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Terbinafine and risperidone drug interaction contributing to clinical changes in a forensic psychiatric patient

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Abstract

Risperidone is a second generation "atypical" antipsychotic that exhibits its clinical effects through a combined effort of risperidone and its active metabolite, 9-hydroxyrisperidone (9-OHR), otherwise known as paliperidone. Risperidone is hepatically metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme into 9-OHR. Significant interference with the metabolism of risperidone may lead to clinical consequences for patients via alterations in the ratio of the parent compound and active metabolite. This patient case reports 1 example of how a drug interaction could contribute to delayed response to a medication increase after psychiatric decompensation. A forensic psychiatric patient was transitioned from oral risperidone to risperidone microspheres long-acting injectable and had worsening of symptoms, necessitating an increased dose of the injection. This increase in symptoms may have been prolonged by addition of a CYP2D6 inhibitor, terbinafine. The changes in clinical symptoms correlate with medication concentrations that were drawn before terbinafine was started, during terbinafine therapy, and after terbinafine was discontinued.

Keywords: terbinafine, drug interactions, risperidone, CYP2D6 inhibitor

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Background

Risperidone is a second generation antipsychotic with FDA indications for schizophrenia, irritability associated with autism, and bipolar I acute manic or mixed episodes. It primarily works as an antagonist at dopamine (D2) and serotonin (5HT2A) receptors. Risperidone is hepatically metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme into 9-hydroxyrisperidone (9-OHR) or paliperidone.[1] The clinical effect exhibited by risperidone is due to the combined activity of risperidone and 9-OHR; however, 9-OHR has clinical effects independent of risperidone.

One difference between the 2 compounds is the binding affinity for dopamine and serotonin receptors. Risperidone has greater affinity for 5HT2A and similar affinity for D2 receptors in comparison to 9-OHR.[2] It is hypothesized that the 5HT2A/D2 ratio should be lower than 1.0 for second generation antipsychotics to be effective. The ratios for both risperidone and 9-OHR are < 1.0, but risperidone's ratio is 5 to 10 times lower than 9-OHR, suggesting differing pharmacodynamic activity. Variation in P-glycoprotein binding, mitochondrial effects, and effects on serotonergic neuronal firing are other important contributors to their distinct clinical effects.[2]

When risperidone concentrations are reported by the lab company, 3 components are generally included: risperidone, 9-OHR, and a combined total. Risperidone:9-OHR ratios may provide information about CYP2D6 phenotype.[3] When normal metabolism occurs, the risperidone:9-OHR ratio is commonly 1:5 to 1:10.[4,5] If any genetic factor, medication, or herbal supplement interferes with this metabolic pathway, this ratio may be shifted. In the absence

