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REVIEW

The Effect of Drug–Drug Interactions on the Pharmacokinetics of Isavuconazole: A Comprehensive Review

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Purpose: Isavuconazole is an azole antifungal drug, which is used for invasive aspergillosis and mucormycosis. The objective of this study was to comprehensive review the impact of drug–drug interactions (DDIs) on isavuconazole pharmacokinetics by categorizing concomitant medications as enzyme inducers (eg, rifampicin), inhibitors (eg, ritonavir), or neutral agents. Additionally, we aimed to evaluate whether the duration of combination therapy modulates the magnitude of DDIs and provide references for clinical medication.

Methods: The literature concerning the interactions of isavuconazole was systematically retrieved from three retrieval platforms, PUBMED, EMBASE, and the Cochrane Library, using the search terms: "isavuconazole" or "isavuconazonium" or "Cresemba" and "interact*", or "cotreatment", or "coadministration", or "combination", or "concomitant". A total of 1051 articles were retrieved and then conduct screening according to the inclusion and exclusion criteria.

Results: Eleven studies involving 23 drugs were included in this study. Rifampicin, flucloxacillin, and phenobarbital decreased the exposure of isavuconazole. Ketoconazole and ritonavir significantly increased the exposure of isavuconazole. Esomeprazole, had no significant effects on the exposure of isavuconazole. Although midazolam, estradiol/norethisterone, atorvastatin, digoxin, metformin, methotrexate, bupropion, repaglinide, dextromethorphan, caffeine, methadone, warfarin, cyclosporine, tacrolimus, sirolimus, prednisone, and mycophenolate mofetil had also no significant effect on isavuconazole pharmacokinetics, a single-dose administration cannot induce or inhibit metabolic enzymes stably, and we consider the results to be unreliable. Therefore, these drugs still need to be used with caution.

Conclusion: This review demonstrates that drug interactions of isavuconazole are predominantly mediated by the CYP3A4/P-glycoprotein pathway: strong inducers (eg, rifampicin) reduce its exposure, while strong inhibitors (eg, ketoconazole) increase exposure. Single-dose interaction studies are unreliable due to insufficient time for enzyme regulation, highlighting the need to consider the duration of combination therapy. Clinical recommendations: avoid coadministration with strong inducers/inhibitors and implement therapeutic drug monitoring (TDM) for patients on long-term combination therapy to optimize dosing regimens.

Keywords: isavuconazole, drug–drug interaction, single-dose, pharmacokinetic

Introduction

Invasive aspergillosis (IA) incidence has risen in immunocompromised populations (eg, hematological malignancies, transplant recipients, HIV-infected),[1–3] with triazoles as first-line therapy per guidelines.[4] Isavuconazole, a second-generation triazole, demonstrates non-inferior efficacy to voriconazole (42-day mortality: 19% vs 20%) and better tolerability (42% vs 60% adverse events),[5,6] positioning it as a preferred agent.

The optimal pharmacokinetic/pharmacodynamic index of azole antifungal drugs is the AUC/MIC.[7] Owing to their highly variable pharmacokinetics, therapeutic drug monitoring (TDM) of azole drugs is recommended. The trough concentration of isavuconazole is strongly correlated with the AUC. Although there is currently no recommendation from

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guidelines or consensus, some studies have reported that its appropriate trough concentration range is 2–5 mg/L.[8,9] A trough concentration that is too low may lead to poor anti-infection effects, whereas a concentration that is too high is associated with the occurrence of adverse reactions.[10]

Isavuconazonium sulfate is the prodrug of isavuconazole. A 372 mg intravenous dose of isavuconazonium sulfate is bioequivalent to 200 mg oral isavuconazole, and dosing regimen is thrice daily for 2 days as loading doses prior to beginning daily therapy. The design of prodrug reduces the first pass effect of oral preparation. The oral absolute bioavailability of isavuconazole amounts to 98% and the same dosing can be used for both intravenous and oral route.[11] It is predominantly metabolized before excretion, as only 34% of the administered dose was recovered as unchanged isavuconazole in faeces (33%) and urine (<1%).[12] In vitro and in vivo studies have indicated that CYP3A4/5 and subsequently uridine diphosphate glucuronosyltransferase (UGT) are involved in the metabolism of isavuconazole.

