DogoRangsang Research Journal
ISSN: 2347-7180

UGC Care Group I Journal
Vol-09 Issue-01 Jan 2019

An unusual occurrence of extra pyramidal side effects perhaps caused by a combination between paliperidone and voriconazole

U.Sri Venkatesh[1], K.V.Rajesh[2], M.D. Kishore[3]

Asst.Professor[1,3], Associate. Professor[2]
Venkateshbalaji230@gmail.com
Sri Sivani College of Pharmacy,

Abstract

Setting the Scene: It is believed that paliperidone, an active metabolite of risperidone, has negligible pharmacokinetic drug-drug interactions (DDI) potential because of its low metabolism by CYP3A4 and CYP2D6. A potential interaction between paliperidone and voriconazole has been observed, however, based on interactions between risperidone and strong CYP3A4 inhibitor azoles, there have been reports of DDIs regarding other drugs.

Purpose: To detail the first known case of a drug-drug interaction (DDI) resulting in extrapyramidal side effects (EPSEs) involving paliperidone and voriconazole.Medical information:Confidence that clozapine was the cause of febrile neutropenia led a 34-year-old man to seek medical attention. Due to a suspected fungal infection, the patient's empiric piperacillin/tazobactam medication was adjusted to include voriconazole and paliperidone instead of clozapine. It is believed that the patient had antipsychotic-induced tremors and stiffness in all of her limbs two days after beginning voriconazole. Withholding paliperidone caused the EPSEs to resolve.

Results: The patient was able to take greater dosages of paliperidone for an extended period of time before switching to clozapine. A possible paliperidone adverse drug response (ADR) owing to significant CYP3A4 inhibition by voriconazole was indicated by the development of EPSEs two days after azole commencement. Additional research, including therapeutic medication monitoring, is necessary to validate these results, but this example seems to be the first recorded instance of this earlier theoretical DDI in reality.

It is important to keep an eye on patients for adverse drug reactions (ADRs) when paliperidone is given with CYP3A4 inhibitors because of the potential for pharmacokinetic drug-drug interactions.

Keywords: paliperidone,voriconazole,azole,druginteraction,CYP3A4.

INTRODUCTION

An active metabolite of risperidone, paliperidone is an atypical antipsychotic.Paliperidone has a higher incidence of extrapyramidal side effects (EPSEs) compared to other atypical antipsychotics.2Paliperidone is mostly eliminated from the body via the kidneys (59% unaltered in urine), and only 6.5% of the dosage is accounted for by cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2D6 (CYP2D6) metabolism.Paliperidone is a substrate for the P-glycoprotein (P-gp).1

Paliperidone DDIs have been reported seldom (Table 1). Some of the mechanisms include alterations in gastric transit and altered CYP3A4, CYP2D6, or renal P-gp function.Some DDIs have caused significant shifts in paliperidone concentrations 3-5,7 and severe psychosis (9, 10).10According to Stockley's Drug Interactions, paliperidone has the potential to interact with voriconazole, a powerful CYP3A4 inhibitor, in a way that might increase the corrected QT interval (QTc). This is based on the DDIs between risperidone and azoles.It seems that no instances of this hypothetical interaction have been documented so far.

CASEREPORT

The Royal Melbourne Hospital Human Research Ethics Committee (10 July 2023, Coordinator, Office for Research) exempted this study from local policy regulations that pertain to research. The patient's consent to be published was acquired and recorded in a way that was free, prior, and informed.

It was thought that clozapine was the cause of febrile neutropenia when a 34-year-old male patient arrived to a quaternary referral metropolitan teaching hospital in Melbourne, Australia.Previous stabilization of the patient was achieved on

Table1Paliperidoneandrisperidone pharmacokinetic drug–druginteractions(DDIs)

