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NORTRIPTYLINE TOXICITY INDUCED BY INTERACTION WITH TERBINAFINE

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Abstract

Tricyclic antidepressants are widely used and associated with neurological compromise at supratherapeutic doses. Cases of toxicity from tricyclic antidepressants induced by systemic antifungal agents have been infrequently documented in the literature, and postulated to occur as a consequence of inhibition of the CYP2D6 pathway. Caution is recommended with regard to concurrent prescriptions of these medications; however this interaction does not appear to be widely appreciated in clinical practice. We present a case report of Nortriptyline toxicity from the interaction of Terbinafine. Given the frequent usage of both classes of medications in primary and tertiary care, increased awareness of this interaction is essential in preventing morbidity, and in early recognition and management of toxicity when it occurs.

Keywords: anti-depressive agents, tricyclic antidepressants (TCAs), antifungal agents, drug–drug interactions, Terbinafine, Cytochrome-P450.

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Introduction

Tricyclic antidepressants (TCAs) are widely used worldwide for the treatment of major depressive disorder, anxiety, chronic neuropathic pain and insomnia. In recent years in the United Kingdom, TCAs have been the most commonly prescribed group of anti-depressant medications (1). Fungal infections are a significant global health problem and prescribing rates of systemic antifungals are increasing globally. Terbinafine is amongst the most commonly prescribed antifungal in middle and high income countries (2). Although TCAs are known to be susceptible to drug interactions, lack of recognition and monitoring for these interactions is possible, especially in the climate of increasing health care demands, patient comorbidities and reduced continuity of care with multiple patient prescribers in the community setting. We present a case report of probable toxicity from the interaction of Nortriptyline with Terbinafine, occurring in New Zealand.

Case Presentation

Mr F, a 69 year old man with chronic back and neuropathic leg pain attributed to a past accident and subsequent spinal surgery, had been treated long term with high dose Nortriptyline (150mg nocte). His other regular medications included Morphine Sulphate modified release (30mg mane, 90mg nocte) and Clonazepam (250mcg mane, 500mcg nocte). His medical history was also significant for previous recurrent venous thromboembolic events for which he was on Warfarin. One week prior to presentation he was prescribed a two week course of Terbinafine 250mg daily by his general practitioner for intertrigo.

Mr F presented to the Emergency Department with a 3 day history of involuntary limb twitching, speech difficulty and ataxia. He had had a fall and sustained a resultant rotator cuff injury as a consequence of his unsteady gait. His admission examination was largely unremarkable, except for mild gait instability. His blood tests revealed only a mildly elevated creatinine kinase (CK) level at 319U/L (60-220U/L). His prothrombin ratio was therapeutic 2.0 (2.0-3.0). His chest x-ray showed moderate faecal loading in the upper abdomen, and a computer tomography (CT) scan of his head revealed a chronic left cerebellar infarct (first noted 10 years earlier), but no acute pathology. He was admitted to the medical ward for further assessment and monitoring.

The next day, Mr F had persistent muscle twitching, a low grade fever and became drowsy, responding only to vigorous physical stimulation. He had evidence of respiratory depression with a respiratory rate of 4-5 breaths per minute, hypoxia (oxygen saturations of 83%

on air), and hypercapnia on arterial blood gas (pCo2 8.3kpa, reference range 5.3-6.7). He was noted to have small constricted pupils at 2mm and urinary retention. Repeat blood tests demonstrated a mild acute kidney injury (Creatinine of 114 umol/L, baseline 88umol/L), a further increase in CK to 1910 U/L and mildly deranged liver function (Bilirubin 9 U/L Reference range <25, GGT 61 U/L, Reference range 0-60, AST 91 U/L Reference range <45, ALT 47 U/L reference range <45 U/L.) His drowsiness improved, but did not completely reverse with 100mcg of Naloxone and intravenous fluids. A repeat CT of his head demonstrated no significant change. Mr F was assessed acutely by a neurologist with the impression of a non-toxic metabolic issue being most likely. His Terbinafine and Nortriptyline were stopped, and sedating medications withheld.

The following day Mr F's Glasgow coma score (GCS) was 15 and his muscle twitching had resolved. His Morphine and Clonazepam were recommenced. Over subsequent days Mr F was able to independently mobilise, his constipation and urinary retention resolved. His serum creatinine returned to baseline and Creatinine kinase came down to 617U/L. His Nortriptyline level returned at 280 ug/L (70-170). A serial level was taken after 48 hours, which returned 5 days later at 180ug/L. Given the patients' long term use of high dose Nortriptyline, ongoing chronic pain and in order to avoid potential cardiac arrhythmias or side effects from complete TCA withdrawal Mr F recommenced Nortriptyline at a reduced dose of 75mg daily. He was seen by a dermatologist for his skin rash and commenced on a topical antifungal formulation for his intertrigo.

