Parkinsonism Associated with Fluoxetine and Cimetidine: A Case Report

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ABSTRACT

Fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) are effective for the treatment of depression in the elderly and offer a safer side-effect profile as compared to tricyclics and monoamine oxidase inhibitors. We report a case in which a patient treated with fluoxetine developed parkinsonism following the introduction of cimetidine. Inhibition of hepatic P450 cytochrome enzymes by cimetidine with an increase in serum levels of norfluoxetine may have precipitated this extrapyramidal syndrome, which has been related to agonism of the serotonergic input to nigrostriatal tracts and basal ganglia. Parkinsonism as a side effect of SSRIs occurs infrequently, suggesting an idiosyncratic response resulting from a functional imbalance of serotonergic and dopaminergic activity in susceptible individuals. Careful monitoring of geriatric patients treated with fluoxetine is indicated, particularly for those on high doses, those with impaired hepatic functioning, or those treated with concurrent medications that slow the metabolism of fluoxetine. (*J Geriatr Psychiatry Neurol* 1995; 8:231–233).

Depression often accompanies and contributes to the morbidity of Parkinson's disease (PD) and has been correlated with low cerebrospinal fluid 5-hydroxyindoleacetic acid levels.[1] Selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, are thus theoretically attractive for the treatment of depression in PD and offer some advantages over tricyclic antidepressants, having a more favorable side-effect profile, especially in older subjects and in those with cardiovascular disease. However, several case reports have described the development of extrapyramidal symptoms, including parkinsonism, in patients treated with fluoxetine.[2–14] Some patients with PD experienced an exacerbation of symptoms with fluoxetine.[15,16] In some cases, the development of extrapyramidal symptoms was associated with the concomitant use of other agents (e.g., neuroleptics,[4,6,13] lithium,[2,6] carbamazepine,[6,9] or metoclopramide[6,7]). Such drug interactions might increase the bioavailability of either fluoxetine or other drugs capable of producing extrapyramidal symptoms.[7,17] We report a case of a patient with no prior history of PD, who developed severe parkinsonism following treatment with fluoxetine and cimetidine. To our knowledge, this is the first report in the literature of parkinsonism arising from this drug combination.

CASE REPORT

A 68-year-old male was admitted with complaints of weakness and falling of three week's duration. He had been treated for depression with fluoxetine 20 mg t.i.d. for 1 year. Two months prior to admission, naproxen was started for arthritis, and cimetidine (400 mg q.d.) was also initiated. A note by his psychiatrist 6 months earlier revealed the presence of mild cogwheel rigidity of both arms. However, no resting tremor, bradyphrenia, bradykinesia, postural instability, or gait disturbances were noted on subsequent neurologic evaluation, and he was not diagnosed as having PD. He had been caring for his invalid wife at home until 3 weeks prior to admission, when he developed a rapidly increasing disability related to shuffling gait, postural instability, and frequent falls.

On examination, the patient was bradyphrenic, bradykinetic, hypomimic, and hypophonic. An action tremor was noted in both upper extremities, without resting tremor. There was slight rigidity of the neck and arms, with normal tone in the legs. He was dysarthric and had facial masking. Cranial nerves were intact. Slowing of finger tapping and rapid, alternating hand movements were noted bilaterally. There was neither finger-to-nose dysmetria, nor focal motor or sensory deficits. He required

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assistance to sit up and to stand. His posture was markedly stooped. Gait was notable for prominent start hesitation and freezing, reduced steppage, marked spontaneous instability with a tendency to fall backwards, and "en bloc" turning. CT scanning of the head revealed cortical atrophy. Both fluoxetine and cimetidine were withdrawn, while naproxen was continued. Within 4 days, there was a marked improvement in the patient's parkinsonism. His speech volume increased, and he was able to arise from a chair without assistance. His gait showed festination but no freezing. After an additional 3 days, the hypophonia had virtually resolved, but there was mild impairment of hand dexterity. His posture was greatly improved, although righting reflexes were still impaired when he closed his eyes in the Romberg position. Gait was without festination, but it was slow and there was mild instability on turning. Physical therapy and Sinemet 25/100, 1 tablet t.i.d. were initiated with continued clinical improvement.

DISCUSSION

In rats, high-dose fluoxetine has been shown to inhibit the synthesis of catecholamines in dopamine-rich areas of the forebrain, hippocampus, and caudate-putamen.[18] A relationship between serotonin-containing raphe nuclei and dopamine-rich areas has been supported by anatomic and histochemical techniques.[19] Neurophysiologic and electric stimulation studies demonstrated the inhibitory effects of raphe fibers on striatal neurons, which can be reversed by serotonin antagonists.[20] These data support the hypothesis that potent inhibitors of neuronal serotonin reuptake, such as fluoxetine, may inhibit nigrostriatal dopaminergic neurons and, thereby, aggravate parkinsonism. Our patient may have had subtle underlying PD that was aggravated by the addition of cimetidine. Fluoxetine alone is unlikely to explain the worsening of his PD, since he had taken fluoxetine uneventfully for 10 months prior to the addition of cimetidine.

Previous reports suggesting an association between fluoxetine and extrapyramidal symptoms have, at times, been confounded by the concomitant use of agents (e.g., neuroleptics, metoclopramide) that can contribute to the development of parkinsonism. Both fluoxetine and cimetidine inhibit the hepatic P450 cytochrome enzymes,[21] including 2D6 and 3A enzymes. It is expected that the combination resulted in a pharmacokinetic interaction producing increases in serum levels of both cimetidine and norfluoxetine, the demethylated active metabolite of fluoxetine. Unfortunately, serum norfluoxetine levels were not secured in the case described. There have been no reports in the literature that suggest that cimetidine is capable of precipitating or aggravating Parkinson's disease.

While there have been unpublished observations of worsening parkinsonism in patients receiving other SSRIs,[4,22] comparable effects have not been reported in PD subjects treated with sertraline or fluvoxamine. Clinical experience with these agents is more limited. One might postulate that the shorter half-lives of these drugs would result in less enduring serotonergic agonism and, thereby, reduce the likelihood of clinically significant depression of central dopaminergic systems. Furthermore, sertraline and fluvoxamine, in usually effective minimum doses, may be less potent inhibitors of the 2D6 enzymes.[23,24] Thus, drug interactions like the one posited here may be less likely to occur with these agents.

The relative infrequency with which parkinsonism has been reported in association with fluoxetine use suggests individual, perhaps idiosyncratic, responses.[11] In certain individuals, extrapyramidal symptoms may arise in response to fluoxetine treatment because of a resultant imbalance between serotonin and dopamine activity. Patients vulnerable to this imbalance include those whose capacity for metabolism is decreased (e.g., the elderly or those with reduced hepatic functioning). Additionally, those on high doses of fluoxetine, or those treated with concurrent medications that slow the metabolism of fluoxetine, may be vulnerable to extrapyramidal symptoms. Although further experience will be necessary to confirm the cause-and-effect relationship here, our case suggests a need for caution when coadministering fluoxetine, and possibly other SSRIs, with drugs acting on the hepatic P450 system.

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