Eur J Drug Metab Pharmacokinet (2018) 43:281–290
https://doi.org/10.1007/s13318-017-0445-7

REVIEW ARTICLE

A Review of the Clinical Pharmacokinetics and Pharmacodynamics of Isavuconazole

Kyle John Wilby[1]

Published online: 4 November 2017

Abstract Invasive fungal infections are a major cause of morbidity and mortality, especially for immunocompromised patients. Treatment options are few and most are limited by safety and formulation concerns. Isavuconazole is a new triazole antifungal agent with official indications for the treatment of invasive fungal infections caused by *Aspergillus* and *Mucormycosis*. Its clinical efficacy has been proven in two landmark trials, SECURE and VITAL. This review aims to summarize and evaluate the published literature reporting clinical pharmacokinetic and pharmacodynamic outcome data of isavuconazole in humans. Data from healthy volunteers demonstrated high oral bioavailability, high hepatic metabolism, and an extended elimination half-life. Data from diseased patients confirmed these findings and also consistently demonstrated that regular dosing of isavuconazole results in achievement of concentrations and exposures that meet pharmacodynamic targets for therapeutic efficacy. Additionally, it was found that renal dysfunction, and mucositis do not majorly affect pharmacokinetic or pharmacodynamic outcomes yet further study is required for severe hepatic and gastric impairment. Future studies should further attempt to understand dose and concentration response relationships, investigate the role (if any) of therapeutic drug monitoring, and strive to optimize dosing in special populations.

Key Points

Population analyses report a two-compartment model as best fit for the pharmacokinetic profile of isavuconazole.

Isavuconazole standard dosing appears to result in optimal exposure for attainment of pharmacodynamic targets.

Dosage adjustments are likely not required for patients with renal impairment yet the same are unknown for severe hepatic impairment.

1 Introduction

Infectious diseases remain as one of the greatest disease burdens worldwide [1]. Invasive fungal infections are a subset of infectious diseases that are associated with high morbidity, mortality, and increased economic burden in affected populations and regions [2]. While invasive fungal infections can affect a variety of populations, they are commonly documented in patients with immunosuppression [3]. It is not surprising, therefore, that with the advent of highly immunosuppressive therapies for cancer and other immunological diseases the incidence of these infections has increased over time [4]. Solid organ and hematopoietic stem cell transplant patients, in addition to those with chronic immunosuppression, are all ‘at risk’ populations. The presence of an invasive fungal infection

✉ Kyle John Wilby
kjw@qu.edu.qa

[1] College of Pharmacy, Qatar University, PO Box 2713, Doha, Qatar

in any of these populations can threaten care and overall treatment success [2].

Treatment options for invasive fungal infections are available as monotherapy but also may be used in combination, to maximize success [2]. Although efficacy rates are high for most infections, some safety and formulation concerns exist that limit the use of traditional agents in practice. Amphotericin B, a gold standard antifungal agent effective for most invasive fungal infections, is associated with increased adverse effects that require extensive patient monitoring. Echinocandins provide additional options for candida or *Aspergillus* but are only available for intravenous use. Currently available azole antifungals are typically the cornerstone of antifungal therapy but are unfortunately limited by different spectrum, safety, or formulation concerns. Fluconazole lacks activity against *Aspergillus* and voriconazole lacks activity against *Mucormycosis* and is limited by unique adverse effects and administration concerns [5]. Although posaconazole has a greater spectrum of action, clinical data is lacking regarding its effectiveness in diseased patients and therefore lacks official indications for treatment of infections caused by *Aspergillus* or *Mucormycosis* [6].

