CASE REPORT   **Open Access**

Possible inhibitory effects of terbinafine on aripiprazole metabolism: Two case reports

Ian R. McGrane, PharmD[1]
Tori J. Lindbloom, PharmD candidate[2]
Robert C. Munjal, MD[3]

Abstract

Aripiprazole, an atypical antipsychotic, is a metabolic substrate for cytochrome P450 (CYP)3A4 and 2D6. Terbinafine, an antifungal agent used for onychomycosis, is a CYP2D6 inhibitor and could theoretically reduce the metabolism of aripiprazole. However, there are no published reports describing this interaction. We present 2 female patients hospitalized in a psychiatric unit who were both taking aripiprazole 15 mg daily and terbinafine 250 mg daily prior to admission. The first patient was a 58-year-old female who was prescribed aripiprazole and terbinafine concomitantly for approximately 5 months prior to admission. A commercial pharmacogenetic testing platform classified this patient as a normal metabolizer for CYP3A4 and 2D6. The first patient's serum trough aripiprazole concentration at steady-state concentration (Css) was 207.5 ng/mL. The second patient was a 43-year-old female who was taking aripiprazole and terbinafine concomitantly for approximately 2 weeks prior to admission who had a Css aripiprazole concentration of 278.9 ng/mL. Aripiprazole has a wide therapeutic range (100 to 350 ng/mL) and a reference dose-related drug concentration of 11.7 (mean) $\pm$ 5.6 (SD) ng/mL/mg/d. Our patients had Css aripiprazole concentrations 18% and 59% higher than guideline-supported dose-related drug concentrations. Through the use of therapeutic drug monitoring, pharmacogenetic data, electronic pharmaceutical claims data, and the Drug Interaction Probability Scale, we suggest terbinafine possibly increases aripiprazole concentrations 18% to 59%. Further reports are needed to confirm these findings prior to using this information in clinical practice.

Keywords: antipsychotic, aripiprazole, cytochrome P-450, drug interaction, mood disorder, terbinafine

[1] (Corresponding author) Associate Professor, Skaggs School of Pharmacy, The University of Montana, Missoula, Montana, ian.mcgrane@umontana.edu, ORCID: https://orcid.org/0000-0002-9889-7260; [2] Student, Skaggs School of Pharmacy, The University of Montana, Missoula, Montana, ORCID: https://orcid.org/0000-0002-7331-9659; [3] Psychiatrist, Providence St Patrick Hospital, Department of Psychiatry, Missoula, Montana, ORCID: https://orcid.org/0000-0003-2709-6981

Background

Terbinafine is an antifungal agent used for onychomycosis and a cytochrome P450 (CYP)2D6 inhibitor, which can increase the dextromethorphan/dextrorphan ratio 97-fold after 14 days of administration.[1,2] Several reports show that the CYP2D6 inhibiting effects of terbinafine occur within the first 4 days to 3 weeks of administration,[2-4] and this degree of inhibition is considered "moderate"[5] due to a $\geq$2-fold but <5-fold increase in area under the concentration-time curve of the CYP2D6 substrate (ie, victim drug).[2-4] The duration of time during which the

victim drug is moderately inhibited is at least 3 weeks following discontinuation of terbinafine.[4] Aripiprazole is an atypical antipsychotic that is a metabolic substrate of CYP3A4 and 2D6.[6] Theoretically, terbinafine can inhibit aripiprazole metabolism although no published drug-drug interaction (DDI) reports exist between these medications. Both aripiprazole and terbinafine have long elimination half-lives of 75 hours and 200 to 400 hours, respectively.[1,6] As terbinafine causes moderate CYP2D6 inhibition within the first few weeks, treatment emergent adverse events (TEAEs) from aripiprazole may not present immediately given its time to reach steady-state concentration (Css).[6] We present 2 female patients hospitalized in a psychiatric unit due to mental health decompensation who were taking aripiprazole and terbinafine prior to admission. Through the use of therapeutic drug monitoring (TDM),[7,8] pharmacogenetic data, electronic pharmaceutical claims data (EPCD),[9] and the Drug Interaction Probability Scale (DIPS),[10] terbinafine possibly increases serum aripiprazole concentrations to a clinically relevant degree.

