POSSIBLE CARBAMAZEPINE TOXICITY WITH TERBINAFINE

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ABSTRACT

Objective
To report a case of carbamazepine and terbinafine interaction resulting in an elevated level of carbamazepine and associated symptoms of toxicity.

Case summary
A 50-year-old Caucasian man developed an elevated carbamazapine level after starting terbinafine, which caused symptoms of toxicity with gait ataxia, dizziness and falls.

Discussion
This is a first report of a drug-drug interaction between carbamazapine and terbinafine. Although the mechanism for this interaction is not fully known, it is suspected that terbinafine decreased the metabolism of carbamazapine and led to increased levels that continued even days after the carbamazapine had been stopped. The Naranjo Scale suggests that this was a probable interaction (score 6).

Conclusions
While several drug-drug interactions have been reported with carbamazapine, there are no previous reports of its interaction with terbinafine. Prescribers should exercise caution when prescribing these medications together.

Keywords: *Terbinafine, carbamazepine drug-drug interaction*

Possible Carbamazepine Toxicity with Terbinafine

Pharmacokinetic interactions are the effects of one drug on another in the body. These interactions alter the way the body generally metabolizes a drug to eliminate it. Several factors, i.e., body weight, amount of drug taken, and adequateness of the body's metabolic and excretory systems affect the drug levels.[1] Pharmacokinetic drug-drug interactions can also lead to alterations in absorption, distribution, metabolism, and excretion.

These interactions can lead to potentially serious complications due to increased or decreased levels of one or both the drugs.[2] Carbamazepine is a commonly prescribed medication, often used for the treatment of epilepsy and bipolar disorder.[3] While several drug-drug interactions have been reported for carbamazepine, there are no reports in the literature of a possible interaction between carbamazepine and terbinafine (an antifungal medication). We report a case in which terbinafine probably led to high levels of carbamazepine.

Case Report

A 50-year-old male diagnosed with bipolar disorder (Diagnostic and Statistical Manual of Psychiatric Disorders, 4th edition criteria[4]), was maintained on carbamazepine 900 mg daily, bupropion 300 mg daily, and quetiapine 300 mg

every night. He was also diagnosed with hypertension, for which he was prescribed hydrochlorothiazide 25 mg per day; hyperlipidemia, for which he was not taking any medications; gastroesophageal reflux disease, for which he was taking omeprazole 20 mg per day; and erectile dysfunction, for which he was taking sildenafil 50 mg per day as needed. He followed up with his psychiatrist regularly and adhered to his medication regimen and denied any current alcohol and/or drug abuse. His carbamazepine level was stable - between 5 and 7ug/ml (Normal range: 4-10 ug/ml).

During a routine visit with his primary care provider, he was found to have yellow, brittle thickened toe and fingernails, which was diagnosed as onychomycosis. Two hundred fifty (250) mg daily of terbinafine was prescribed. Within two to three days, he felt dizzy, but did not report this to either of his physicians (PCP or the psychiatrist). He continued his medications as prescribed. Within two weeks, his terbinafine prescription ran out and his dizziness stopped as well. He did not seek any refills for this medication. About one month later, he received a refill of terbinafine by mail, and promptly restarted this medication as prescribed. Within three days, he noticed a recurrence of dizziness, which gradually became worse, causing him to fall on two occasions. He also noted gradually worsening blurred and double vision. This frightened him, causing him to go to the emergency room (ER).

The ER physicians noted nystagmus and numbness of the left face. A CT scan of the head showed no abnormality. His laboratory workup was normal except for elevated AST (55 IU/L), ALT (89 IU/L) and elevated carbamazepine at 17.2 ug/ml (Normal range: 4-10 ug/ml). He reported restarting the terbinafine as the only recent medication change. His symptoms were attributed to carbamazepine toxicity. He was discharged home with instructions to discontinue all medications and follow-up with the outpatient physician. He presented for his psychiatric appointment 10 days later. At this time, he was off all medications, but a repeat blood workup showed that the carbamazepine level was still approximately 2 ug/ml. The AST and ALT continued to increase. After a month of stopping medications, his AST and ALT returned to normal. The carbamazepine level became undetectable. At this point, because of worsening manic symptoms, carbamazepine was restarted and gradually increased initially to 600 mg per day. Then in one month, it was increased to 900 mg per day in divided doses. He did not feel any dizziness. Gradually the bupropion and quetiapine were restarted as well. He again did not feel dizzy. The carbamazepine level increased to between 4-6 ug/ml. He refused a rechallenge of the terbinafine again because of concerns of potential drug interaction.