Isavuconazole is a new triazole antifungal available in both oral and intravenous dosage forms. It is administered as isavuconazonium (BAL8857), a prodrug formulated to increase its water solubility and ability to be administered intravenously. The isavuconazole product is structurally similar to voriconazole, however, it has a thiazolyl-benzonitrile side chain and lacks the 5-fluoropyrimidine moiety [4]. It works similarly to other triazoles, by inhibiting ergosterol synthesis through inhibition of 14-a-demethylase. It has a broad spectrum of action, including activity against both yeast and mold. It is currently the only antifungal officially indicated for invasive *Mucormycosis* [4, 7]. Isavuconazole has been studied in both preclinical and clinical trials, resulting in generation of extensive data regarding its pharmacokinetic and pharmacodynamic profiles in healthy, diseased, and special populations. Research is ongoing, with publication of additional studies after the publication of previous reviews. Therefore, the purpose of this narrative review is to provide an updated overview and critical discussion of the literature reporting clinical pharmacokinetic and pharmacodynamic outcomes in patients receiving isavuconazole.

2 Data Sources

Studies for this review were identified using a keyword search of Pubmed and EMBASE with dates inclusive of August 31, 2017. The keywords of 'isavuconazole', 'BAL4815', and 'BAL8557' were combined using OR with no limits on publication dates, language, or population. Articles were reviewed if they reported pharmacokinetic and/or pharmacodynamic outcomes in human subjects receiving at least one dose of isavuconazole.

3 Review of Clinical Efficacy

Before introducing the literature pertaining to pharmacokinetics and pharmacodynamics, the clinical efficacy of isavuconazole should be understood. Data from these studies was also used in other post hoc pharmacokinetic and pharmacodynamic analyses. One of the most influential studies was the SECURE trial, which confirmed the role of isavuconazole in treating *Aspergillus* [8]. It was a randomized, controlled, non-inferiority study designed to compare isavuconazole versus voriconazole for the primary treatment of invasive mold disease. A total of 527 patients were randomized to receive isavuconazole or voriconazole at standard doses. The primary outcome was all-cause mortality at day 42 in the intention to treat (ITT) population (all randomized and received at least one dose of study drug). End of treatment response was measured in the modified ITT (mITT) population (proven or probable invasive mold disease) as a secondary outcome. Non-inferiority was established using a margin of 10% or less of treatment difference. Results from the primary analysis demonstrated non-inferiority between the two agents with all-cause mortality at day 42 in the ITT population at 19% of patient with isavuconazole and 20% with voriconazole (adjusted treatment difference -1.0%, 95% CI -7.8 to 5.7). End of treatment response in the mITT population was similar between those receiving isavuconazole (35% success) versus voriconazole (36% response) (adjusted treatment difference 1.6%, 95% CI -9.3 to 12.6). Fewer patients reported adverse effects in the isavuconazole group versus the voriconazole group (42 versus 60%, respectively, $p < 0.001$), and patients treated with isavuconazole had lower frequencies of hepatobiliary disorders, eye disorders, skin or subcutaneous tissue disorders.

A second trial that supported the approved indication for *Mucormycosis* was the VITAL trial [9]. This was a single arm open-label study of adults with invasive fungal disease caused by rare fungal species, including *Mucormycosis*. For 2 days, isavuconazole was given 200 mg three times daily either orally or intravenously. This was followed by 200 mg/day dosing until infection resolution, failure, or for 180 days (or more). By the end of the study period, 37 patients were treated with isavuconazole for *Mucormycosis*. By the outcome assessment at day 42, 4 patients had a partial response, 16 had stable disease, one had disease progression, 3 had missing assessments, and 13 died. No major safety concerns were noted in this study.

Furthermore, Thompson et al. reported a subset of data from the VITAL study, solely evaluating results from *Cryptococcosis* or dimorphic mycoses [10]. A total of 38 patients were included in this subset (*Cryptococcus*, *Paracoccidioides*, *Coccidioides* spp., *Histoplasma* spp., *Blastomyces* spp.). At end of therapy (median length of therapy = 180 days), 24/38 (63%) of patients documented a successful response. Eight (21%) had stable disease without progression at the end of treatment. Six (16%) had progressive disease. Authors concluded that isavuconazole may be an alternative agent to treat these types of fungal infections yet no official indication currently exists.

In addition to the studies described above, evidence from a phase II study shows potential efficacy for esophageal candidiasis [11] and case report data signaled efficacy in allergic bronchopulmonary *Aspergillosis* [12]. However, further study is required to determine the role of isavuconazole in treatment of these specific indications.