Interactingdrug	Studytype	Samplesize;duration(weeks)	ProposedDDImechanism	Outcome
PaliperidoneERParoxetine[6]	Randomised crossover	50;1.86	PotentCYP26Dinhibitor	17%increaseinpaliperidoneAUCNot clinically significant
Carbamazepine[3]	Caseseries	6;2–4	PotentCYP3A4and renalP-gpinduction	44–66% dose-dependent reduction inpaliperidone concentration(subtherapeutic for most)
Carbamazepine[4]	Casereport	1;ND	RenalP-gpinduction	35–48% dose-dependent reduction inpaliperidone concentration Noworseningofpsychosis
Carbamazepine[5]	Open-label,two-treatment, sequential	55;3	RenalP-gpinduction	37%reductioninpaliperidoneAUCandC_{max}, mainly due to 35% increase inrenal clearance
ValproatesemisodiumER[9]	Open-label,two-treatment, single sequence	23;2.71	Prolongedgastric residencedue to expansionofvalproate ERtablets	51%increaseinpaliperidoneAUCand C_{max} but half-life unchangedNot clinically significant
TS-1(containinga5-fluorouracilderivative)[10]	Casereport	1;4	TS-1induceddiarrhoea that reducedgastric transittime	Consistently lower paliperidoneconcentration Developedseverepsychotic symptoms
RisperidoneItraconazole[7]	Caseseries	19;1	StrongCYP3A4 inhibition	Risperidone and paliperidone(metabolite)concentrationincreasedby82% and 70%, respectively
Ketoconazole[8]	Open-label, randomised, two-phasecrossover	10;0.43	StrongCYP3A4 inhibition	IncreasedrisperidoneAUCby67%butreduced that of paliperidone(metabolite) by 48%; attributed topossible increased renal excretion ofpaliperidone

AUC = area under the curve; C_{max}= maximum concentration; CYP26D = cytochrome P450 2D6; CYP3A4 = cytochrome P450 3A4;DDI=drug–druginteraction;ER=extendedrelease;ND=notdisclosed;P-gp=P-glycoprotein;TS-1=tegafur/gimeracil/oteracil.

treating refractory schizophrenia with paliperidone intramuscular injections; nevertheless, two years ago, I switched to clozapine since I hate needles. In the past, patients were able to take 12 mg of oral paliperidone every day without experiencing any side effects. There was no record of the patient having any bad drug responses in the past, and they were not taking any other medications. His renal function was within normal range, but his liver function tests (LFTs) were abnormal, most likely because to clozapine. His aspartate transaminase, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transferase levels were 463, 555, 402, and 441 units/L, respectively. On admission, the patient's clozapine trough level was 1292 micrograms/L, which is high compared to the standard aim of 350-500 micrograms/L and the previous dosage increase six months ago. This might be because the patient stopped smoking a few weeks ago.2We began paliperidone extended release at 3 mg daily and gradually increased the dosage to 9 mg over the course of 10 days, while withholding clozapine. At first, piperacillin/tazobactam was used to treat the patient's febrile neutropenia. Adding voriconazole was necessary because of the patient's persistent fever and a chest CT scan that showed signs of a fungal infection. The patient was given 6 mg/kg orally every 12 hours for two doses, and then 4 mg/kg orally every 12 hours from then on. It all began the day after the dosage of paliperidone was raised from 6 to 9 milligrams per day (see Figure 1 for the timeframe). Two weeks after receiving granulocyte colony stimulating factor, white blood cell recovery was seen.

The patient had a heightened awareness of all limb reflexes and hypertonia two days after starting voriconazole. This raised concerns for neuroleptic malignant syndrome (NMS) when coupled with a temperature of 39°C and an increased creatinekinase level of 755 units/L. Neither myoclonus nor serotonergic medications had been administered to him.

Concerned that voriconazole may raise paliperidone concentrations, the clinical pharmacist stepped in.

