Dothiepin-induced transient hypomania and extrapyramidal syndrome

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ABSTRACT

A case has been reported here, who developed transient hypomaniac symptoms as well as extrapyramidal symptoms after being switched from sertraline to dothiepin therapy. The possible mechanisms and clinical implications of the same are discussed.

Key words: Dothiepin, extrapyramidal syndrome, hypomania

INTRODUCTION

Induction of mania and extrapyramidal symptoms with tricyclic antidepressants (TCAs) such as imipramine, desipramine, clomipramine, amitriptyline, nortriptyline, and doxepin has been well reported.[1] However, apart from an isolated report,[2] there is no other report of any such presentations with dothiepin (also known as dosulepin).

CASE REPORT

Mrs. P, a 25-year-old married female and a homemaker, was admitted to our adult psychiatry inpatient service for management of her depressive disorder, which did not show any response to outpatient treatment. She had been suffering from an illness, of 2 years duration, with an insidious onset, continuous course, with partial remissions and periods of exacerbations, beginning after the demolition of her husband’s general store, leading to a loss of the only source of family income. After the financial setback, she had been accusing him of not earning enough for their livelihood. Her symptoms included frequent irritability, persistent sadness of mood, ideas of hopelessness, helplessness, and worthlessness, occasional suicidal idea, decreased sleep, decreased appetite, and multiple somatic complaints. Since the onset of her illness, she also experienced four panic attacks. There was no other significant history, apart from the fact that there had been marital discord, leading to regular verbal fights with her husband, due to less involvement by her husband in their children’s affairs. Medical history was remarkable only for reports of dysmenorrhea and menorrhagia, for the last several months. Six months prior to this admission, patient was started on treatment on an outpatient basis, and was prescribed tablet mianserin 30 mg HS; it was gradually increased to 45 mg per day, in divided doses. Initial improvement was shortlasting, and hence mianserin had to be increased to 60 mg per day and capsule fluoxetine 20 mg per day had to be added. However, patient did not show any response to the combination, and hence her antidepressant medications were gradually tapered off and she was admitted to review the diagnosis and formulate a fresh management plan. Mental status examination on the day of admission revealed decreased pitch, tone, and volume of speech, sadness of mood, and depressed affect, which was reactive to the environment. There were ideas of hopelessness, helplessness, and death wish, and insight into the illness was partial. On admission, patient was started on tablet sertraline 50 mg per day, which was increased to 100 mg per day, over a 4-day period. Patient complained of epigastric pain for which referral to gastroenterologist was made, and she was prescribed tablet pantoprazole 40 mg before breakfast. However, as the pain...
did not show any sign of improvement, sertraline was discontinued, and dothiepin, 75 mg per day, was started from the next day [Figure 1]. After about 1½ days of starting dothiepin, it was noted that the patient was speaking more than usual. The next day, additionally, patient had an elated affect, reported increased self-confidence, and was making new, but big plans for future to make up the monetary loss. Young Mania Rating Scale (YMRS) was administered, and the patient scored 18 on the scale. In addition, it was noted that the patient had bradykinesia, fine tremors in the hands, and sialorrhea. At this time, the patient also developed cough with fever, and was sent to the medical OPD where she was prescribed tablet amoxicillin 500 mg TID along with tablet ibuprofen 400 mg TID, for 5 days.

Patient continued in this state for the next 4½ days, after which her mood and her behavior became normal. YMRS was repeated on that day, and the patient’s score was 8. However, sialorrhea, bradykinesia, and tremors persisted.

Patient was euthymic for 1 day, after which, following an altercation with her husband, who came to visit her in the ward, her depressive symptoms re-emerged and continued subsequently. Throughout her subsequent inpatient stay, the hypomanic symptoms did not reappear. Sialorrhea, bradykinesia, and tremors gradually decreased, and by the time of discharge, after about 10 days of the onset of her hypomanic and extrapyramidal syndrome, the patient did not have any extrapyramidal symptom.

**DISCUSSION**

All antidepressants have been associated with induction of mania. Bunney (1978) reviewed the literature and reported an incidence of 8.6% of TCA-induced manic or hypomanic switch. Another report described an incidence of 6.5%, with more rigorous criteria. It was also reported that patients switching to mania or hypomania, subsequent to TCA use, were young, had an early onset of illness, high frequency of hospitalization, and a positive family history of psychiatric illness.

On the other hand, despite case reports since 1970, TCA-induced extrapyramidal side effects have not been reported in literature reviews on drug-induced Parkinsonism. Vandel et al. (1997) have reviewed antidepressant-induced extrapyramidal side effects, and have identified dyskinesia, akathisia, myoclonus, rabbit syndrome, and dystonia as the extrapyramidal side effects. They have reported that these are not related to age or sex, are often dose-related, and respond to antiparkinsonian agents or reduction in the TCA dose.

In our case report, it is clear that the hypomanic symptoms appeared only after the patient received dothiepin. However, it is worth noting that the patient had been on sertraline 100 mg per day till 1 day prior to the start of dothiepin. It is known that the half-life of sertraline and its metabolites is from 26 to 104 h. Thus, it is likely that sertraline and its metabolites persisted in the patient’s body when dothiepin was started. Moreover, both sertraline and dothiepin are metabolized in the liver, and sertraline is an inhibitor of cytochrome P450 2D6 isoenzyme. It is thus probable that sertraline inhibited the metabolism of dothiepin, leading to increased blood levels of dothiepin and its metabolites and subsequent induction of hypomanic and extrapyramidal symptoms. After about 4½ days (about 104 h), when all the metabolites of sertraline might have been eliminated from the patient’s body, the inhibition of dothiepin metabolism caused by sertraline and its metabolites must have ended, leading to normalization of the blood levels of dothiepin and subsequent reduction in the dothiepin-induced hypomanic symptoms. This is evident in the case report, where there

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**Figure 1: Chart of hypomanic symptoms and EPS in relation to therapy duration**

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was a decrease in the hypomanic symptoms, after about 4½ days of stopping sertraline, while dothiepin was being administered. If the hypomanic symptoms were exclusively due to dothiepin, they would have persisted for a longer time than just 4½ days. Reason for the extrapyramidal symptoms, persisting even beyond this period, could be dothiepin only.

To our knowledge, none of the published literature has identified dothiepin as a potential candidate for the induction of either mania or hypomania or EPS. Moreover, the profile of the EPS, reported with TCAs,[1] is different from that found in our case. More systematic studies are required to explore these findings further.

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