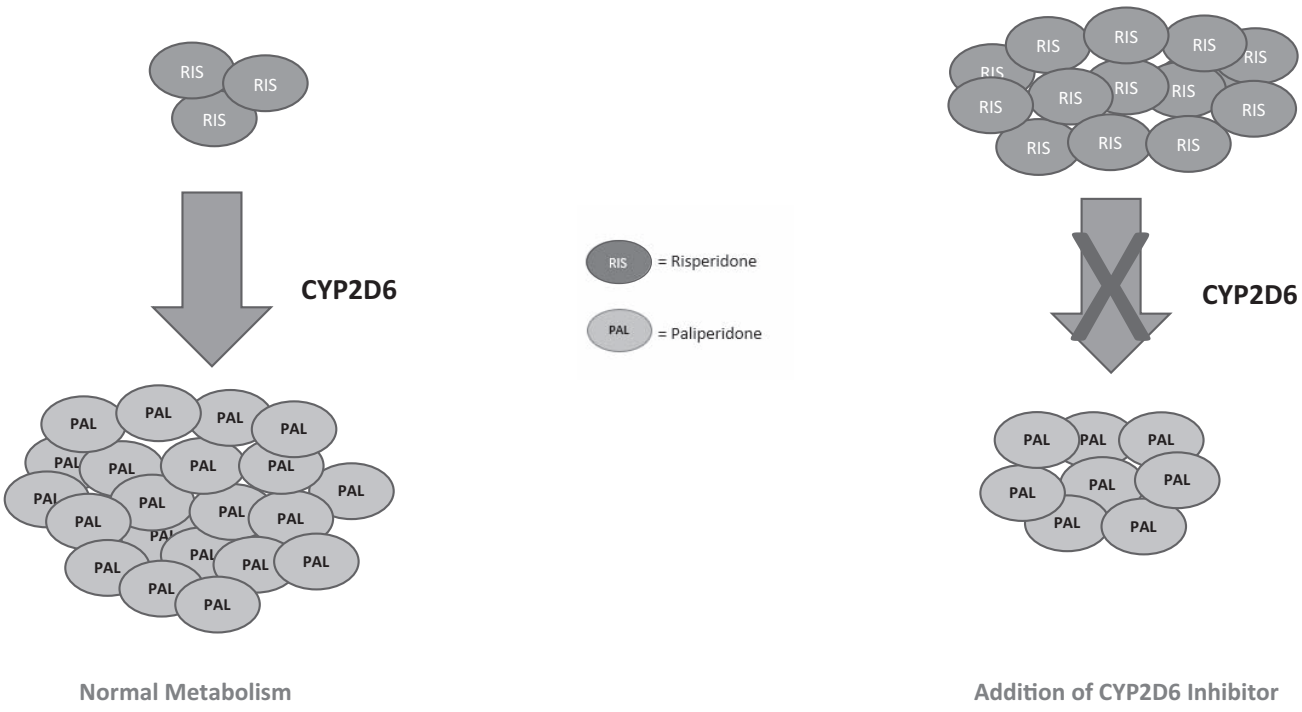

FIGURE: Metabolism of risperidone to paliperidone

of medication interactions, if drug concentrations result in a ratio of less than 1:10, we may infer that the individual is an ultrarapid metabolizer. Poor metabolizers or those taking CYP2D6 inhibitors may demonstrate a ratio greater than 1:1 (Figure).[3] Due to pharmacodynamic factors outlined previously, patients could have differing clinical responses to the 2 compounds and potential decompensation when the risperidone:9-OHR ratio is altered.[4]

Terbinafine is an allylamine antifungal used for the treatment of onychomycosis. It is a moderate inhibitor of CYP2D6 and may affect metabolism of CYP2D6 substrates to their metabolites.[6] Previous terbinafine interactions with CYP2D6 substrates amitriptyline, paroxetine, and perphenazine have been reported.[7-9] These interactions mainly led to increased side effects. The case below demonstrates 1 example of how a terbinafine drug interaction with risperidone could contribute to delayed response to medication changes after psychiatric decompensation.

In the forensic psychiatric population, medication interactions may lead to catastrophic consequences for both patients and staff. Forensic patients have a history of criminal charges, which makes stabilization on medications and symptom control crucial. It is of paramount importance to assess for drug interactions with psychiatric medications. If an interacting medication is needed, the patient should be closely monitored for emergence of psychiatric symptoms to prevent decompensation. A medication dose adjustment may be warranted to account for metabolic changes. Oral coverage may also be considered if the patient is prescribed a long-acting injectable antipsychotic.

Decompensation may lead to longer inpatient hospital stays and increased time away from friends and family. Inpatients begin to lose autonomy and start to rely heavily on the facility's structure and schedule.[10] The longer they spend in a restrictive environment, the more difficult self-organization becomes. This may result in the inability to complete activities of daily living or refrain from harmful or self-destructive behavior upon release. In addition to effects on the patient, increased length of stay at psychiatric facilities has economic implications.