4 Review of Data from Healthy Volunteers

A number of studies were completed in healthy volunteers before testing in diseased populations. These data helped to understand the pharmacokinetic parameters of isavuconazole and key pharmacokinetic considerations (such as potential for drug interactions). Summaries of important studies are provided below.

Schmitt-Hoffmann et al. completed an initial study to explore the pharmacokinetic and safety of isavuconazole in healthy volunteers [13]. Subjects were divided into different cohorts based on route of administration and dose. Subjects received a single dose of one of the following (administered as BAL8557 prodrug): placebo, 100 mg orally, 200 mg orally, 400 mg orally, 50 mg intravenously, 100 mg intravenously, or 200 mg intravenously. Blood samples were collected at baseline and at 15, 30, 45, 60, 75, and 90 min, and 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 288 h after administration (or until concentrations were below detection). No serious or severe adverse events were documented. Intravenous doses were given over a 1-h infusion. Study details and pharmacokinetic results are provided in Table 1. The high bioavailability of oral dosage forms, along with favorable pharmacokinetic parameters found in this study supported the development of isavuconazole as a systemic treatment agent.

Schmitt-Hoffman et al. completed a second pharmacokinetic study to evaluate pharmacokinetic and safety parameters of isavuconazole (administered as its prodrug, BAL8557) in healthy male volunteers [14]. The details of this study are presented in Table 1. Briefly, participants were divided into four cohorts and randomized to receive study drug or placebo within each cohort. Cohorts were designated based on route of administration (oral or intravenous) and dose (high or low). Cohorts 1 and 2 (oral) received drug for 21 days and cohorts 3 and 4 (intravenous) received drug for 14 days. Blood samples were taken on days 1, 8, and 14 at predose, 15, 30, 45, 60, 75, and 90 min, and 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h after dose. On day 21, blood samples were taken predose and at 15, 30, 45, 60, 75, and 90 min, and 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 60, 72, 96, 120, 240, 360, and 480 h after dose. Pharmacokinetic results are presented in Table 1. Major findings included dose proportional increases of C_{max} and AUC, and a 4–5 fold accumulation of active drug in plasma during once-daily dosing. Comparable C_{max} values for oral and intravenous administration signal little to no inhibition or induction of CYP3A4, which was also confirmed with the urinary 6-B-hydroxycortisol/cortisol test. Finally, no patient experienced a serious adverse event at any time during the study.

Townsend et al. reported the results of two studies to assess pharmacokinetic parameters and elimination of isavuconazole in healthy volunteers [15]. Subjects ($n = 7$) in study 1 received an oral dose of the radiolabeled compound [cyano-^{14}C]isavuconazonium sulfate (equivalent to 200 mg isavuconazole). In study 2, subjects ($n = 6$) received an intravenous dose of [pyridinylmethyl-^{14}C] isavuconazonium sulfate (equivalent to 75 mg of the inactive cleavage product, BAL8728). Pharmacokinetic results are reported in Table 1. Notably, isavuconazole-derived radioactivity was recovered in both urine and feces (46.1 and 45.5%, respectively).

In summary, data from healthy volunteers established an understanding of isavuconazole's pharmacokinetic parameters. The high bioavailability of the oral route of administration supports oral dosing, where applicable. It has a large volume of distribution, allowing for the treatment of widespread, invasive disease throughout different body tissues. Clearance is largely hepatic in nature, which should be less affected by impaired renal function. There was also no evidence of significant induction or inhibition of metabolizing enzymes. Finally, the long elimination half-life supports convenient dosing and potentially the maintenance of target concentrations for longer periods of time.

