Familiarity with the diagnoses of EPM and CPM is relevant to psychiatric practice because water intoxication leading to hyponatremia is a well-known phenomenon that requires treatment in a subgroup of patients with chronic psychiatric disorders.[13]

In retrospect, NMS was an unlikely cause of the features in our patient. She did not exhibit generalized rigidity, extreme hyperthermia, labile autonomic signs, or other secondary symptoms of NMS.[1,2] The elevation of creatine kinase was nonspecific and does not confirm the diagnosis of NMS.[1,2] Although SGAs may produce a mild form of NMS, we believe that quetiapine was not a factor in this case.[4,5] She received quetiapine for 2 years without incident and previously received more potent antipsychotics without NMS. In fact, there are still few unequivocal reports implicating quetiapine monotherapy in causing NMS.[14] Theoretically, the low affinity and fast dissociation of quetiapine in relation to dopamine receptors should diminish the risk of NMS with this agent.[15]

We previously proposed that the liability of SGAs in causing extrapyramidal symptoms, including NMS, may be significant only when they are administered in high-risk populations.[16] Risk factors for the development of NMS may include hyponatremia and preexisting basal ganglia dysfunction.[1,2,17,18] It follows that patients who sustain basal ganglia damage associated with EPM after hyponatremia and who are also receiving SGAs could be at increased risk of developing NMS. Hence, it can be difficult to distinguish EPM from NMS in these patients, and we cannot exclude entirely the possibility of a transient NMS-like effect of quetiapine in our case.

In conclusion, we report the first case of EPM mimicking NMS. Although these are rare conditions, EPM and CPM have been associated previously with catatonia and parkinsonism and should also be included in the differential diagnosis of NMS. Furthermore, this case underscores the importance of identifying serious medical disorders as well as NMS in patients presenting with fever and neurological changes during treatment with antipsychotic drugs. Errors in excluding either category of illness prematurely can be fatal.

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Impaired Glucose Homeostasis After Imipramine Intake in a Diabetic Patient

To the Editors:

The tricyclic antidepressant (TCA) imipramine is primarily indicated for the treatment of depression, but in practice, it is also used for other disorders. We describe a patient with type II diabetes mellitus, in whom changes in insulin need were closely associated with the use and dose changes of imipramine, which was prescribed for the treatment of urinary incontinence.

CASE DESCRIPTION

A 62-year-old woman was treated for several years for type II diabetes mellitus with the oral hypoglycemic agent glimepiride (4 mg daily). Since November 27, 1998, she additionally used NPH insulin before the night, but the correction of the blood glucose was only moderately successful because the average $HbA1_C$ level was 9.0% (normal value, 4.4%–6.1%). On July 13, 2000, a urologist prescribed imipramine (25 mg at bedtime) because of urinary incontinence. On September 12, 2000, the diabetologist switched the oral hypoglycemic treatment in combination with bedtime NPH insulin to intensive insulin therapy (multiple daily injection regimen) with blood glucose self-monitoring and algorithm-based adjustment of insulin dose. Glucose measurements as well as the amount of injected insulin were monitored and registered by the patient on a daily basis in a ''diabetes diary.'' From September 12, 2000, to May 29, 2002, the average insulin dose was 81 IU/d, and the $HbA1_C$ level was 8.4% on August 16, 2001, and 6.8 % on March 13, 2002. On May 30, 2002, the dose of imipramine was increased from 25 mg once daily to 25 mg twice daily

(in the morning and at bedtime). After 1 month, the need for insulin increased. Between May 30, 2002, and January 10, 2003, the average insulin dose was 95 IU/d, corresponding to an increase of 17% of insulin dose relative to the period that she used imipramine 25 mg daily. The $HbA1_C$ level was 7.5% on October 9, 2002. In agreement with her urologist, the patient tapered the use of imipramine between January 11, 2003, and February 5, 2003. On February 6, 2003, the use of imipramine was discontinued completely. During the tapering period, the average insulin dose dropped to 91 IU/d, and after complete discontinuation of imipramine on February 6, 2003, the average insulin dose decreased further to 48 IU/d. This corresponded to a decrease of 51% relative to the period when imipramine 50 mg daily was used. On March 14 and July 23, 2003, the $HbA1_C$ level was 6.8% and 7.4%, respectively. Further analysis revealed that the changes in the amounts of insulin administered particularly concerned the nightly dose. Concomitantly used medication included atenolol, lisinopril, simvastatin, and clodronic acid which did not, besides glimepiride (discontinued on September 12, 2000), essentially change during the entire period. During the entire period, no substantial changes in body weight occurred, and the patient was not aware of changes in eating behavior and pattern.