One study reported that isavuconazole has fewer interactions, which is an advantage in its clinical use.[13] This may be related to the fact that its inhibitory effect on CYP3A4 is weaker than that of fluconazole, itraconazole, etc.[14,15] However, its metabolism via CYP3A4/5 and UGT pathways raises concerns about drug–drug interactions (DDIs), which remain undercharacterized.

This review systematically evaluates DDIs affecting isavuconazole's pharmacokinetics, differentiating single- vs multi-dose effects to inform clinical dosing and TDM.

Methods

Search Strategy

We conducted a systematic search of PubMed, Embase, and the Cochrane Library for articles published up to August 8th, 2024, to identify all studies describing the interaction effects on isavuconazole pharmacokinetics, using the search terms: "isavuconazole" or "isavuconazonium" or "Cresemba" and "interact*", or "cotreatment", or "coadministration", or "combination", or "concomitant". Two investigators (Yanlei Sang and Qiang Xu) independently screened the articles for inclusion, and disagreements were resolved by a third investigator (Anna Gao). The full search strategy is available in Supplementary Table 1.

Inclusion Criteria

The inclusion criteria were as follows: all the published papers; the interaction of isavuconazole was studied; and all the age groups.

Exclusion Criteria

The exclusion criteria were as follows: vitro study; animal study; conference abstract; review; effectiveness study; protocol; no pharmacokinetic outcome of isavuconazole reported; and pharmacokinetic changes not caused by a certain drug.

Data Collection

Two investigators (Yanlei Sang and Qiang Xu) independently extracted data from the included studies. The pharmacokinetic outcomes included the AUC, Cmax, Cmin, CL, CL/F and Tmax. Other data included the publication year, study design, concomitant medication, coadministration time, and route of administration.

Results

A total of 1051 articles were retrieved, and after screening by three investigators on the basis of the inclusion and exclusion criteria, 11 articles and 23 drugs were included in the study. Seven of them are Phase I studies, and 4 are Phase IV studies, as shown in Figure 1.

The Combination of Drugs Reduces the Exposure of Isavuconazole

According to current reports, a total of three drugs, rifampicin,[16] phenobarbital,[17] and flucloxacillin,[18,19] can reduce the exposure of isavuconazole.

