Aripiprazole in Association with Acathisia, Sleep Disorders and Suicide – a Possible Mechanism

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Aripiprazole is a new antipsychotic agent for the treatment of schizophrenia with partial agonistic activity at dopamine-2(D2) receptors and partial agonistic activity at 5HT1A-receptors and antagonistic activity at 5HT2A-receptors[1,2]. The partial D2-agonism means that despite complete receptor occupation only 30% of the receptors will be activated by aripiprazole[3]. The activation will vary among individuals.
Aripiprazole has a higher affinity for D2-receptors than dopamine itself. If aripiprazole has bond, dopamine won't be capable of binding to these receptors. As a consequence, in areas with a lot of dopamine activity aripiprazole works as a relative dopamine antagonist[3]. In literature a possible association is described between suicidal ideation and suicide attempts and starting aripiprazole treatment[4]. The patients who attempted or successfully committed suicide seemed to have done this impulsively. None of them had a history of suicidal behaviour. They reported also akathisia and insomnia. A possible mechanism is introduced here through which these ADRs could be explained.

In schizophrenia dopamine levels are decreased in the prefrontal cortex, what is considered to be the cause of the negative symptoms, like apathy, depressed mood and inactivity[5]. Both classical and atypical antipsychotics, which are D2-antagonists, decrease dopamine activity in all areas. This decrease is associated with an increase in negative symptoms.
In contrast with these drugs, aripiprazole has little affinity for the postsynaptic D1-receptors in the prefrontal cortex and it inhibits the action of the 5HT2A-receptors through which dopamine release increases. This results in a decrease in negative symptoms and consequently in an improvement in cognitive and emotional functioning. Behavioural motivation and actual initiative will increase[2,3,6,7]. This could be the cause of the restlessness, the sleeplessness and the impulsive suicides or suicide attempts.
This hypothesis will be of more concern in patients who have used the D2-antagonistic drugs prior to treatment with aripiprazole, because a decreased dopamine activity will lead to an up-regulation of the dopamine receptors[5,8]. If someone has used these drugs prior to treatment with aripiprazole, the latter might have an agonistic effect in the first weeks. An increase in behavioural motivation and initiative then could be the result as well. Patients who are going to be treated with aripiprazole should be closely monitored, because the effect of aripiprazole is hard to predict due to its partial agonistic character.

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