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Letter to Editor

DOES ARIPIPRAZOLE PROTECT FROM SEROTONIN SYNDROME?

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Dear Editors,

Serotonin syndrome (SS) is an adverse drug reaction induced by hyperstimulation of postsynaptic serotonin receptors (Boyer & Shannon 2005). The syndrome includes psychiatric symptoms (unrest, disturbed sleep, elevated mood, confusion, semicoma or coma, …), neurological symptoms (myoclonus, tremors, hyperreflexia, impaired coordination, …), and autonomic symptoms (fever, hyperhidrosis, diarrhea, tachycardia, tachypnea, …) (Boyer & Shannon 2005, Ener et al. 2003, Lane & Baldwin 1997). Symptom severity may vary from minimal to potentially life threatening. We want to present a patient in whom pharmacokinetic interactions led to extremely high serum levels of serotonergic agents, yet causing only very subtle symptoms of SS. As this patient was concomitantly treated with aripiprazole we want to discuss the hypothesis that the coadministration of aripiprazole might have exerted a protective effect against SS.

A 22-year-old female patient was admitted to psychiatric inpatient treatment with diagnoses of depressive episode and comorbid borderline personality disorder. She was on a regimen of venlafaxine 300mg, fluoxetine 60mg and aripiprazole 10mg. The reasons for admission were sleep disturbance, nightly panic-like fits with heavy crying, sweating and restlessness. At day the patient appeared depressed but without special symptoms except a slight tremor of hands at rest and in action. Serum levels of antidepressants were 1618 ng/ml for venlafaxine (recommended therapeutic range 200-400ng/ml) and 1013 ng/ml for fluoxetine plus norfluoxetine (recommended range 120-300ng/ml). The level of the metabolite o-desmethy-venlafaxine (ODV), which is usually higher than the parent compound's level (Thase & Sloan 2009), was too low to be detected, indicating a massive inhibition of CYP 2D6. We assumed that fluoxetine had accumulated due to the high dose and its long half-life and that its potent inhibition of CYP 2D6 (Stahl 2005) impeded the metabolism of venlafaxine. This led to serum levels of both drugs four times above recommended limits. There are reports on severe manifestations of SS in patients with about equally high serum levels of venlafaxine (Dagtekin et al. 2011, Kolecki 1997) as well as of fluoxetine (Lange-Asschenfeldt et al. 2002). Considering this severe excess of serotonergic activity by the two drugs simultaneously, one wonders that symptoms of SS were confined to a subtle tremor. A possible explanation might be found in the co-medication with aripiprazole.

Blockers of 5HT2A receptors (the drug usually recommended is cyproheptadine) are considered a treatment option for SS (Boyer & Shannon 2005). Yet it is not clear whether SS is primarily mediated by stimulation of 5HT1A (Birmes et al. 2003, Ener et al. 2003) or 5HT2A (Boyer & Shannon 2005) receptors. Aripiprazole binds with high affinity not only to 5HT2A receptors, but also to 5HT1A receptors, where it acts as a partial agonist (Jordan et al. 2002, Stark et al. 2007). In the latter respect aripiprazole is different to other SGA such as olanzapine, clozapine or risperidone, which display only very low affinities to 5HT1A receptors (Buckley 2007). Aripiprazole's agonist action on somatodendritic autoreceptors has been shown to profoundly reduce firing of dorsal raphe serotonergic neurons (Stark et al. 2007). The high affinity of aripiprazole to 5HT1A as well as 5HT2A receptors provides the potential to protect both relevant types of postsynaptic receptors from a surplus of serotonin. Dosage of aripiprazole was low (10mg) but it is very probable that serum levels of aripiprazole were elevated too (serum levels not available) since the high levels of fluoxetine should have inhibited the metabolism of aripiprazole as well: aripiprazole is metabolized by CYP 2D6 and 3A4, which are both inhibited by fluoxetine (Stahl 2005).

We assume that the combined action of aripiprazole on 5HT1A and 5HT2A receptors might have spared our patient a full blown SS. If these considerations are valid aripiprazole could be considered as an especially useful agent for treatment of SS. Further more systematic investigations of this possibility are warranted.

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