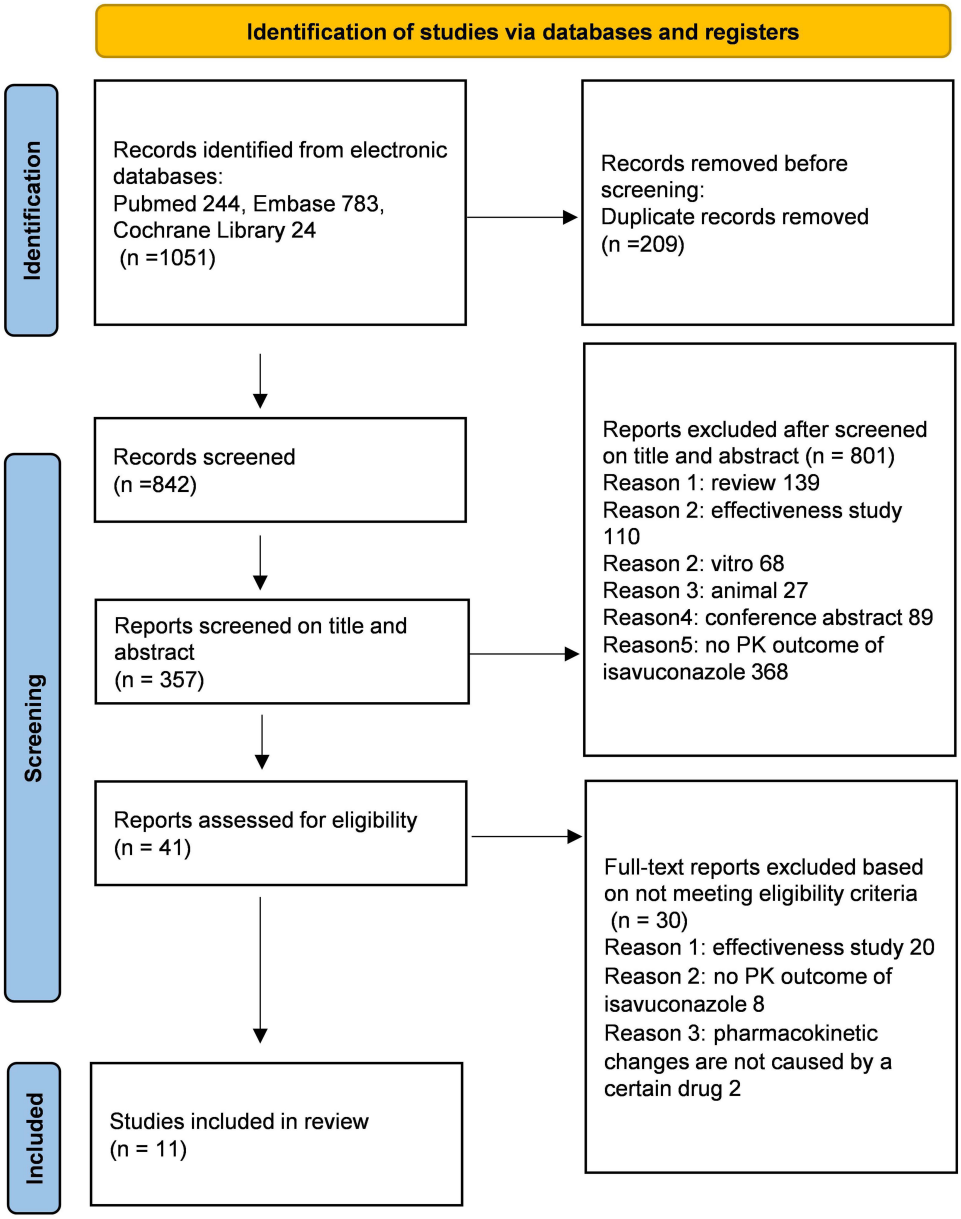

Figure 1 Study selection flow diagram.

Rifampicin is a potent enzyme inducer. The interaction between it and isavuconazole was explored in a Phase I clinical study, and it had a significant impact on the metabolism of isavuconazole. The induction ability of phenobarbital is weaker than that of rifampicin. However, decrease in the concentration of isavuconazole has also been reported in the clinic. After the dose was increased, the concentration reached the therapeutic range. Three cases have reported interactions between flucloxacillin and isavuconazole, all showing significantly decreased isavuconazole concentrations, warranting clinical attention. See Table 1 for details.

The interaction between rifabutin and isavuconazole has also been reported in 2 cases.[17] One case involved the concomitant use of tacrolimus, a CYP enzyme inhibitor, while in the other case, rifampicin and flucloxacillin had been used in the earlier stage, and CYP enzymes may have already been induced. Therefore, these 2 cases were excluded from the final included literature.

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Table 1 Concomitant Medications Reduce the Exposure of Isavuconazole

Concomitant Medications	Publication Year	Study Design	Dosage and Administration of Concomitant Drugs	Dosage and Administration of Isavuconazole	Pharmacokinetics of Isavuconazole When Used Alone	Pharmacokinetics of Isavuconazole When Used in Combination.	The Combined Drug Administration Regimen Before the Pharmacokinetics of Isavuconazole Were Determined
Rifampicin[16]	2017	Phase I	600mg, oral, day 36-71	400 mg day 44; 100 mg QD days 45–57	$AUC_{0-\infty}$: 233.1 (122.9) h μg/mL; C_{max}: 2.4 (0.5) μg/mL; CL/F: 2.8 (0.6) L/h.	$AUC_{0-\infty}$: 5.8 (1.4) h μg/mL; C_{max}: 0.6 (0.2) μg/mL; CL/F: 27 (6.2) L/h.	25 days
Phenobarbital[17]	2021	Case	Oral	Loading dose 200 mg q8h and maintenance dose 200 mg q24h from day 3 to day 11; then 200mg q12h to day 37; intravenous		Day 11: C_{min} 1.6mg/L; Day 23: C_{min} 3.7mg/L.	NA
Flucloxacillin[18,19]	2021	Case1	2g, q4h; intravenous; day 1–15	200 mg q8h for 2 days, maintenance dose of 200 mg q24h; intravenous; from day 8		Day 13: C_{min} 0.37 mg/L; Day 14: C_{min} 0.37 mg/L; Day 16: C_{min} 0.44 mg/L; Day 17: C_{min} 0.38 mg/L.	7 days
	2021	Case2	2g, q4h; intravenous; day 1−34	200 mg q8h for 2 days, maintenance dose of 200 mg q24h; day 7–11; 200mg q12h; day 12–19 200mg q8h; day 20–43 200mg q12h; day 44–88	Day 39: C_{min} 2.9 mg/L; Day 46: C_{min} 2.2 mg/L; Day 56: C_{min} 2.9 mg/L; Day 70: C_{min} 2.6 mg/L.	Day 8: C_{min} 0.6 mg/L; Day 12: C_{min} 0.5 mg/L; Day 14: C_{min} 1.0 mg/L; Day 18: C_{min} 1.0 mg/L; Day 21: C_{min} 1.2 mg/L; Day 25: C_{min} 1.5 mg/L.	34 days
	2022	Case3	2g, q4h; intravenous; day 1–41	200 mg q8h for 2 days, maintenance dose of 200 mg q24h; intravenous; day 26–42; day 77-	Day 85: C_{min} 1.7mg/L; Day 92: C_{min} 5.2mg/L.	Day 35: C_{min} 0.3mg/L	41 days