5 Review of Data from Diseased Patients

A number of studies have been completed to assess the pharmacokinetic and pharmacodynamic outcomes of diseased patients and those with invasive fungal infections. Cornely et al. completed a study with $n = 24$ patients experiencing neutropenia from AML and who did not have a history of invasive fungal infection [16]. Isavuconazole

Table 1 Clinical pharmacokinetic and pharmacodynamic of isavuconazole in healthy subjects and diseased patients

Reference	Population	Dosing	Pharmacokinetic–pharmacodynamic results	Clinical efficacy	Clinical safety
[13]	Healthy male volunteers with $n = 6$ patients receiving active drug in each cohort and $n = 2$ patients receiving placebo in each cohort (randomized, double-blinded study)	Oral dosing cohorts: 100, 200, or 400 mg Intravenous dosing cohorts: 50, 100, 200 mg	T_{max} observed 1.5–3 h after oral dosing and at the end of the intravenous infusion. Elimination half-life was 56–77 h after oral administration and 76–104 h after intravenous dosing. Volume of distribution was 155–292 l after oral administration and 304–494 l after intravenous dosing. Clearance was 1.9–2.8 l/h after oral administration and 2.8–5.0 l/h after intravenous dosing. Urinary recovery was less than 0.4% of prescribed dose	NA	No severe or serious adverse effects were reported
[14]	32 healthy male volunteers assigned to four cohorts ($n = 6$ active and $n = 2$ placebo in each cohort) (randomized, double-blinded study)	Cohort 1: oral loading dose of 100 mg equivalents of isavuconazole (as prodrug, BAL8557), then 50 mg daily up to day 21 Cohort 2: oral loading dose of 200 mg equivalents of isavuconazole, then 100 mg daily up to day 21 Cohort 3: constant rate 1 h intravenous infusion of 100 mg loading dose, then 50 mg up to day 14 Cohort 4: constant rate 1 h intravenous infusion of 200 mg loading dose, then 100 mg up to day 14	Plasma concentrations and AUC were dose proportional for both routes of administration Other PK parameters: Mean volume of distribution (308–542 l) Mean clearance (2.4–4.1 l/h) Mean half-life (84.5–117 h) No indication of CYP3A4 induction or inhibition	NA	79% of subjects reported at least 1 adverse event. No serious adverse events were reported. Most common adverse events were headache, nasopharyngitis, and rhinitis. 1 subject on oral high dose had reversible elevation of GGT, ALT, and AST on day 14
[15]	Study 1: $N = 7$ healthy volunteers Study 2: $N = 6$ healthy volunteers	Study 1: single oral dose of [cyano-^{14}C]isavuconazonium sulfate (200 mg isavuconazole). Study 2: single intravenous dose of [pyridinylmethyl-^{14}C]isavuconazonium sulfate (75 mg of the inactive cleavage product, BAL8728)	Study 1: isavuconazole PK parameters (mean ± SD) AUC_{0-inf} 96.2 ± 30.7 μg·h/ml C_{max} 2.5 ± 0.4 μg/ml T_{max} (median [range]) 2.0 h [2.0–3.0] Half-life 99.9 ± 44.6 h Cl/F 2.3 ± 0.7 l/h V/F 301.8 ± 105.7 l Isavuconazole radioactivity recovered in urine (46.1%) and feces (45.5%) Study 2: BAL8728 radioactivity recovered predominantly in urine (96.0%)	NA	3 of 13 total patients experienced a total of 13 adverse effects (6 deemed to be due to drug) and all were mild to moderate (type not reported)