Case Reports

Patient 1 was a 58-year-old, 86 kg, white female with a BMI of 33.59 kg/m² and a past medical history of recurrent major depression, generalized anxiety disorder, restless leg movements, onychomycosis, and AUD. The patient presented to our facility with intensification of severe depression and intolerable anxiety. Laboratories relevant to this patient include serum creatinine 0.89 mg/dL, albumin 3.9 g/dL, ALT 29 U/L, and AST 14 U/L. Pharmacokinetic gene results from the GeneSight psychotropic panel, Assurex Health, were CYP1A2 *1/*1 (normal metabolizer [NM]), CYP2B6 *1/*1 (NM), CYP2C19 *17/*17 (ultrarapid metabolizer), CYP2C9 *1/*1 (NM), CYP3A4 *1/*1 (NM), CYP2D6 *1/*2A (NM), UGT1A4 *1/*1 (NM), and UGT2B15 *15/*15 (NM). Medications on admission were albuterol inhaler as needed, aripiprazole 15 mg daily, aspirin 81 mg daily, cholecalciferol 2000 units daily, ferrous sulfate 325 mg daily, fluticasone-umeclidinium-vilanterol 100-62.5-25 mcg/puff daily, lisinopril 10 mg nightly, lorazepam 1 mg every 8 hours as needed for anxiety or insomnia, metoprolol tartrate 25 mg twice daily, pantoprazole 40 mg before breakfast, and terbinafine 250 mg daily. No information upon hospital admission suggested the patient was nonadherent to medications. A possible DDI was suspected between the patient's home medications aripiprazole and terbinafine at time of admission due to suspected akathisia and the established pharmacokinetic properties of these medications.

Based on EPCD[9] and chart review, this patient had been prescribed aripiprazole and terbinafine concomitantly for approximately 5 months prior to admission. Terbinafine and aripiprazole were initiated and being titrated concurrently; therefore, there was no appreciable baseline for restlessness symptoms while taking aripiprazole alone. A serum trough aripiprazole concentration was obtained the second day of hospitalization and resulted after the patient discharged from the hospital at 207.5 ng/mL. Serum concentrations were quantified using liquid chromatography-tandem mass spectrometry at ARUP Laboratories. During this hospitalization, the patient elected to discontinue aripiprazole due to concern of restlessness and was discharged home after 3 days. Several medication changes occurred after hospital discharge, including (1) duloxetine replaced escitalopram and gabapentin was initiated after 1 week for mood and anxiety, (2) terbinafine was discontinuation after 3 weeks, and (3) aripiprazole was restarted at 5 mg daily after 2 months and increased slowly to 15 mg daily over a 3-month period. Restlessness and anxiety were still present but no longer of major concern 3 weeks following terbinafine discontinuation, but there are many factors related to this.

Patient 2 was a 43-year-old, 111.7 kg, white female with a BMI of 40.67 kg/m² with a past medical history of asthma, bipolar disorder, hidradenitis suppurativa, insomnia, onychomycosis, panic disorder, paresthesia, PTSD, and type 2 diabetes mellitus. The patient presented to our facility with worsening depression, anxiety, irritability, and difficulty sleeping. The patient's symptoms during decompensation included recurrence of previous self-harm and escalation of suicidal ideation; with stressors being chronic, a TEAE was suspected. Laboratories relevant to this patient include serum creatinine 0.76 mg/dL, albumin 3.3 g/dL, ALT 16 U/L, and AST 12 U/L. Medications on admission were adalimumab 40 mg every week, aripiprazole 15 mg daily, clonazepam 2 mg twice daily as needed for anxiety or panic, diclofenac 75 mg twice daily, doxepin 6 mg nightly, dulaglutide 0.75 mg every week, ergocalciferol 50 000 units twice a week, escitalopram 20 mg daily, fexofenadine 60 mg twice daily, fluticasone propionate/salmeterol inhaler (250-50 mcg/dose) twice daily, glipizide 10 mg daily, lisinopril 10 mg daily, omeprazole 20 mg daily, pramipexole 0.125 mg nightly, and terbinafine 250 mg daily. Available evidence indicated the patient was medication adherent, and a possible DDI was suspected between aripiprazole and terbinafine.

Based on EPCD[9] and chart review, this patient was taking aripiprazole for several months, and terbinafine was started approximately 2 weeks prior to admission. A serum trough aripiprazole concentration was ordered and obtained the second day of hospitalization. The aripiprazole serum trough at Css was 278.9 ng/mL. Serum concentrations were quantified using liquid chromatography-tandem mass spectrometry at LabCorp Laboratories. The patient discontinued terbinafine during hospitalization and continued aripiprazole. No long-term outcomes

TABLE: Probability of drug-drug interaction between aripiprazole and terbinafine using the Drug Interaction Probability Scale[10]