Abbreviations: AUC, area under the concentration–time curve; C_{max}, maximum concentration; C_{min}, minimum concentration; CL/F, Clearance/Bioavailability; NA not available.

The Combination of Drugs Has No Significant Effect on the Exposure of Isavuconazole

Several phase I studies have reported that concomitant drugs, including esomeprazole,[11] midazolam,[16] estradiol/norethisterone,[16] atorvastatin,[20] digoxin,[20] metformin,[20] methotrexate,[20] bupropion,[21] repaglinide,[21] caffeine,[21] dextromethorphan,[21] methadone,[21] warfarin,[22] cyclosporine,[23] mycophenolate mofetil,[23] prednisone,[23] sirolimus,[23] and tacrolimus,[23] have no significant effect on the pharmacokinetics of isavuconazole. For details, please refer to Table 2.

In addition, a case-control study on letermovir with isavuconazole was reported.[24] Letermovir is a moderate inhibitor of CYP3A4/5, CYP2C8, organic anion transporting polypeptides 1B1 and 3, and P-glycoprotein. Terrier and others used the combination of letermovir and isavuconazole as the study group and isavuconazole alone as the control group among patients who underwent allogeneic haematopoietic stem cell transplantation, and retrospectively analyzed the differences between the two groups. As a result, there was no significant difference in trough concentration between the study group (median, 3.20 mg/L; interquartile range [IQR], 2.40) and the control group (median, 2.35 mg/L; IQR, 1.50) (P = 0.17).

Marchesi et al reported the pharmacokinetic situation of a patient with acute lymphoblastic leukemia using isavuconazole.[13] When the chemotherapy drugs were used in combination with isavuconazole, the concentration of isavuconazole was 4.6 mg/L. Ten days after the chemotherapy drugs were discontinued due to liver damage, the concentration of isavuconazole was 5.2 mg/L, with an insignificant change range. Since chemotherapy regimens involve a combination of multiple drugs, this study was not included.

The Combination of Drugs Increases the Exposure of Isavuconazole

In vitro experiments, in which isavuconazole was incubated with human liver microsomes expressing cytochrome P450 enzymes, revealed that the ratio of the remaining isavuconazole was lower for CYP3A4 (33.8%) or CYP3A5 (68.4%) than for CYP2B6, CYP2C8, or CYP3A7 (all >98%).[16] Therefore, there are numerous inhibitors of CYP3A4/3A5 that can increase the concentration/AUC of isavuconazole. Currently, the drugs reported in the literature include ketoconazole[16] and lopinavir/ritonavir.[25] For details, please refer to Table 3. A 5.5-fold increase in isavuconazole's AUC caused by ketoconazole confirms its status as a sensitive CYP3A4 substrate.

