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Important drug interaction involving phenytoin and quetiapine

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Abstract

Objective: To describe a patient case in which a drug interaction involving quetiapine and phenytoin resulted in an absence of clinical response and serum quetiapine levels below the point of detection.

Case Summary: This patient was on concurrent phenytoin, valproic acid, and quetiapine therapy for 10 months. Prior to discontinuing phenytoin, a serum quetiapine level was found to be less than 10 ng/mL. It took approximately 1 month after phenytoin's discontinuation for quetiapine levels to attain measurable concentrations. The patient's clinical response to quetiapine improved significantly after this interaction resolved.

Discussion: Phenytoin is an inducer of cytochrome P450 3A4, and quetiapine is a substrate of this enzyme. Patients on concurrent phenytoin and quetiapine therapy may require monitoring of quetiapine concentrations, which is often not routine practice, as this drug interaction can result in a clinically significant reduction in quetiapine levels contributing to a lack of efficacy.

Keywords: quetiapine, phenytoin, valproic acid, drug interaction

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Background

Many of the older anticonvulsants are known for their propensity to participate in drug interactions. These medications are commonly combined with psychotropics, as patients often have comorbid neurologic or mood disorders. Phenytoin and carbamazepine are strong cytochrome P450 (CYP450) enzyme inducers, including the 3A4 enzyme system (CYP3A4).[1] Divalproex is an enzyme inhibitor sometimes implicated in psychotropic drug-drug interactions.[1] Quetiapine is a substrate for the CYP3A4 enzyme.[2] The labeling of quetiapine states that coadministration of phenytoin may increase the mean oral clearance of quetiapine 5-fold and that divalproex may increase serum quetiapine levels by 17%.[2] We report a case where phenytoin, divalproex, and quetiapine were coadministered, resulting in quetiapine levels below the limits of assay detection. While there has been 1 previous report of undetectable quetiapine levels with carbamazepine coadministration, there have been no reports when phenytoin was coadministered. It is critical that clinicians understand the potential significance of this drug interaction to prevent worsening of psychiatric symptoms.[3] This case report was reviewed by the University of Maryland, Baltimore Institutional Review Board and deemed exempt.

Case Report

A 45-year-old male, who was an inpatient at a state psychiatric hospital for 6 years, carried the psychiatric diagnoses of autism spectrum disorder and psychosis, not

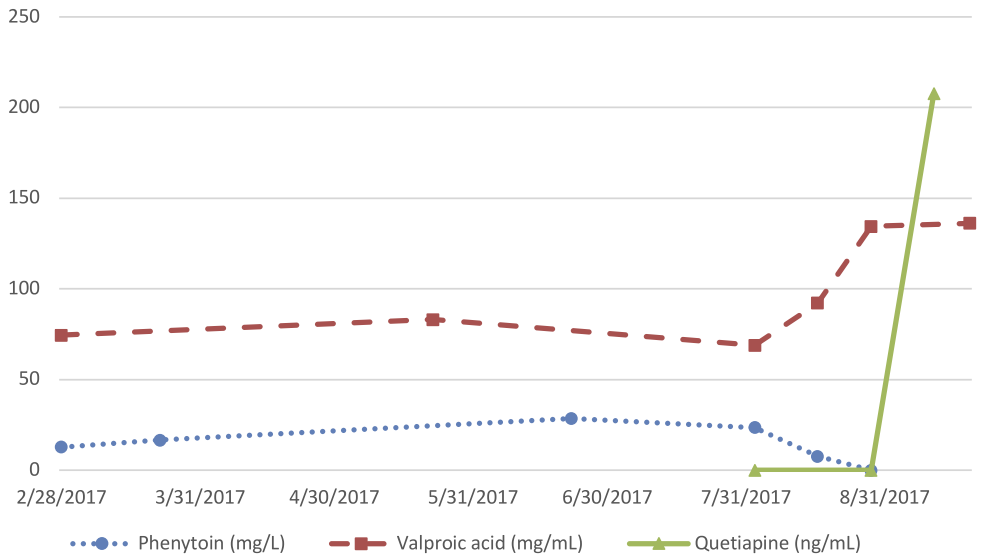

FIGURE: Medication levels over time

otherwise specified, as well as the somatic diagnoses of seizure disorder, hypertension, hyperlipidemia, gastroesophageal reflux disorder, allergic rhinitis, bilateral deafness, asthma, and obesity. His pharmacotherapy included haloperidol and quetiapine for psychosis, divalproex for mood liability and seizures, and phenytoin for seizures. Other medications included aspirin, cetirizine, montelukast, fluticasone nasal spray, azelastine nasal spray, hydrochlorothiazide, calcium/vitamin D, docusate, imipramine, paroxetine, clonazepam, pantoprazole, and multivitamin with minerals. The patient was adherent with his medication regimen based on nursing observation and the medication administration record.