DISCUSSION

In our patient, there were 3 interventions regarding imipramine: (1) starting imipramine, (2) dose increase of imipramine, and (3) discontinuation of imipramine. All interventions were followed by changes in the daily amounts of insulin requirements. Especially regarding the second and third interventions, the time relationship between the intervention and the change in insulin requirement is highly suggestive of a pharmacological effect of imipramine. We did not identify other factors that could explain the change in requirements of insulin dose. For the first intervention, the time relationship is less obvious. Nine weeks after the first intervention, the diabetologist switched from a fixed regimen of an oral agent combined with bedtime NPH insulin to an intensive insulin-dosing scheme with self-monitoring and adjustment of insulin dose on measured blood glucose level. The measured $HbA1_C$ level was moderately high before the start of imipramine. Therefore, the switch to the intensive insulin-dosing scheme probably was not caused by the use of imipramine. Earlier evidence in literature suggests that imipramine, as well as other antidepressants, may affect glucose homeostasis.[1–13] A strong feature of this case is that imipramine was not used for depressive disorder, which itself may be associated with changes in food intake and altered glucose homeostasis, but for urinary incontinence. Moreover, this case report is unique because we were able to illustrate in detail the changes in insulin requirements, which are a very sensitive marker for altered glucose homeostasis. In addition, we could show a dose-response relationship, as well as a dechallenge. In at least 2 of 3 interventions regarding imipramine, we found a strong time relationship between the use and dose of imipramine and the insulin requirement (Fig. 1). Theoretically, glucose homeostasis could be affected by a direct effect on blood glucose levels and/or insulin levels and/or insulin sensitivity. Several mechanisms have been described in literature that may be involved in imipramine-induced glucose deregulation. Like most TCAs, imipramine inhibits the synaptic reuptake of both norepinephrine and serotonin (5-hydroxytryptamine [5-HT]) at nerve terminals. Norepinephrine may stimulate glycogenolysis and gluconeogenesis resulting in raised blood glucose levels[1] or reduced insulin release.[2] Because these effects occur in a short time span, these mechanisms could not explain the time gap between the interventions with imipramine and effects on glucose homeostasis. Another mechanism encompasses a blockade of TCAs of M_3 receptors in beta cells, resulting in suppression of insulin secretion and increased leptin levels, also inhibiting insulin secretion by the pancreas.[4,14] In rats, imipramine induced a dose-dependent decrease in glucose-stimulated insulin secretion which appears to be mediated by inhibition of voltage-sensitive Ca^{2+} channels[5]. In mice studies, imipramine-induced hyperglycemia has been related to inhibition of the central 5-HT_{2C} receptor.[7] Blockade of the 5-HT_{2C} receptor may result in craving for ''sweets'' and ''carbohydrates'' and increase body weight.[15] TCAs also block histaminic-, M_3-, and α_1-adrenergic receptors, causing adverse drug reactions such as dry mouth, followed by drinking large quantities of soft drinks. Both effects on food intake will complicate the diabetic's ability to follow a controlled diet. In this patient, however, no changes in body weight occurred. Finally, TCAs may enhance tissue sensitivity to insulin, thereby reducing compensatory beta-cell hypersecretion of insulin and, therefore, an increase of external insulin need.[4] Tissue sensitivity does not necessarily go together with weight changes and is altered by delay which could explain the time gap between the interventions with imipramine and changes insulin need without changes in body weight.