DISCUSSION

Potentially serious, but rare side effects can occur with terbinafine (i.e., hepatic dysfunction, cytopenia, etc.) and carbamazepine (i.e., agranulocytosis, ataxia, hyponatremia, Steven Johnson Syndrome, etc.)[3,5] but incidence is rare. Further, while several drug-drug interactions have been reported with both these medications, an interaction between carbamazepine and terbinafine has not been reported. This case, with a temporal relationship between the onset of symptoms and increase in carbamazepine level, suggests a possible drug-drug interaction between these two medications.

Carbamazepine is an anticonvulsant that was first approved in 1974 for the treatment of seizures.[6] Since then, it has been used effectively for the control of bipolar disorder.[7] The absorption of oral carbamazepine is slow, erratic, and unpredictable. Peak plasma concentrations generally occur 4-8 hours after ingestion, but may require up to 26 hours. Carbamazepine is distributed rapidly into the body and has about 75-78% protein binding. Carbamazepine is metabolized in the liver by the cytochrome P450 system and undergoes almost complete biotransformation to several metabolites. Blood tests usually help in appropriate dosing. Blood levels of 4-10 are generally reported to be effective for mania, epilepsy, and paroxysmal pain syndromes. Most neurological side effects occur with serum concentrations over 9ug/ml.[8]

Terbinafine is an allylamine, which has a broad-spectrum antifungal activity. It interferes specifically with fungal sterol biosynthesis by inhibition of squalene epoxidase in the fungal cell membrane. Its inhibition leads to a deficiency in ergosterol and to an intracellular accumulation of

squalene, resulting in fungal cell death. When given orally, the drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity. Seventy percent of the dose is absorbed by gastrointestinal tract. Terbinafine binds strongly to plasma proteins (99%) and is strongly lipophilic. It is widely distributed in the body, including adipose tissue. Oral terbinafine is excreted mainly in urine (80%) and in feces (20%). Following absorption, the liver metabolizes terbinafine rapidly and extensively. However, after reaching a steady state, the half-life increases to about 36 hours.[9] The terminal half-life of terbinafine is up to 400 hours, which is the time when all the medication will be eliminated from the body (as opposed to half-life, when half the medication is eliminated from the body).[9] At least seven cytochrome P450 isoenzymes are involved in its metabolism with major contributions from CYP 2C9, CYP 1A2, CYP 3A4, CYP 2C8 and CYP 2C19. Terbinafine inhibits, but is not metabolized by CYP 2D6.[10] Carbamazepine, on the other hand, is metabolized by CYP 3A4, CYP 2C8, CYP 2C9, and CYP 1A2. Carbamazepine itself is a potent inducer of CYP 3A4, CYP 1A2 and CYP 2C19.[11]

Several possibilities may explain the pharmacological interactions above. Since terbinafine's protein binding (99%) is stronger than that of carbamazepine (75-78%), terbinafine might have displaced carbamazepine from the protein binding sites, increasing its serum level and causing toxicity. It is also possible that terbinafine may have displaced bupropion and/or quetiapine from their binding sites, increasing their levels and causing the described side effects. However, the presence of high carbamazepine serum level, with the onset of symptoms, and normalization of its serum level, with the resolution of symptoms, suggests a probable cause. Further, terbinafine and carbamazepine share the metabolic pathway at CYP450 3A4, 2C9, 1A2, 2C19, and 2C8 isoenzymes. It is possible that terbinafine displaced the carbamazepine at these isoenzyme sites, leading to its own metabolism. Further, carbamazepine's potent induction at CYP 3A4, 1A2 could also have caused the metabolism and excretion of terbinafine, while carbamazepine levels continued to increase. The half-life of carbamazapine, in most cases, is less than 24 hours. However, in the above case, carbamazepine levels were detectable after 10 days of stopping medications. This might be explained by the long terminal half-life of terbinafine. In this patient, with enzymatic induction of carbamazepine, terbinafine metabolism was probably accelerated, at the expense of carbamazepine metabolism. This extended the presence of the carbamazepine in the body, increasing the AST and ALT, even after the discontinuation of medications. A re-challenge of terbinafine with the carbamazepine might have provided a clearer picture of this interaction. However, due to the risks of serious complications, this was not done. Using the Naranjo Scale,[12] which was used to estimate the probability of adverse drug reactions, our patient's adverse event is ranked as probable (score of 6).

Poly-pharmacy carries an inherent risk that needs to be assessed before patients are prescribed multiple medications. Also, this case may represent a drug-drug interaction due to genetic polymorphism, which may not apply to the majority of the population. However, this report suggests that a probable relationship exists between carbamazepine and terbinafine. Until further research is available, care should be exercised whenever they are prescribed together.

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