The Effect of Combined Drug Administration Duration on the Pharmacokinetics of Isavuconazole

In the above reports, only the case of phenobarbital[17] did not explicitly mention the number of days used before determining the concentration of isavuconazole. The reports on flucloxacillin[18,19] had long induction times, and the final concentration of isavuconazole was very low. In phase I trial, rifampicin was administered alone for 7 days, followed by co-administration with isavuconazole for 13 days, and then the concentration of isavuconazole was measured.[16] Long-term administration can fully exert the induction effect of drugs on enzymes. In contrast, midazolam,[16] estradiol/norethisterone,[16] atorvastatin,[20] digoxin,[20] metformin,[20] methotrexate,[20] bupropion,[21] repaglinide,[21] dextromethorphan,[21] caffeine,[21] methadone,[21] warfarin,[22] cyclosporine,[23] tacrolimus,[23] sirolimus,[23] prednisone,[23] and mycophenolate mofetil,[23] administered only a single-dose before measuring isavuconazole concentrations. The main outcomes of these studies focused on the impact of isavuconazole on concomitant drugs. A single-dose administration regimen cannot achieve stable blood drug concentrations and metabolic enzyme inhibition or induction states, and the concentration determination of isavuconazole is mostly extended to 24 hours after administration. We thought the conclusion that there is no significant effect on isavuconazole pharmacokinetics is unreliable.

Discussion

The predominance of phase I studies in our analysis underscores a critical gap in post-marketing surveillance for isavuconazole DDIs. This imbalance may reflect the underutilization of TDM in clinical practice, as highlighted by the scarcity of real-world data on long-term coadministration scenarios.

While package inserts contraindicate coadministration with potent CYP3A4 inducers (eg, rifampin, carbamazepine), our analysis reveals nuanced differences in their effects. Rifampin, a prototypical inducer, reduces isavuconazole exposure by 97% in phase I studies,[16] necessitating strict avoidance. In contrast, phenobarbital, a weaker inducer, only

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Table 2 Concomitant Medications Have No Significant Effect on the Exposure of Isavuconazole in Phase I Studies

