

CITALOPRAM-INDUCED MAJOR DEPRESSION IN A PATIENT WITH PANIC DISORDER - A CASE REPORT

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INTRODUCTION

Citalopram represents a very selective drug inhibiting the reuptake of serotonin 3,400 times more than that of norepinephrine (Hiemke & Härter 2000). It has almost no affinity for acetylcholine, histamine, norepinephrine, dopamine, γ -aminobutyric acid (GABA) or opiate receptors (Hiemke & Härter 2000). In a dose range of 20 to 60 mg/day citalopram has proven to be an effective agent in depression (Keller 2000). Citalopram is also effective in the treatment of panic disorder, especially in a dose of 20 to 30 mg/day (Lepola et al. 1998). The anti-panic effect of citalopram is explained by a deficient serotonergic neurotransmission in panic disorder (Humble & Wistedt 1992).

CASE REPORT

The outpatient (Ms. S.) is a 31-year-old single female who presented to the Psychosomatic Clinic of the University Hospital Bonn with major depression and panic disorder. She reported that three weeks ago she had merely suffered from panic attacks and as a medication against panic disorder she had been prescribed citalopram in a dose of 10 mg/day for two weeks in the morning, followed by one week of 20 mg by her psychiatrist. Initial psychiatric assessment of Ms S. on the basis of SCID-I interview clearly ruled out the presence of any sign of mood disorder. One week before initial psychiatric assessment a comprehensive clinical examination ruled out drug or alcohol abuse or any relevant comorbid physical conditions. Two days after the first intake of citalopram, Ms. S. reported to have started suffering from depressed mood and loss of energy and concentration, furthermore the feeling of pleasure was markedly reduced and a feeling of worthlessness and extremely low self-esteem had developed. She found it difficult to fall asleep and would awake early in the mornings. Besides, she reported a weight loss of about 3 kg in the last three weeks. Her concentration was clearly worse than before. Moreover she observed impulsive thoughts such as "you are a sadist", "you could hurt somebody", that made her anxious and that she had never experienced before. Ms. S. denied suicidal thoughts. The SCID-I interview

confirmed the diagnoses of major depressive disorder and panic disorder as defined by DSM-IV. Psychodiagnostic testing by the Beck depression inventory (BDI) showed an elevated raw score of 27 points (cut-off for clinically relevant depression is 18). Further clinical examination on the basis of SCID-I and SCID-II led to the exclusion of additional psychiatric disorders. Case history revealed no family history of psychiatric disorders.

Ms. S. terminated citalopram medication after 28 days of intake. Within three days she started to feel better, regained energy and initiative and obsessive thoughts stopped. Ms. S. completely recovered in the course of one week and further examination on the basis of SCID-I confirmed the absence of any sign of major depressive disorder and BDI score was within the normal range (10 points). Consequently, we recommended her to start outpatient psychotherapy to treat her anxiety disorder. A diagnostic evaluation two weeks later confirmed the stability of recovery from the depressive episode.

DISCUSSION

To our knowledge this is the first report of a citalopram-induced major depression. This side effect is unexpected, especially as citalopram is usually administered effectively as antidepressant medication (Keller 2000). However, SSRIs have been associated with adverse mood effects (Peet 1994, Chun & Dunner 2004). Citalopram in particular was reported to induce mania and euphoria (Barak et al. 2000, Beckwith 2008). In the official Food and Drugs administration (FDA) information on citalopram a worsening of depression and the emergence of suicidality in major depressed children, teenagers and young adults is mentioned. However, as citalopram is prescribed frequently as a medication against panic disorder without concomitant depression, it is important to be aware of adverse side effects in this patient population (Rampello et al. 2006).

From what we see this is not only the first report of Citalopram induced depression but the first report of any SSRI induced depression even though in the official FDA information the possibility of depression worsening is mentioned. How can this curious fact be

explained? In panic disorder the suffering patients often lives with a persistent worry of having another attack. This overwhelming worry may overshadow other symptoms. Consequently the clinician may underdiagnose depression while focusing too exclusively on anxiety symptoms and the induction of hypomania or mania with SSRIs (Zastrow et al. 2008). It is important to note that in our case the induction of depression is associated with the emergence of inappropriate aggressive thoughts. This adverse side effect is highly relevant with regard to the development of suicidality, even though Ms S. denied specific suicidal thoughts.

Which pharmacological mechanism could underlie the induction of major depression? Humble and Wistedt (1992) emphasize that the therapeutic effect of SSRIs in panic disorder shows a latency of 2 to 6 weeks and in the initial phase of treatment, even paradoxical anxiogenic effects of SSRIs have been observed (Humble & Wistedt 1992, Zuardi 1990). Under acute SSRI treatment, the initial increase of anxiety could be due to the activation of presynaptic 5-HT autoreceptors (Blier et al. 1988) leading to an attenuation of the firing activity of the serotonergic neurons.

Thus, post-synaptic serotonin response is decreased. After 2-3 weeks of sustained SSRI administration, the firing activity of 5-HT neurons will gradually recover and return to normal because the autoreceptors are desensitized (Blier & Montigny 1999). Since 5-HT reuptake blockade is established by the SSRI 5-HT transmission will eventually be increased. Interestingly, patients with panic disorder are supposed to be more sensitive to these initial adverse effects (Zuardi 1990). Although serotonin deficiency alone is not supposed to fully account for mood disorders, there is evidence for deficient serotonergic functioning in 5-HT-containing neural systems in major depression (Kalia 2005). As in panic disorder, the increase of serotonergic neurotransmission in depressed patients under chronic SSRI treatment follows a temporal sequence similar to that of the clinical treatment response. That is, the onset of the antidepressant clinical response in depressed patients is delayed by 2-3 weeks (Blier & Montigny 1999, Kalia 2005). It is assumed (Humble & Wistedt 1992) that all states associated with a deficient serotonergic function can occur early in SSRI treatment although they eventually improve with proserotonergic drugs. This mechanism can explain an initial depressive reaction after the acute administration of SSRI to treat panic disorder. The sudden onset of depression in our patient after only 2 days of citalopram administration could originate in a particularly strong reactivity of 5-HT autoreceptors to citalopram leading to a strong reduction of firing rate and serotonergic neurotransmission. The high reactivity on the one hand and a slow desensitization of autoreceptors on the other may also account for the lack of improvement of depression during the 28 day intake period of citalopram in the sense of a specific vulnerability of Ms S.' phenotype.

CONCLUSIONS

In summary, citalopram-induced depression could be explained by the activation of presynaptic autoreceptors leading to a decrease of post-synaptic serotonin response (Blier et al. 1988). As such deterioration cannot be predicted we agree with Humble and Wistedt (1992) to commence the treatment in panic disorder patients with a low dose of 5 mg/day. The dosage can then be gradually increased to the target dosage with two-week-phases of stable dosage in-between. If initial deterioration can be observed despite a bisection of the starting dose, then alternative medical treatments might comprise a noradrenergic antidepressant such as reboxetine or open-label use of a combined serotonin-norepinephrine reuptake inhibitor such as venlafaxine (Davidson et al. 2004).

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