Scale Item	Patient 1	Patient 2
1. Are there previous credible reports of this interaction in humans? (Yes = 1, No = −1, Unknown or N/A = 0)	0	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug? (Yes = 1, No = −1, Unknown or N/A = 0)	+1	+1
3. Is the observed interaction consistent with the known interactive properties of the object drug? (Yes = 1, No = −1, Unknown or N/A = 0)	+1	+1
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)? (Yes = 1, No = −1, Unknown or N/A = 0)	+1	+1
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (Yes = 1, No = −2, Unknown or N/A = 0)	0	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug? (Yes = 2, No = −1, Unknown or N/A = 0)	0	0
7. Are there reasonable alternative causes for the event? (Yes = −1, No = 1, Unknown or N/A = 0)	−1	−1
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction? (Yes = 1, No = 0, Unknown or N/A = 0)	+1	+1
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)? (Yes = 1, No = 0, Unknown or N/A = 0)	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased? (Yes = 1, No = −1, Unknown or N/A = 0)	0	0

Total Score
  Highly Probable: >8
  Probable: 5-8
  Possible: 2-4
  Doubtful: <2
	+3	+3

N/A = not applicable.

of these changes are known due to the patient receiving care outside our health system.

Discussion

Terbinafine is a moderate CYP2D6 inhibitor that may increase aripiprazole concentrations; however, no published reports have assessed this potential DDI. TDM is a useful tool in psychiatric practice and consensus guidelines are available.[7,8] There are 19 scenarios in which antipsychotic TDM may be valuable to optimize pharmacotherapy, including (1) uncertain adherence to medication, (2) lack of clinical response at therapeutic doses, (3) TEAEs, (4) when antipsychotics are combined with medications that have inducing or inhibiting properties, and (5) in special populations.[8] Aripiprazole TDM is recommended (level 2) as opposed to strongly recommended (level 1) due to fewer data linking blood concentrations to clinical benefit or harm.[7,8] Aripiprazole has a wide therapeutic range (100 to 350 ng/mL) and a dose-related drug concentration (DRC) of 11.7 (mean) ± 5.6 (SD) ng/mL/mg/d.[7] The DRC values are based on adult patients with no pharmacokinetic-altering comorbidities, no genetic metabolism abnormalities, no comedications causing DDIs, and a body weight of 70 kg.[7] To obtain the dose-related reference concentration for a drug, the DRC is multiplied by the daily dose of medication that a patient takes.[7]

In our cases, because Css aripiprazole concentrations prior to the initiation of terbinafine were not available, we compared the patients' Css aripiprazole concentrations against guideline-based aripiprazole DRCs.[7] The first patient was a CYP2D6 and 3A4 NM with an aripiprazole concentration of 207.5 ng/mL while taking 15 mg aripiprazole daily. Patient 1's aripiprazole concentration was 18% higher than the guideline-based dose-related reference concentration (ie, 11.7 DRC × 15 mg aripiprazole daily = 175.5 ng/mL) but within 1 SD (ie, 11.7 DRC + 5.6 SD × 15 mg aripiprazole daily = 259.5 ng/mL).[8] Patient 2 did not have pharmacogenetic testing data available and had a Css aripiprazole concentration of 278.9 ng/mL while taking 15 mg aripiprazole daily. Patient 2's aripiprazole concentration was 59% higher than the guideline-based mean dose-related reference concentration and above 1 SD of the mean.[8]

Aripiprazole metabolism is not altered to a clinically significant degree based on age, sex, weight, race, hepatic or renal function, or smoking.[11] Patient 2 was not taking

other medications that impact aripiprazole metabolism, but patient 1 was taking the moderate CYP2D6 inhibitor metoprolol. Based on analysis of 11 patients, metoprolol may increase aripiprazole concentrations by 40% ($P < .05$).[12] Finally, aripiprazole is 99% albumin bound, but patient 1's albumin was normal, so this has little influence on free drug concentration.[11] Patient 2's albumin of 3.3 g/dL (reference range 3.5 to 5 g/dL) may have led to a higher free aripiprazole concentration, but free aripiprazole concentrations were not obtained, and no human studies are available that assess the impact of albumin on aripiprazole concentrations.

The probability of a DDI was assessed using the DIPS,[10] which is not a validated scale, but based on consensus is a recommended tool for assessing DDIs.[13] A DDI between aripiprazole and terbinafine was considered possible in both patients (Table).[10] The DIPS takes into account the limitations of our report, which include (1) the availability of a single aripiprazole concentration, (2) lack of previous reports documenting this DDI, (3) other reasonable causes for increased aripiprazole concentrations, (4) medication adherence not being confirmed objectively, and (5) the absence of pharmacogenetic testing for patient 2.