This patient had been receiving haloperidol 20 mg daily for 1 year and quetiapine 800 mg daily at bedtime for approximately 10 months. The dose of phenytoin (200 mg twice daily) had been adjusted to achieve a target therapeutic level of 20 to 23 mg/L to maintain seizure control at the recommendation of a consultant neurologist. After several years of phenytoin therapy, the neurologist recommended discontinuing phenytoin due to the development of significant gingival hyperplasia. Psychiatrically, he was angry, demanding, unpredictable, and had difficulty maintaining appropriate behavior.

Prior to discontinuing phenytoin, serum levels of quetiapine and valproic acid were obtained. The quetiapine level was reported as <10 ng/mL, the lowest level of detection. Phenytoin was tapered to discontinuation over a 2-week period and oxcarbazepine was initiated in its place. Two weeks after the last dose of phenytoin, a repeat quetiapine level again resulted at <10 ng/mL. Quetiapine continued to be administrated at 800 mg/d. After approximately 2 more weeks (27 days post phenytoin discontinuation), the quetiapine level was 207 ng/mL. See the Figure.

The patient's behavior gradually improved, and he began participating in therapeutic activities on the nursing unit. Two weeks after the serum quetiapine level was found to be 207 ng/mL, the patient's behavior stabilized, and he was allowed to go to supervised activities off the nursing unit.

In addition, this patient's valproic acid level increased after phenytoin was discontinued. The patient had been maintained on divalproex 2 grams twice a day with levels between 68 to 83 mg/mL. Once phenytoin was discontinued the valproic acid level was measured at 136 mg/mL.

Discussion

Phenytoin is an antiepileptic medication indicated for the treatment of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures and for the prevention and treatment of seizures occurring during or following neurosurgery.[4] It has a half-life of approximately 24 hours and demonstrates non-linear pharmacokinetics. Phenytoin is metabolized via CYP2C19 (major), CYP2C9 (major), CYP3A4 (minor); is a strong inducer of CYP2C8, CYP2C9, and CYP3A4; and is a weak inducer of CYP1A2 and CYP2B6.

Quetiapine is a second-generation antipsychotic indicated for the treatment of schizophrenia, bipolar disorder type 1 with mania, and bipolar disorder with depressive episodes. Quetiapine is exclusively metabolized by the CYP3A4.[5] The major metabolic pathways are sulfoxidation and oxidation forming metabolites that are pharmacologically

inactive.[2] Quetiapine is unlikely to interfere with the metabolism of other drugs metabolized by CYP450 enzymes.

A literature search, limited to the English language and using the keywords phenytoin and quetiapine, resulted in one article involving a drug interaction between phenytoin and quetiapine. Wong et al[6] conducted an open-label, nonrandomized, multiple-dose study to assess the effect of phenytoin on quetiapine pharmacokinetics. This study involved 17 subjects who were titrated to quetiapine 250 mg 3 times daily. On day 13, phenytoin 100 mg 3 times daily was added. Quetiapine concentrations were measured on days 11 to 13 and 21 to 23. Clearance of quetiapine increased more than 5-fold after phenytoin coadministration. The authors concluded the mechanism for this drug interaction was the induction of CYP3A4 by phenytoin resulting in a significant reduction in quetiapine serum levels. It is important to note that in this study, phenytoin was only given for 10 days before the serum levels of quetiapine were measured. The full effect of phenytoin's induction can take several weeks.[7] It is possible that, if phenytoin was given for a longer period of time, there would have been an even greater impact on quetiapine clearance as noted in our case report.

The addition of quetiapine to phenytoin therapy may result in minimal or complete lack of response. Our patient was taking the maximum recommended dose of 800 mg/d and had undetectable serum quetiapine levels. Once an enzyme inducer is discontinued, metabolic activity is gradually reduced usually over 1 to 3 weeks.[6] Quetiapine levels were not detected until 27 days post phenytoin discontinuation. Valproic acid levels also increased dramatically after phenytoin was discontinued. It has been reported that phenytoin administration reduces the serum levels of valproic acid.[8]

In our patient, the impact of phenytoin on quetiapine clearance was substantial and prolonged. It resulted in serum quetiapine levels essentially below the level of detection during concurrent therapy, and quetiapine levels did not reach a therapeutic range until 27 days after phenytoin was discontinued. This had clinical significance on the patient's behavior. Several weeks after phenytoin was discontinued, our patient's behavior was stable and privileges were advanced. Quetiapine levels are not routinely followed in practice. Clinicians should be aware of the potential significance of combining quetiapine and phenytoin. In addition, it may take several weeks for quetiapine levels to increase after phenytoin is discontinued. Patients should be monitored for changes in psychiatric signs and symptoms as well as changes in routine quetiapine levels, whenever phenytoin is added, discontinued, or the dose is changed.

Conclusion

Patients are at risk for significantly reduced efficacy when quetiapine is administered concurrently with phenytoin. Also quetiapine toxicity can occur with phenytoin dose reduction or discontinuation. This case demonstrates the significance of this drug-drug interaction and highlights the additional type and duration of monitoring that should occur when patients are treated with this medication combination.

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