5 weeks later Mr F re-presented with recurrence of lower limb muscle twitching, difficulty controlling limb movements, impaired mobility, and stuttering speech with difficulty word finding. He reported being symptom free until 2 days prior to this presentation. Again, he had a mild acute kidney injury (Creatinine of 115 umol/L) and a repeat CT of his head showed no acute intracranial abnormalities. His Nortriptyline was discontinued and his symptoms improved during the admission. He was reviewed again by the neurology service and started on Gabapentin 100mg three times per day. Of note his repeat Nortriptyline level was in the therapeutic range at 130ug/L.

Discussion

To our knowledge, this is the third case report of Nortriptyline toxicity related to concurrent Terbinafine use, although case reports exist for other agents in the TCA class. In 1998 Van der Kuy and Hooymans(3)reported a 74 year old man with fatigue, vertigo, loss of energy and elevated Nortriptyline levels after a combination of Nortriptyline for depression and Terbinafine for onychomycosis. His Nortriptyline levels normalised with Terbinafine cessation and reduction of Nortriptyline dose. On a re-challenge with Terbinafine 3 weeks later, the patients symptoms returned. In 2002 Van der Kuy et al. reported a case of a 48 year old woman treated with long term Nortriptyline for major depression, and then one month of Terbinafine for onychomycosis (4). The patient described tremor, constipation, impaired coordination and speech disturbance which improved with dose reduction of Nortriptyline. Her symptoms recurred on a subsequent rechallenge. Two case reports have described similar phenomenon with other TCAs: Imipramine (5) and Desipramine (6)when combined with Terbinafine. This is first case report of this kind from New Zealand.

Mr Fs case was initially challenging to diagnose given the non-specific nature of his symptoms and his multiple regular medications with potential for adverse effects. His history of previous stroke and Warfarin use resulted in an initial high index of suspicion for a cerebrovascular event. However, his presentation highlights key potential pharmacokinetic and pharmacodynamic mechanisms by which toxicity can occur.

Terbinafine is a CYP2D6 inhibitor, which can lead to increased TCA toxicity and increased recovery times. Inhibition of cholinergic receptors produces effects including blurred vision, dry mouth, urinary retention, constipation, and delirium (7). Delayed gastric emptying and decreased intestinal motility can lead to lower peak levels but more sustained plasma concentration, as well as prolonged plasma concentrations of other drugs taken concurrently (7). This may have contributed to Mr Fs respiratory depression, from concurrent opiate use. Because Tricyclic antidepressants also block other receptors including peripheral alpha adrenergic, histaminic, muscarinic and central serotonin receptors, cases of serotonin syndrome in association with TCA toxicity have been documented (8). Elevated CK levels and hyperpyrexia have been recorded in cases of both acute TCA overdose (8)and therapeutic dosing (9) (10).

Restarting TCAs in the setting of toxicity is problematic due to risk of symptom recurrence, however abrupt cessation can precipitate withdrawal (8). In the setting of co-ingestion with cytochrome p450 inhibitors, interactions can be prolonged. Although it has been stated that for a 250mg/day dose of Terbinafine the elimination half-life is 16 days (12), one in vivo study model predicted Nortriptyline-Terbinafine interactions to last up to 400 days (13). Although it has been postulated that individual responses may be variable owing to genetic variations in CYP2D6 activity, previous research has suggested that TCA- Terbinafine interactions may occur even in patients without deviations in CYP2D6 (4). Nortriptyline is a precursor for Amitriptyline which also has active metabolites, making this interaction more complex as these metabolites may also contribute to increasing toxicity for a patient, and the combined effect in overdose may delay the recovery beyond the expected duration, for the half-life of the parent drug (7).

Due to the potential for significant harm resulting from interactions, the concurrent administration of TCAs and Terbinafine is generally best avoided. However, in the event of inadvertent concomitant use of the these agents, previous pharmacological models have advised both discontinuation of the Terbinafine, and dose reduction of the Nortriptyline. Measurement of plasma concentrations are recommended, where applicable for both the parent drug and active metabolites (7). When available, serial plasma concentrations may guide safer reintroduction (7). In the case of Mr F even with declining plasma Nortriptyline levels, he experienced significant symptoms on rechallenge. Measurements of active metabolites (Amitriptyline levels) were not measured, but may have been of value. Because depression and fungal infections are common, and in some instances chronic treatment for both is required, some studies have suggested that a combination of selective serotonin reuptake inhibitors (SSRIs) and Azole class antifungals may be safer than TCAs (14). However other authors have advised cautious monitoring in patients treatment with Terbinafine and either TCA or SSRI therapy (15).

Conclusion

This case demonstrates the significant potential for harmful interactions with use of Terbinafine and Nortriptyline. The mechanisms for interaction are mediated by the Cytochrome p450 pathway, and complex in the setting of polypharmacy. Although TCAs are often third line agents for depressive disorders they remain widely used in the management of chronic pain. Given this, and the alternative for many superficial fungal conditions to be treated with topical agents, this case highlights a need for greater awareness of this interaction, and avoidance of concurrent prescribing of these medications.

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Conflict of interest

Nil

Inform Consent

Written Consent was obtained from the Patient.

Ethical Statement

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