Increase in Clozapine Levels Following The Introduction of Venlafaxine: A Case Report

Liam Dodge

Dear Editor,

Polypharmacy is a commonly encountered problem in cases of chronic mental illness, particularly where treatment resistance has been a concern. There are many resources documenting potential interactions among medications, however the possibility remains that interactions can occur even when a combination is thought to be safe. Here we report one such case.

Mr. A is a 42 year-old male with a diagnosis of treatment resistant paranoid schizophrenia. He had been a resident in a low security inpatient rehabilitation unit for 9 months and had been receiving treatment with clozapine at a dose of 400mg throughout that time. Repeated serum clozapine assays showed his serum levels to be around 0.50 mg/L (target 0.35-0.50) and norclozapine around half of this at 0.25mg/L, indicating good compliance. His other psychotropic medication included lofepramine 140mg, diazepam 2mg twice daily, Hyoscine Hydrobromide 300mcg twice daily, as well as a regular combination inhaler for COPD. The patient was a smoker.

Around 6 months into his admission, Mr. A requested to change his antidepressant as he felt he was no longer getting any benefits from lofepramine. He requested to switch back to modified release venlafaxine, which he had tried previously. This was done following a recommended cross-titration schedule and the dose of venlafaxine increased to 150mg. daily.

Two months after this, Mr. A began demonstrating some additional psychotic symptoms. A clozapine serum level was requested to see if there was any change in his levels and to consider if an increase in dose of this medication. The results of this test showed serum clozapine levels of 0.90mg and norclozapine levels of 0.47mg/L, a significant increase and a level which could lead to toxicity. There were no other changes in our patient’s medications or physical condition which we could identify for the increase in serum level.

The data about interaction between clozapine and venlafaxine are inconsistent. While the British National Formulary (BNF) reports an increase in plasma concentrations of clozapine while taking venlafaxine (1), several other sources, including the summary of product characteristics from the manufacturer Novartis, report no interaction (2-5). A study by Repo-Tiihonen et al (6) also found no effect on plasma clozapine levels, when low doses of venlafaxine were added to high doses of clozapine.

However the Micromedex database lists a possible interaction, pointing out that venlafaxine is a weak inhibitor of the CYP450 2D6 isomer which is responsible for metabolising both itself and clozapine. It suggests that further competitive inhibition as a result of co-administration may lead to enhanced serum concentrations of both clozapine and venlafaxine.

The CYP450 2D6 isomer is responsible for the metabolism of a number of psychotropic medications. It is important to consider the impact of starting new medications may have on the levels of existing medications, particularly when there is a potential for toxicity.

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This letter was accepted for publication in December 3, 2011.

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3. AFHS Database. www.afhsdruginformation.com