Parkinsonism and Tremor Complicating Long-term Cinitapride Use

Sir,

A 66-year-old man presented with progressive difficulty in writing for 2 years. He complained of tremulousness immediately upon attempting writing, without pain or abnormal posturing of the limb, resulting in his handwriting becoming progressively illegible. Although he had no other complaints, he was found to be hypomimic with mild rigidity and bradykinesia bilaterally, more prominently in the right upper limb. Arm swing was reduced on the right. No rest or postural tremor was seen. On writing and on performing other fine movements such as buttoning or flipping a coin, an irregular fine tremor was seen without dystonia [Video 1]. No other neurologic deficits were evident. He had previously had a magnetic resonance imaging of the brain, which was normal.

The patient admitted to receiving cinitapride 1 mg TID for the past 7 years, for gastroesophageal reflux. With a presumptive diagnosis of drug-induced Parkinsonism and tremor, a course of levodopa 100 mg TID was prescribed, without any benefit after 1 month [Video 1]. Similarly, tremor did not improve with propranolol and clonazepam. Cinitapride was stopped after consultation with his gastroenterologist, leading to a marked improvement in tremor when seen 6 months later. Mild residual bradykinesia in the right upper limb persisted.

Cinitapride is a novel gastrointestinal (GI) prokinetic agent used in many countries as a treatment for functional dyspepsia, gastroesophageal reflux, hiatus hernia, constipation, and other functional GI disorders. Its substituted benzamide structure confers agonist actions at 5-HT_4 and 5-HT_1 serotonergic receptors and antagonist actions at D_2 dopaminergic and presynaptic 5-HT_2 serotonergic receptors in the myenteric plexus, promoting acetylcholine release, and thereby augmenting GI contractility and accelerating gastric emptying.

[1,2] Central serotonergic and dopaminergic actions are also known and may be responsible for occasional side effects, albeit with a very low incidence not different from placebo. [1,2] Other substituted benzamides such as levosulpiride and metoclopramide are regularly associated with tremor and other extrapyramidal side effects likely due to their actions in presynaptic dopamine depletion and postsynaptic dopamine receptor blocking.[3,4] Such drug-induced tremors may be due to striatal dopaminergic blockade and consequent oscillations in activity of the cortico–striato–thalamo–cortical loop. Tremor, Parkinsonism (often asymmetric), and tardive dyskinesias have all been reported with levosulpiride, with only 49% responding to drug cessation or medication.[5]

In a study of 383 patients using cinitapride, jaw and head tremors were seen in only one patient, attributed to central dopaminergic blockade.[1] In another study, no neurological side effects were noted in 19 patients on long-term cinitapride.[2] The occurrence of tremor while performing complex tasks such as writing has not been noted after cinitapride use previously. The improvement in writing 6 months after cessation of cinitapride therapy supports a causative role for this medication in the genesis of the movement disorder. A drug challenge, which would have definitely established the causative nature of the association of the movement disorder to cinitapride use, was not performed as it was felt to be unethical.

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Conflicts of interest
There are no conflicts of interest.

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