Table 1 continued

Reference	Population	Dosing	Pharmacokinetic–pharmacodynamic results	Clinical efficacy	Clinical safety
[16]	24 adult neutropenic patients with acute myeloid leukemia without history of invasive fungal infection (open-label phase 2 study)	Low dose cohort: day 1: 400 mg, 200 mg, and 200 mg doses at equal intervals intravenously. Day 2: 200 mg twice intravenously (10 h between doses). Patients subsequently received 200 mg once daily intravenously until end of treatment. High dose cohort: the same protocol was followed but with 2 times the doses (800/400/400 mg day 1, 400/400 mg day 2, then 400 mg daily until end of treatment)	Day 1 [mean (SD)]: C_{12} (μg/ml) = 1.5 (0.4) in 10 low dose patients and 2.5 (0.8) in 11 high dose patients. Day 7: C_{max} (μg/ml) = 3.6 (1.0) in 8 low dose patients and 8.0 (2.8) in ten high dose patients. AUC_{0-24h} (μg·h/ml) = 60.1 (22.3) in 8 low dose patients and 113.1 (19.6) in 10 high dose patients	18 (90%) of patients completing study had treatment success. Two patients in the low dose cohort and 0 patients in the high dose cohort met criteria for possible fungal infection during the study	Most common adverse drug reactions were headache ($n = 3$) and rash ($n = 3$). One patient in high dose cohort had a serious adverse event (respiratory distress). Two patients in each group discontinued the study due to adverse drug reactions. Documented liver enzyme increases were observed in high dose cohort
[17]	56 patients with mucositis and 194 patients without mucositis from SECURE and VITAL trials	See SECURE and VITAL in Review of Clinical Efficacy section	Mucositis patients: F (%): 86.0 ± 18.5 (mean, SD), 98.3 [50.3–99.7) (median, range) AUC (mg·h/l): 105.3 ± 55.9 (mean, SD), 91.9 [45.9–315.5] (median, range) Non-mucositis patients: F (%): 97.4 ± 6.9 (mean, SD), 99.8 [70.2-99.9) (median, range) AUC (mg·h/l): 114.1 ± 141.2 (mean, SD), 100.2 [30.8–1944.3] (median, range)	Overall response at end of treatment was successful in 58% 95% CI (42.12, 72.99) and 42.9% 95% CI (35.68, 50.42) in mucositis and non-mucositis patients, respectively. All-cause mortality through day 42 was 7.1 and 14.4% in mucositis and non-mucositis patients, respectively	NR

NA not applicable, *PK* pharmacokinetic, *GGT* gamma-glutamyl transferase, *AST* aspartate amino transferase, *ALT* alanine amino transferase, *AUC* area under the concentration-time curve, C_{max} maximum concentration, T_{max} time to maximum concentration, *Cl/F* apparent oral clearance, *V/F* apparent oral volume, *SD* standard deviation, C_{12} concentration at 12 h after starting therapy, *F* bioavailability, *CI* confidence interval, *NR* not reported, *CYP* cytochrome P450

was used as prophylaxis in these patients. The objective was to study both pharmacokinetic parameters and clinical safety. Study details and results are provided in Table 1. Briefly, patients were separated into two dosing cohorts, with the high dose cohort receiving doses at twice amount of the low dose cohort. Blood samples were obtained on day 1 (predose, 4, 6, 12, and 24 h after start of infusion) and day 7 (predose and 2, 3, 4, 6, 12, and 24 h after start of infusion). Pharmacokinetic results showed relatively low interpatient variability for day 7 C_{max} and $AUC_{0–24}$. However, dose proportionality could not be confirmed based on the data obtained. Adverse events were mild in nature with no major differences between dosing groups (aside from documented liver enzyme increases in the high dose group). Although small, this study provides evidence that isavuconazole is likely safe in neutropenia patients requiring fungal prophylaxis but further study is required to better understand the linearity of its pharmacokinetic profile.

Kovanda et al. completed an analysis of isavuconazole pharmacokinetic parameters relating to absorption and exposure in patients with mucositis based on data obtained from the SECURE and VITAL trials [17]. Study details and results for the Kovanda et al. analysis are provided in Table 1. Briefly, the mucositis population consisted of 56 patients with documented mucositis who received oral drug during the mucositis episode. The non-mucositis population consisted of 194 patients that did not meet these criteria. Blood samples were collected on days 7, 14, 42, and at the end of treatment. Results showed that oral bioavailability was significantly lower in mucositis versus non-mucositis patients (98.3 and 99.8%, respectively, $p < 0.001$) but that did not result in different average AUC values. Clinical responses were fairly similar but the lack of information provided and nature of the secondary analysis preclude firm conclusions being made based on clinical outcomes. Considering mucositis did not appear to affect exposure, this analysis provides evidence that mucositis may not be a reason to not offer oral therapy in patients with mucositis. However, the differences in oral bioavailability should be studied further in adequately powered trials to determine if associations exist with clinical outcomes.