Concomitant Medications	Publication Year	Study Design	Dosage and Administration of Concomitant Drugs	Dosage and Administration of Isavuconazole	Pharmacokinetics of Isavuconazole When Used Alone	Pharmacokinetics of Isavuconazole When Used in combination.	The Combined Drug Administration Regimen Before the Pharmacokinetics of Isavuconazole Were Determined
Esomeprazole[11]	2016	Phase I	40 mg oral once per day on days 1–10	Oral 200 mg TID on days 6 and 7, followed by QD on days 8 to 10	AUCτ 112.8 (26.7) h μg/mL; C_{max}, 6.9 (1.5) μg/mL; t_{max}, 3.0 (2.0–8.0) hours	AUCτ 123.2 (38.5); h μg/mL C_{max}, 7.3 (1.9) μg/mL; t_{max}, 4.0 (1.5–4.0) hours	10 days
Midazolam[16]	2017	Phase I	A single oral dose of 3mg on day 12	Oral 200 mg TID on days 3 and 4followed by 200 mg QD on days 5 to 13	AUCτ 89.8 (22.9) h μg/mL; C_{max}, 5.2 (1.4) μg/mL; t_{max}, 4.0 (3.0−23.9) hours	AUCτ 88.2(22.0) h μg/mL; C_{max}, 5.0 (1.1) μg/mL; t_{max},4.6 (2.0−23.9) hours	A single-dose
Estradiol/ norethisterone[16]	2017	Phase I	A single oral dose of ethinyl estradiol 35μg /norethindrone 1 mg on day 13	Oral 200 mg TID on days 9 and 10followed by 200 mg QD on days 11 to 16	AUCτ 80.8 (18.7) h μg/mL; C_{max}, 5.8 (1.3) μg/mL; t_{max}, 2.5 (2.0−3.0) hours	AUCτ 81.4 (19.0) h μg/mL; C_{max}, 6.1 (1.5) μg/mL; t_{max}, 2.0 (1.0−4.0) hours	A single-dose
Atorvastatin[20]	2017	Phase I	A single oral dose of oral atorvastatin calcium 20 mg on day 12	Oral 200 mg TID on days 8 and 9, followed by 200 mg QD on days 10 to 15	AUCτ77.3 (22.0) h μg/mL; C_{max}, 5.3 (1.2) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	AUCτ81.2 (22.3) h μg/mL; C_{max}, 5.5 (1.3) μg/mL; t_{max}, 2.5 (1.5–4.0) hours	A single-dose
Digoxin[20]	2017	Phase I	A single dose of oral digoxin 0.5 mg on day 19	Oral 200 mg TID on days 15 and 16, followed by 200 mg QD on days 17 to 26	AUCτ101.8 (30.2) h μg/mL; C_{max}, 6.1 (1.7) μg/mL; t_{max}, 3.0 (2.0–4.1) hours	AUCτ101.1 (29.5) h μg/mL; C_{max}, 6.2 (1.7) μg/mL; t_{max}, 3.0 (2.0–5.0) hours	A single-dose
Metformin[20]	2017	Phase I	A single oral dose of metformin hydrochloride 850 mg on day 8	Oral 200 mg TID on days 4 and 5, followed by 200 mg QD on days 6 −9	AUCτ105.7 (31.0) h μg/mL; C_{max}, 7.1 (2.2) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	AUCτ111.7 (33.7) h μg/mL; C_{max}, 7.2 (2.0) μg/mL; t_{max}, 2.8 (2.0–4.0) hours	A Single-dose
Methotrexate[20]	2017	Phase I	A single oral dose of methotrexate 7.5 mg on day 8	Oral 200 mg TID on days 4 and 5, followed by oral isavuconazole 200 mg QD on days 6 −9	AUCτ99.4 (30.8) h μg/mL; C_{max}, 6.2 (1.5) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	AUCτ102.7 (29.5) h μg/mL; C_{max}, 6.4 (1.6) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	A single-dose
Bupropion[21]	2017	Phase I	A single oral dose of bupropion 100 mg on day 15.	Oral 200 mg TID on days 8and 9, followed by 200 mg QD on days 10 to 20	AUCτ94.3 (13.1) h μg/mL; C_{max}, 6.20 (1.00) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	AUCτ93.3 (14.8) h μg/mL; C_{max}, 6.32 (1.18) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	A single-dose
Repaglinide[21]	2017	Phase I	A single oral doses of repaglinide 0.5 mg on days 14	Oral 200 mg TID on days 5 and 6, followed by 200 mg QD on days 7 to 17	AUCτ122.9 (29.6) h μg/mL; C_{max}, 7.33 (1.51) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	AUCτ123.2 (26.6) h μg/mL; C_{max}, 7.44 (1.59) μg/mL; t_{max}, 3.0 (1.5–4.2) hours	A single-dose
Caffeine[21]	2017	Phase I	A single oral doses of caffeine 200 mg on days 16	Oral 200 mg TID on days 5 and 6, followed by 200 mg QD on days 7 to 17	AUCτ122.9 (29.6) h μg/mL; C_{max}, 7.33 (1.51) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	AUCτ131.6 (28.9) h μg/mL; C_{max}, 7.98 (1.72) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	A single-dose
Dextromethorphan[21]	2017	Phase I	A single oral dose of dextromethorphan 30 mg on day 10	Oral 200 mg TID on days 6 and 7, followed by 200 mg QD on days 8 to 12	AUCτ92.4 (36.1) h μg/mL; C_{max}, 5.82 (1.8) μg/mL; t_{max}, 3.0 (1.5–5.1) hours	AUCτ95.6 (38.0) h μg/mL; C_{max}, 6.3 (1.9) μg/mL; t_{max}, 2.0 (1.2–4.3) hours	A single-dose
Methadone[21]	2017	Phase I	A single oral dose of methadone 10 mg on day 20	Oral 200 mg TID on days 16 and 17, followed by200 mg QD on days 18 to 28	AUCτ 99.5 (44.1) h μg/mL; C_{max}, 6.8 (3.0) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	AUCτ102.6 (46.3) h μg/mL; C_{max}, 6.6 (2.7) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	A single-dose
Warfarin[22]	2017	Phase I	A single dose of oral warfarin 20 mg on day 20	Oral 200 mg TID on days 16 and 17, followed by 200 mg QD on days 18 to 28	AUCτ 93.2 (25.2) h μg/mL; C_{max}, 6.2 (1.4) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	AUCτ97.2 (24.8) h μg/mL; C_{max}, 6.1 (1.5) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	A single-dose
Cyclosporine[23]	2017	Phase I	A single oral dose of cyclosporine 300 mg on day 15	Oral 200 mg TID on days 11 and 12, followed by 200 mg QD on days 13 to 18	AUCτ107.7(31.2) h μg/mL; C_{max}, 5.7(1.9) μg/mL; t_{max}, 3.0 (1.5–4.0) hours	AUCτ109.3(29.2) h μg/mL; C_{max}, 7.3 (1.8) μg/mL; t_{max}, 4.0 (3.0–5.0) hours	A Single-dose
Mycophenolate mofetil[23]	2017	Phase I	A single oral dose of MMF1 g on day 13	Oral 200 mg TID on days 9 and 10, followed by 200 mg QD on days 11 to 16	AUCτ101.4 (37.6) h μg/mL; C_{max}, 3.7 (2.0) μg/mL; t_{max}, 3.0 (1.0–4.0) hours	AUCτ100.5 (32.3) h μg/mL; C_{max}, 3.7 (2.0) μg/mL; t_{max}, 3.0 (1.5–5.0) hours	A single-dose