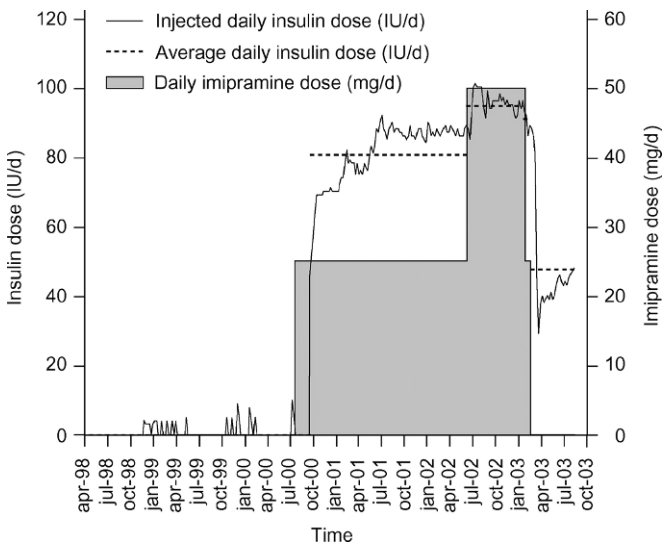

FIGURE 1. Time relationship between insulin dose and imipramine dose.

This case report illustrates that imipramine can affect glucose homeostasis in diabetic patients. Although the mechanism is still unclear, physicians have to be conscious that imipramine, and probably other antidepressants, can impair diabetes control in some sensitive patients. Further research is needed to elucidate the mechanism for this effect and to find out which patients are at risk.

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Diplopia With Citalopram

A Case Report

To the Editors:

Citalopram is an antidepressant which effects serotonergic neurotransmission through potent and selective inhibition of serotonin reuptake. Neuroendocrine studies suggest decrease of serotonergic responsively in patients with major depression. Citalopram is (1) superior to placebo in the treatment of depression; (2) is similar to that of the tricyclic and tetracyclic antidepressants and to other selective serotonin reuptake inhibitors; and (3) is safe and well tolerated in the therapeutic dose range of 20 to 60 mg/d.[1] Data from 3107 patients from 24 clinical trials[2] showed that nausea, dry mouth, somnolence, increased sweating, tremor, diarrhea, and ejaculation failure, mostly of mild to moderate severity, occurred with a significant frequency with citalopram.

However, bruxism, cutaneous reactions, torsade de pointes, bradycardia and hypotension, hyponatermia secondary to syndrome of inappropriate secretion of antidiuretic hormone, priapism, panic attacks, palpebral twitching, photopigmentation, galactorrhea, and hypertriglycemia have been reported rarely with citalopram.

Diplopia is an unusual phenomenon that may occur after citalopram ingestion.[3] Diplopia is defined as double vision. Binocular diplopia is a type of double vision that is eliminated when either eye is occluded.[4] Causes of binocular diplopia are isolated third, fourth, and sixth cranial nerve palsy, orbital diseases, cavernous sinus/superior orbital fissure syndrome, posttraumatic status, intranuclear ophthalmoplegia, vertebrobasilar artery insufficiency, other central nervous system lesions, and spectacle problem.[4]

Here, we report a 28-year-old man who developed diplopia after citalopram ingestion. To our knowledge, there is no report on the interval after which this side effect is eliminated after discontinuation of the drug.

CASE REPORT

MZ was a 28-year-old, single, medical student, who lived in a university dormitory, and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* nonpsychotic major depressive disorder criterion for 6 months before his referral. There was no history of past psychiatric problem in childhood and adolescence. His condition deteriorated day by day that led him to drop several courses. He was urged by the university to visit our clinic.

After his referral, he was examined in our clinic. The patient's score on 21-Item Hamilton Depression Scale was 34. There was a positive history of major depressive disorder in his father.

Citalopram, 20 mg/d in the morning, was prescribed to him. After 12 days, incapacitating diplopia appeared. This condition was accompanied with diarrhea and memory complaints. He was frightened and described the condition as ''It is terrible. I see everything in 2. I don't know which is real and which is artificial. If I concentrate and close one eye, I will be able to differentiate the real one.''

There was no positive finding in neurological and ophthalmologic consultations. Citalopram, the only medication he was taking, was discontinued. After 60 hours, the diplopia disappeared completely, and he felt relaxed.