Patient Case

The patient is a 49-year-old white male currently housed in a state forensic psychiatric facility. He has a history of bipolar I disorder with psychotic features, grandiose delusions, religious preoccupation, and assaultive behavior. He was charged with first-degree domestic assault, which led to a forensic commitment with a legal status of not guilty by reason of mental disease or defect. After treatment at a maximum security state forensic psychiatric facility for 3 years, he was transferred to our minimum security facility. At the time of transfer, he was stabilized on 2 mg oral risperidone. A risperidone drug concentration was collected during routine laboratory monitoring December of year 1 (risperidone $<$ 5 ng/mL; 9-OHR 23 ng/mL; ratio

TABLE: Risperidone and paliperidone (9-OHR) drug concentration and ratios

Date	Risperidone Dose and Formulation	Terbinafine Prescribed (Yes or No)	Risperidone Level, ng/mL	9-OHR Concentration, ng/mL	Ratio (risp:9-OHR)
December of year 1	2 mg oral	No	< 5[a]	23	1:4.6
October of year 2	2 mg oral	No	< 5[a]	21.3	1:4.3
July of year 3	25 mg IM every 2 weeks	No	3	14	1:4.7
August of year 3	37.5 mg IM every 2 weeks	Yes	19.8	16.5	1:0.8
October of year 3	37.5 mg IM every 2 weeks	No	6	10.7	1:1.8
May of year 4	37.5 mg IM every 2 weeks	No	2.4	12.7	1:5.3

IM = intermuscular.

[a]A laboratory company change occurred between October of year 2 and July of year 3. Laboratory 1 reported low values as < 5, whereas laboratory 2 reports the true value. For the two values of < 5, 5 was used for the risperidone component of the ratio calculation.

1:4.6). A concentration collected the next October showed similar results: risperidone < 5 ng/mL; 9-OHR 21.3 ng/mL; ratio 1:4.3 (Table).

The patient agreed to start risperidone microspheres 25 mg in May of year 3 to demonstrate willingness to continue medications upon discharge. Risperidone 2 mg oral was continued for 3 weeks after the first injection. The second and third risperidone microspheres 25-mg doses were given in June of year 3. He began showing signs of religious preoccupation and requested a baptism in early July of year 3. This may have been the first documented sign of decompensation as he did not voice prior interest in baptism. He received his fourth injection in mid-July of year 3. A few days later, off-baseline behaviors were noted, including carrying around Bibles, making religious posters, collecting information regarding donating money to televangelistries, and playing religious music loudly while singing along.

Risperidone microspheres reach steady state concentration after 4 injections. A non–steady state drug level was obtained 1 week after the fourth injection (risperidone 3 ng/mL; 9-OHR 14 ng/mL; ratio 1:4.7).[4] A day after this blood draw, he met with his health care provider, expressed discomfort from onychomycosis, and specifically requested an oral treatment option. The provider prescribed terbinafine 250 mg daily starting week 3 in July of year 3.

Staff noted additional changes in behavior over the next week. One day, he was found praying in his closet at 4:30 AM. When asked about this behavior, he said that he was okay and was meditating. His sleep had also decreased, averaging 2 hours per night. Due to these noted changes in behavior, risperidone microspheres were increased from 25 to 37.5 mg in late July. Another routine risperidone concentration was collected at the end of August (risperidone 19.8 ng/mL; 9-OHR 16.5 ng/mL). A clear change in metabolism was occurring as the ratio had shifted from ~1:5 to 1:0.8. At this point, a pharmacist reviewed the patient's medication profile and discovered a drug interaction between terbinafine and risperidone that likely accounted for the drug ratio alterations. A Naranjo scale score of 7 suggests that terbinafine was a probable cause for this change. These alterations may help explain the persistent off-baseline behavior despite administration of 3 injections of the increased dose of risperidone microspheres. No other drug interactions were present. Terbinafine was discontinued, and ciclopirox topical solution was started at this time. Upon further review, the pharmacist discovered that no CYP2D6 interaction was flagged by the computer system when the order was placed. A moderate CYP2D6 interaction flag would have alerted the prescriber and pharmacist. This problem has since been addressed.