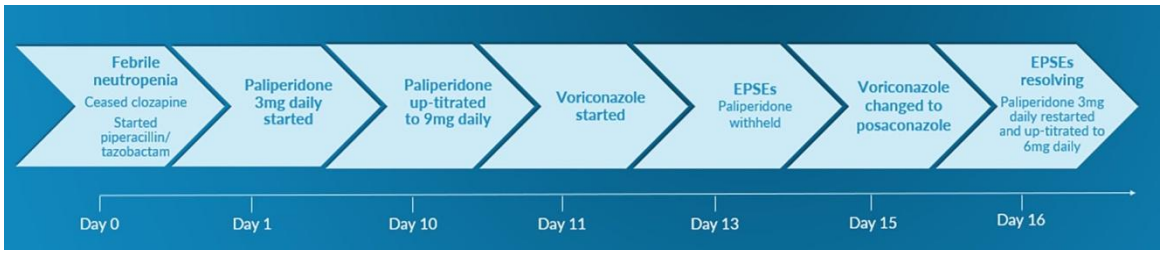

Figure1Thepatient'sjourney.EPSEs=extrapyramidalsideeffects.

via strong CYP3A4 inhibition and additively prolongthe QTc, potentially increasing the risk of the arrythmia, torsade de pointes.[1,11]The patient's QTc, however, remainednormalthroughoutadmission(maximumQT c was 430 ms). Paliperidone was withheld and agitation and EPSEs were managed with diazepam and benzatro- pine. The patient's day two voriconazole level was ele- vated(9.6 mg/L;normaltarget1–5 mg/L)althoughnot a true trough, being 7.5 h post dose rather than the recommended 12 h post dose.[13]The true level was therefore likely lower. Voriconazole was replaced with posaconazole based on antifungal coverage and pipera- cillin/tazobactam was ceased.

After being withheld for three days, paliperidone was restarted at 3 mg daily and up-titrated to 6 mg after a further three days given the significant risk of relapse from psychosis. At this point, the patient's EPSEs had resolved and did not reappear when paliperidone was restarted. Creatine kinase was down-trending and LFTs resolved spontaneously. He was discharged, psychiatri- cally stable, on paliperidone 6 mg daily. Posaconazole 300 mg oral daily was continued for a presumed fungal respiratory infection that was culture negative. The patient most likely had antipsychotic induced EPSEs.

DISCUSSION

A Naranjo score of 6 indicates that paliperidone is likely to cause an adverse drug response (ADR) in this situation.14Previous convincing reports of EPSEs with paliperidone,1temporality with dosing, and relief of symptoms on dis-continuation provide evidence for causation. We could not find any other possible reason. The patient had an undetectable level when the action happened, and clozapine is unlikely to trigger electroconvulsive seizures.Symptoms of 2NMS include hyporeflexia, hypertension, and a high creatine kinase level (more than 1000 units/L).15

Although paliperidone does not have significant DDIs because of its restricted metabolism,1 research has shown that CYP450-mediated DDIs may significantly change the concentration of paliperidone (Table 1). In most instances, carbamazepine considerably lowered paliperidone (around 40%) owing to CYP3A4 and/or renal P-gp upregulation.3-5Some investigations suggested that the latter mechanism was more plausible because of the small impact on metabolism.The therapeutic significance of the increased paliperidone exposure caused by 4,5-Paroxetine's CYP2D6 inhibition was not determined.6Itraconazole inhibited CYP3A4, which led to an 82% rise in risperidone levels and a 70% increase in paliperidone levels (its active metabolite).While ketoconazole, another CYP3A4 inhibitor, raised risperidone (67% rise) and decreased paliperidone (48% decrease) in a single-dose trial, the latter may have been attributable to paliperidone's greater renal excretion.These results provide credence to the idea that the adverse drug reaction (ADR) in this instance was probably caused by voriconazole's significant suppression of CYP3A4, as it happened two days after the azole was started. Because it seems to be the first study to describe this theoretical DDI in reality, this article is important.

Notably, the patient's EPSEs happened three days after the paliperidone dosage increase, which may provide an other reason for the adverse drug reaction. Increasing the dosage of paliperidone increases the likelihood of EPSEs.2Since the patient had no problems with greater dosages in the past, this is not likely to account for the adverse drug reaction. Switching from voriconazole to posaconazole had no negative impact on the adverse drug reaction. Posaconazole may inhibit P-gp in addition to CYP3A4, which is very comparable.11Perhaps the reduced paliperidone dosage when posaconazole was given is to blame for the lack of a comparable DDI; nevertheless, the exact explanation remains a mystery.

That this interaction's theoretical underpinnings rest on low-quality, small-scale investigations is a major drawback of this case study. The possible impact of voriconazole on paliperidone concentrations cannot be measured since therapeutic drug monitoring (TDM) was

not conducted for this patient.