These studies provide data from diseased patients that enhance knowledge pertaining to pharmacokinetic and safety concerns. Notably, the findings that mucositis does not appear to interfere with exposure are promising for oral dosing of isavuconazole patients who do not necessarily require intravenous administration.

6 Review of Population Pharmacokinetic Analyses

Desai et al. performed a population pharmacokinetic analysis based on data obtained from Phase 1 studies and the SECURE trial for invasive infections caused by *Aspergillus* and other filamentous fungi [18]. Patients were a mixture of healthy volunteers, non-diseased patients with comorbidities, and diseased patients. Sampling times varied, due to the merged nature of study data. A two-compartment model with a Weibull absorption function and a first-order elimination process best fit the data. Pharmacokinetic results are provided in Table 2. It was noted that race affected clearance, with approximately 36% lower clearance in Asians versus Caucasians. Probability of target attainment was determined using simulations of the standard dosing regimen (including loading doses). When considering an MIC of 1 mg/l (European Committee on Antimicrobial Susceptibility testing methodology), it was found that adequate exposures were achieved in > 90% of simulated patients. It was also found that > 90% of patients would meet the MIC target of 0.5 mg/l (Clinical and Laboratory Standards Institute Methodology). Therefore, standard dosing regimen is likely to be effective for treating invasive infections caused by these pathogens.

Kovanda et al. performed a population pharmacokinetic analysis based on the results of the VITAL study [19]. VITAL, as described above, enrolled patients with invasive fungal disease caused by rare molds, yeasts, and dimorphic fungi. Out of 136 patients included in the analysis, 53 (39%) had renal impairment, defined as an estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73 m^2. Blood samples were collected on treatment days 7, 14, 42, and at the end of treatment. A two-compartment model with first-order absorption was found to best fit the data. Pharmacokinetic results are given in Table 2. Asian ethnicity and eGFR did not significantly influence clearance. Weight was found to influence both clearance and central-compartment volume but inclusion as a covariate did not improve model fit and was therefore not included in the final model. From a pharmacodynamic perspective, target attainment analyses demonstrated that clinical dosing will result in total AUC/MIC targets of 50.5 for *Aspergillus*. Exploratory analyses also confirmed that AUC/MIC targets would be met for *Candida* but no patients were included with Candida infections for the VITAL trial.

It appears from the data presented in these studies that few covariates influence the pharmacokinetic parameters of isavuconazole, and therefore pharmacodynamic target attainment is more predictable. Additionally, target attainment was achieved with standard dosing. These factors allow for straightforward and convenient dosing of isavuconazole in target patients.

7 Data Pertaining to Special Populations

Special populations are a primary concern for drug developers when evaluating dosage considerations in diseased patients and those with comorbidities. Altered absorption,

distribution, metabolism, or elimination could potentially interfere with efficacy and safety of the intended treatment. The following studies report pharmacokinetic and clinical outcomes for patients with hepatic, renal, and gastric impairment.

Schmitt-Hoffmann et al. completed a study to assess the pharmacokinetics and safety of isavuconazole in patients with liver impairment [20]. Study design and results are given in Table 3. Briefly, three groups of 16 subjects (healthy volunteers, mild liver impairment, and moderate liver impairment) were randomized to receive a single 100 mg dose of either oral or intravenous prodrug (BAL8557). Mild disease was defined as Child–Pugh class A and moderate defined as Child–Pugh class B. Blood samples were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 72, 96, 120, 144, 168, 216, 288, 360, 432, and 480 h (21 days total). Major findings included significantly increased AUC and half-life and significantly decreased clearance when comparing liver impairment subjects against healthy volunteers. These results demonstrate that mild to moderate liver impairment likely influences exposure and elimination of isavuconazole and further study is required to determine to what extent this finding is relevant from a clinical perspective. A simulation analysis suggested that maintaining the current loading dose strategy of 200 mg three times daily for 2 days but shifting the maintenance dose from 200 to 100 mg per day will result in similar concentrations to those obtained from healthy subjects. However, no dosage adjustments are currently recommended for these patients. Few adverse events were noted but this was only a single-dose study and therefore adverse events are expected to be rare.

