treated with guanabenz (4 mg/day) and an oral hypoglycemic agent (gliclazide) for hypertension and diabetes mellitus, respectively, from ten years ago. When guanabenz was switched to another antihypertensive agent, temocapril (an angiotensin-converting enzyme inhibitor), she suddenly developed symptoms similar to those of the above two cases. After temocapril was replaced with clonidine (75 μg/day), she became asymptomatic with fair control of hypertension.

Central alpha-2 activation causes stimulation of endogenous opioid system in rats (3–5) and ameliorates human opiate withdrawal syndrome (6). It is, therefore, likely that the sudden decrease in tone of the endogenous opioid system is responsible for the development of alpha-2 agonist withdrawal syndrome, resulting in symptoms similar to those of opiate withdrawal syndrome, as in the present cases. The effectiveness of an opiate agonist in one of the present cases supports this hypothesis. Furthermore, increased tone of the peripheral sympathetic nervous system has been considered to be involved in the withdrawal syndrome, although the reports of urinary or plasma catecholamine levels during the withdrawal attack are conflicting; some suggested an increase in the levels and others reported no change (1, 2). All of the present cases were associated with diabetic autonomic neuropathy, which might have acted to exaggerate the manifestations of withdrawal syndrome. However, to our knowledge, there has been no report suggesting an increased frequency of alpha-2 agonist withdrawal syndrome in diabetes mellitus. Whatever the mechanisms, the present cases suggest a possibility that the indication for alpha-2 agonists might be limited in cases with diabetes mellitus.

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