Voriconazole is thought to have enhanced this patient's exposure to paliperidone by its high CYP3A4 inhibitory effects, which might have resulted in the development of

REFERENCES

1 1 Chue PS, MacKenzie EM, Chue JA, Baker GB • Research Group. Paliperidone prolonged release: a pharmacological and formulational study. Review of Neuroscience 2012, 12: 1399–1410.
2 2With contributions from Barnes TRE, Young AH, and Taylor DM. A guide to psychiatric medication administration, the 14th edition of the Maudsley work. Pages 41–193. New York: Wiley–Blackwell; 2021.
3 3With contributions by Yasui-Furukori, Kubo, Ishioka, Tsuchimine, and Inoue.Paliperidone and carbamazepine have an interaction. Medicinal Drug Monitor, 2013; 35: 649-652.
4 Uno T., Yasui-Furukori N., Miura M., Akamine Y., Uehara H.The combination of carbamazepine, paliperidone, and amlodipine has many inductive effects. The citation for this article is J Clin Pharm Ther 2015; 40:480-82.
5 Kerbusch-Herben V, Remmerie B, Vandebosch A, Berwaerts J, Cleton A. Paliperidone extended-release tablet pharmacokinetics at steady-state in relation to carbamazepine. published in 2014 by ClinPharmacol Drug Dev, volume 3, pages 371–377.
6 The authors of the study include Berwaerts, Cleton, Herben, vandeVliet, Chang, vanHoek, and others. Palaperidone extended-release tablet pharmacokinetic effects of paroxetine. Psychopharmacology 2009; 42: Plasma concentrations of risperidone and 9-hydroxyrisperidone in schizophrenia patients are influenced by the cytochrome P450 3A inhibitor itraconazole, according to Jung SM, Kim K, Cho H, Jung IG, Park P, Byun W, et al. Published in Clin Pharmacol Ther 2005, volume 75, pages 521–528, with an abstract.
7 8 et al., Mahattanatrakul, Sriwiriyajan, Ridtitid, Boonleang, Woongnawa, Rujimamahasan, vol. 8. The impact of the cytochrome P4503A4 inhibitor ketoconazole on the pharmacokinetics of risperidone in healthy volunteers will be examined. The article is published in the Journal of Clinical Pharmacy and Therapeutics in 2012 and page 221-25.
8 Remmerrie, Ariyawansa, De Meulder, Coplola, and Berwaerts
9 Paliperidone with divalproex sodium extended-release tablet safety investigations in healthy volunteers and mental illness patients. Publication date: 2016; Journal of Clinical Pharmacology, volume 56, pages 683–692.
10 the authors of the article are Yasui-Furukori, Hashimoto, Kubo, and Tomita. Possible interaction between the oral anticancer medication TS-1 (R), which contains a 5-fluorouracil derivative, and the chizophrenic patient's paliperidone extended release. "Neurophysiology and Clinical Neurosciences" 2013; 9: 317–320.
11 Klatt ME, Eschenauer GA. A look at the pharmacologic aspects of azole antifungals for lung transplant patients. Volume 7, Issue 1, Pages 1-16, Journal of Fungi, 2021.
12 Editors: Baxter K and Preston CL. The medication interactions of Stockley. Cosmetic Press, London, 2017. The reference may be found at <https://www.medicinescomplete.com/#/>. Retrieved on May 9, 2023.
13 Recommendations for Treatment. Following the levels of antimicrobials in the blood. Therapeutic Guidelines Ltd., 2019 (Melbourne 2019).This information may be found at <https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Antibiotic&topicfile=monitoring-antimicrobial-blood-concentrations> for your reference. Retrieved on May 9, 2023.
14 Roberts EA, Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, and others. Approach of predicting the likelihood of harmful medication responses. The clinical pharmacology and therapeutics journal published an article in 1981(30): 239–245.
15 Leonardo-Pelonero, Levenson, and Pandurangi (15). A review of neuroleptic malignant syndrome... Public Health Psychiatry, 1998, 49, 1163–1172.