Conclusion

Our cases suggest the combination of terbinafine and aripiprazole possibly increases aripiprazole concentrations between 18% and 59% compared with mean reference aripiprazole DRCs.[7] We believe the results from patient 1 are of greater importance due to the availability of pharmacogenetic testing data, a metric that is not captured in the DIPS.[10] However, patient 1's aripiprazole TDM was contaminated with the coprescription of metoprolol, another CYP2D6 inhibitor.[12] Clinicians should be aware that terbinafine has increased a CYP2D6 substrates area-under-curve concentration by 115% after 4 days of coadministration despite terbinafine's long elimination half-life.[1,3] We recommend monitoring for TEAEs (eg, akathisia, restlessness, tremor, insomnia, somnolence, nausea)[6] when terbinafine is coprescribed with aripiprazole and considering an aripiprazole dose reduction of 20% to 60% upon initiation of treatment with either medication, especially when higher aripiprazole doses are used. Additional reports evaluating aripiprazole TDM before and after initiation of terbinafine are necessary to confirm this potential DDI as FDA-package labeling changes are not recommended based on results from single case reports.[13]

References

1. Lamisil [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2019.
2. Abdel-Rahman SM, Gotschall RR, Kauffman RE, Leeder JS, Kearns GL. Investigation of terbinafine as a CYP2D6 inhibitor in vivo. Clin Pharmacol Ther. 1999;65(5):465-72. DOI: 10.1016/S0009-9236(99)70065-2. PubMed PMID: 10340911.
3. Saarikoski T, Saari TI, Hagelberg NM, Backman JT, Neuvonen PJ, Scheinin M, et al. Effects of terbinafine and itraconazole on the pharmacokinetics of orally administered tramadol. Eur J Clin Pharmacol. 2015;71(3):321-7. DOI: 10.1007/s00228-014-1799-2. PubMed PMID: 25560051.
4. Madani S, Barilla D, Cramer J, Wang Y, Paul C. Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. J Clin Pharmacol. 2002;42(11):1211-8. DOI: 10.1177/009127002762491299. PubMed PMID: 12412819.
5. Stout SM, Nemerovski CW, Streetman DS, Berg M, Hoffman J, Burke K, et al. Interpretation of cytochrome P-450 inhibition and induction effects from clinical data: current standards and recommendations for implementation. Clin Pharmacol Ther. 2021;109(1):82-6. DOI: 10.1002/cpt.1918. PubMed PMID: 32452536.
6. Abilify [package insert]. Rockvillle (MD): Ostsuka America Pharmaceuticals, Inc; 2019.
7. Schoretsanitis G, Paulzen M, Unterecker S, Schwarz M, Conca A, Zernig G, et al. TDM in psychiatry and neurology: a comprehensive summary of the consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology, update 2017; a tool for clinicians. World J Biol Psychiatry. 2018;19(3):162-74. DOI: 10.1080/15622975.2018.1439595. PubMed PMID: 29493375.
8. Schoretsanitis G, Kane JM, Correll CU, Marder SR, Citrome L, Newcomer JW, et al. Blood levels to optimize antipsychotic treatment in clinical practice: a joint consensus statement of the American Society of Clinical Psychopharmacology and the Therapeutic Drug Monitoring Task Force of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie. J Clin Psychiatry. 2020;81(3):19cs13169. DOI: 10.4088/JCP.19cs13169. PubMed PMID: 32433836.
9. McGrane IR, Gale RK, Loveland JG. Use of Medicaid web portals for outpatient electronic pharmaceutical data. Psychiatr Serv. 2018;69(10):1117-8. DOI: 10.1176/appi.ps.201800258. PubMed PMID: 30277438.
10. Horn JR, Hansten PD, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41(4):674-80. DOI: 10.1345/aph.1H423. PubMed PMID: 17389673.
11. Jovanović M, Vučićević K, Miljković B. Understanding variability in the pharmacokinetics of atypical antipsychotics - focus on clozapine, olanzapine and aripiprazole population models. Drug Metab Rev. 2020;52(1):1-18. DOI: 10.1080/03602532.2020.1717517. PubMed PMID: 32008418:
12. Kirschbaum KM, Müller MJ, Malevani J, Mobascher A, Burchardt C, Piel M, et al. Serum levels of aripiprazole and dehydroaripiprazole, clinical response and side effects. World J Biol Psychiatry. 2008;9(3):212-8. DOI: 10.1080/15622970701361255. PubMed PMID: 17853280.
13. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. Drug Saf. 2015;38(2):197-206. DOI: 10.1007/s40264-014-0262-8. PubMed PMID: 25556085.