Prednisone[23]	2017	Phase I	A single oral dose of prednisone 20 mg on day 9	Oral 200 mg TID on days 5 and 6, followed by 200 mg QD on days 7 to 10	AUCτ88.2 (37.9) h·μg/mL; C_{max}, 5.6 (1.9) μg/mL; t_{max}, 2.0 (1.5–3.0) hours	AUCτ98.8 (36.6) h·μg/mL; C_{max}, 6.7 (2.4) μg/mL; t_{max}, 3.0 (1.5–5.0) hours	A single-dose
Sirolimus[23]	2017	Phase I	A single dose of oral sirolimus 2 mg on day 26	Oral 200 mg TID on days 22 and 23, followed by 200 mg QD on days 24 to 34	AUCτ92.0 (21.0) h·μg/mL; C_{max}, 6.2 (1.4) μg/mL; t_{max}, 2.0 (1.5–3.0) hours	AUCτ100.4 (24.2) h·μg/mL; C_{max}, 6.4 (1.5) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	A single-dose
Tacrolimus[23]	2017	Phase I	A single oral dose of tacrolimus 5 mg on day 20	Oral 200 mg TID on days 16 and 17, followed by 200 mg QD on days 18 to 28	AUCτ89.8 (38.8) h·μg/mL; C_{max}, 4.9 (1.6) μg/mL; t_{max}, 3.0 (0.3–8.0) hours	AUCτ89.8 (38.8) h·μg/mL; C_{max}, 6.1 (1.7) μg/mL; t_{max}, 3.0 (1.5–8.0) hours	A single-dose

Note: t_{max}, time to C_{max}; AUC and C_{max} are expressed as mean (standard deviation), t_{max} is expressed as median (range).
Abbreviations: AUC, area under the concentration–time curve; C_{max}, maximum concentration.

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Table 3 Concomitant Medications Increase the Exposure of Isavuconazole

Concomitant Medications	Publication Year	Study Design	Dosage and Administration of Concomitant Drugs	Dosage and Administration of Isavuconazole	Pharmacokinetics of Isavuconazole When Used Alone	Pharmacokinetics of Isavuconazole When Used in Combination.	The Combined Drug Administration Regimen Before the Pharmacokinetics of Isavuconazole Were Determined
Ketoconazole[16]	2017	Phase I	Oral doses of ketoconazole 200 mg twice daily on days 1 to 24	A single oral dose 200 mg on day 4	AUCτ 84.8 (22.2) h·μg/mL; C_{max}, 2.2 (0.5) μg/mL; t_{max}, 2.0 (2.0–4.0) hours	AUCτ466.4 (199.4) h·μg/mL; C_{max}, 2.4 (0.6) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	3 days
Lopinavir/ Ritonavir[25]	2017	Phase I	400/100 mg twice daily on days 1 to 13.	A loading-dose 100 mg TID on days 1 and 2, followed by 100 mg QD on days 3 to 13	AUCτ54.9 (13.0) h·μg/mL; C_{max}, 3.4 (0.8) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	AUCτ116.2 (19.9) h·μg/mL; C_{max}, 6.6 (1.5) μg/mL; t_{max}, 3.0 (2.0–4.0) hours	10 days
Lopinavir/ Ritonavir[25]	2017	Phase I	400/100 mg twice daily on days 1 to 13.	A loading-dose 200 mg TID on days 1 and 2, followed by 200 mg QD on days 3 to 13	AUCτ113.8 (37.3) h·μg/mL; C_{max}, 7.8 (2.4) μg/mL; t_{max}, 3.0 (2.0–6.0) hours	AUCτ221.6 (63.7) h·μg/mL; $C_{max,}$ 13.6 (3.9) μg/mL; t_{max}, 3.0 (1.0–4.0) hours	10 days

Note: t_{max}, time to C_{max};AUC and C_{max} are expressed as mean (standard deviation), t_{max} is expressed as median (range).
Abbreviations: AUC, area under the concentration–time curve; C_{max}, maximum concentration.