After discontinuation of terbinafine, the patient's psychiatric symptoms waned. He noted irritability in week 2 of September. By late September, he was sleeping more hours per night and napping during the day. In week 3 of October, the pharmacist met with the patient. He endorsed feeling tired, but no other side effects or off-baseline behavior were noted. A follow-up drug concentration was obtained approximately 6 weeks after terbinafine was discontinued (risperidone 6 ng/mL; 9-OHR 10.7 ng/mL; ratio 1:1.8). Another follow-up concentration was collected in May of year 4 (risperidone 2.4 ng/mL; 9-OHR 12.7 ng/mL; ratio 1:5.3). The patient had no further episodes of decompensation after the risperidone microspheres dose was increased to 37.5 mg and terbinafine was discontinued.

Discussion

The above case outlines an episode of psychiatric decompensation that may have been prolonged by a drug interaction. Risperidone and 9-OHR have differing pharmacodynamic effects. This patient appeared to display better symptom control from 9-OHR than risperidone. Prior to addition of terbinafine, the drug concentration showed normal risperidone metabolism. After terbinafine was added, the 9-OHR level and risperidone:9-OHR ratio

were drastically altered due to CYP2D6 inhibition. These changes may have contributed to a lack of response to the increase in risperidone microspheres dose.

Forensic patients must show stability on their medication, active participation in treatment groups, and continued progress toward reintegration into society in order to be discharged from the facility. Any setbacks related to decreased response to medication may prolong the length of stay at the facility. In addition to an immeasurable quality of life component, there is a significant financial component associated with prolonged hospital stays. The average cost to house a single person within the facility is about $500 per day. An increased length of stay, even for a few months, leads to tens or hundreds of thousands of additional dollars spent for a single individual's care.

Conclusion

The patient described in this case exhibited almost 2 months of off-baseline behavior that may have been prolonged by the CYP2D6 inhibitor, terbinafine. This interaction likely increased his length of stay by at least these 2 months, if not longer. This case also outlines the vital importance of thorough medication review and pharmacist involvement in assessment for interactions, especially in a forensic psychiatric setting.

References

1. Risperidone [package insert]. Titusville, NJ: Janssen Pharmaceutical Companies; 2007.
2. Corena-McLeod M. Comparative pharmacology of risperidone and paliperidone. Drugs R D. 2015;15(2):163-74. DOI: 10.1007/s40268-015-0092-x. PubMed PMID: 25943458; PubMed Central PMCID: PMC4488186.
3. Deardorff OG, Jenne V, Leonard L. Making sense of CYP2D6 and CYP1A2 genotype vs phenotype. *Current Psychiatry*. 2018;17(7):41-5.
4. Álamo C, López-Muñoz F. The pharmacological role and clinical applications of antipsychotics' active metabolites: paliperidone versus risperidone. *J of Clin Exp Pharmacol*. 2017;3(1):3-12. DOI: http://dx.doi.org/10.4172/2161-1459.1000117
5. Risperdal Consta® [package insert]. Titusville, NJ: Janssen, L.P.
6. Lamisil [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
7. Castberg I, Helle J, Aamo TO. Prolonged pharmacokinetic drug interaction between terbinafine and amitriptyline. Ther Drug Monit. 2005;27(5):680-2. DOI: 10.1097/01.ftd.0000175910.68539.33. PubMed PMID: 16175144.
8. Yasui-Furukori N, Saito M, Inoue Y, Niioka T, Sato Y, Tsuchimine S, et al. Terbinafine increases the plasma concentration of paroxetine after a single oral administration of paroxetine in healthy subjects. Eur J Clin Pharmacol. 2007;63(1):51-6. DOI: 10.1007/s00228-006-0217-9. PubMed PMID: 17124578.
9. Park Y-M. Prolonged drug-drug interaction between terbinafine and perphenazine. Psychiatry Investig. 2012;9(4):422-4. DOI: 10.4306/pi.2012.9.4.422. PubMed PMID: 23251210.
10. Haney A. The psychological impact of incarceration: implications for post-prison adjustment. US Department of Health and Human Services. 2001 Nov [cited 2022 Sept 1] Available from: https://aspe.hhs.gov/reports/psychological-impact-incarceration-implications-post-prison-adjustment-0