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modestly decreases trough concentrations, which can be normalized via dose adjustment.[17] These findings suggest a graded response among CYP3A4 inducers, warranting a risk-benefit assessment for drugs less potent than rifampin.

In studies on the impact of CYP3A4 inhibitors on the exposure of isavuconazole, only ketoconazole and ritonavir exerted relatively strong effects. Ketoconazole can increase the AUC of isavuconazole by more than five-fold, which proves that isavuconazole is a sensitive CYP3A4 substrate. It can be inferred that there should be many DDIs. However, through retrieval, it was found that the impacts of other drugs did not significantly differ, which may be related to the study design. A single-dose administration cannot achieve a stable blood drug concentration, which affects its induction or inhibition of metabolic enzymes.

For example, cyclosporine is a typical CYP3A4 inhibitor. According to previous reports, cyclosporine can increase the exposure of CYP3A4 substrates, such as letermovir,[26] aliskiren,[27] ticagrelor,[28] and ambrisentan.[29] These studies used different methods of combined drug administration. The first three involved a single combined-drug administration, while the fourth involved a combined-drug administration period of eight days. This might be because the long-term administration of cyclosporine could pose health risks to healthy volunteers. Even though single-dose administration could not achieve a good inhibitory effect, this method was still adopted. In the study of the interaction of isavuconazole, the administration of cyclosporine was also carried out as a single dose, which might not have a significant inhibitory effect and was very different from the drug-administration method for clinical patients.

Numerous reports have suggested that isavuconazole affects tacrolimus, and the initial dose of tacrolimus needs to be reduced.[30–33] The effect of tacrolimus on isavuconazole, similar to that of cyclosporine, is such that the regimen of a single-dose combination in healthy volunteers may not be a good representation of clinical patients. This discrepancy highlights the need for phase IV studies with clinically relevant dosing regimens.

The duration of coadministration emerges as a critical variable. Drugs like rifampin and phenobarbital require prolonged exposure to upregulate CYP3A4 fully, whereas single-dose studies (eg, midazolam, warfarin) fail to capture this dynamic. Clinically, this translates to potential underdosing in patients on long-term inducers or unexpected toxicity with inhibitors.[34]

There are some metabolic enzyme factors that have not been reported in current interaction studies, such as CYP3A5 and UGTs.

Isavuconazole is not only a substrate of CYP3A4 but also a substrate of CYP3A5, and these two metabolic enzymes are often inhibited or induced simultaneously.[35] Genetic polymorphisms of CYP3A5, which have been shown to influence the pharmacokinetics of numerous drugs,[36,37] may also modulate the pharmacokinetic profile of isavuconazole.

UGTs are responsible for catalyzing glucuronidation, a major Phase II biotransformation. UGTs constitute an enzyme superfamily. The nucleotide sequences encoding 22 types of human UGT proteins have been identified,[38] with each protein being approximately 530 amino acids long. Among them, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B10, 2B15, and 2B17 play important roles in liver drug elimination.[38]

Mefenamic acid is a UGT inhibitor and can increase the AUC of the UGT substrate ertugliflozin by 50%.[39] Probenecid and valproic acid are also UGT inhibitors and may also affect the clearance of isavuconazole.[40,41] Rifampicin is an inducer of both CYP3A and UGT,[42] so it has a significant effect on isavuconazole. Genetic polymorphisms of UGT also affect the pharmacokinetics of drugs.[43,44]

In addition, the current population pharmacokinetic studies of isavuconazole also have certain limitations. Existing population pharmacokinetic models[45,46] overlook concomitant medications as covariates, potentially overestimating interindividual variability. For transplant recipients on immunosuppressants (eg, cyclosporine, tacrolimus), integrating DDIs data into dosing algorithms could optimize therapeutic windows.

Conclusion

This review underscores that time-dependent enzyme regulation (via CYP3A4/5) renders single-dose isavuconazole interaction studies unreliable for predicting long-term drug exposure changes. Multidose coadministration with strong inducers/inhibitors significantly alters drug exposure, necessitating routine TDM for patients on prolonged combination therapies to ensure efficacy and safety.

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