The effects of renal impairment and low creatinine clearance (CrCl) on isavuconazole pharmacokinetics were studied in a Phase I trial [21]. In a two-part single-dose study, healthy volunteers were compared with those with mild (CrCl 50–80 ml/min/1.73^3), moderate (30–$<$50 ml/min/1.73^3), severe ($<$30 ml/min/1.73^3), and those with end stage renal disease (ESRD) and requiring hemodialysis ($<$15 ml/min/1.73^3). Each participant received an intravenous dose of isavuconazonium equivalent to 200 mg isavuconazole (approximately 1 h after completion of hemodialysis for ESRD patients). Blood samples were taken on days 6, 8, 11, 13, and 15. Pharmacokinetic results are given in Table 3. Findings showed no major differences between healthy subjects and those with mild, moderate, and severe renal impairment. C_{max}, AUC, elimination half-life, and clearance were all comparable despite high inter-

Table 2 Summaries of studies reporting population pharmacokinetic analyses

Reference	Population	Dosing	Pharmacokinetic–pharmacodynamic results
[18]	A total of 421 subjects provided 6363 drug concentrations for analysis (data obtained between phase 1 and phase 3 trials)	Phase 1 trial: isavuconazonium sulfate administered as single or multiple doses orally or intravenously to provide 40–400 mg isavuconazole. Phase 3 trial: loading dose equivalent to 200 mg isavuconazole given intravenously every 8 h for 6 doses and then once daily until end of treatment	A 2-compartment model with Weibull absorption function and first-order elimination process adequately described data Mean isavuconazole Cl: 2.360 l/h (%CV, 34%) Mean AUC_{0-24h}: 100 mg·h/l Asian patients had 36% lower Cl than Caucasians
[19]	A total of 136 patients provided 458 isavuconazole concentrations from the VITAL study (36% had eGFR $<$ 60 ml/min/1.73 m^2	Equivalent doses of 200 mg isavuconazole (oral or intravenous) every 8 h for 48 h, then daily for maximum of 180 days	A 2-compartment model with first-order absorption best fit the data Calculated parameters: overall (mean ± standard deviation): Cl: 2.5 ± 1.6 l/h V: 361.2 ± 166.3 l AUC (average): 87.1 ± 41.0 mg·h/L F: 96.6% There was no significant impact of eGFR or Asian ethnicity on clearance

Cl clearance, *CV* coefficient of variation, *AUC* area under the concentration-time curve, *eGFR* estimated glomerular filtration rate, *V* volume of distribution, *F* bioavailability

patient variability. The authors conclude that dosage adjustments are likely not required for patients with renal impairments or those with ESRD receiving dialysis.

A case report was published that describes trough and C_{max} concentrations in a patient who was receiving isavuconazole but had previously undergone a Roux-en-Y gastric bypass surgery [22]. Results are provided in Table 3. After a 3-day loading dose of oral isavuconazole (200 mg three times per day) followed by 200 mg once per day, the trough day-7 concentration was 1.05 mg/l (below authors' target of 3 mg/l) and maximum post dose concentration (4 h post dose) was 2.42 mg/l. Upon increasing the dose to 200 mg twice daily, trough concentrations were achieved above the target of 3 mg/l (day 27: 4.43 mg/l). The patient was deemed to achieve clinical success. Due to the potentially altered bioavailability resulting from gastric bypass surgery, these patients should be closely monitored to determine if dosage adjustments are necessary, especially as the role of therapeutic drug monitoring is not yet clear.

Results from these studies suggest that further study is needed to determine the appropriate course of action for treatment and monitoring for patients with hepatic or gastric impairment. Those with renal dysfunction, however, are likely able to be dosed at standard dosing based on currently available published data.

8 Review of Other Pharmacodynamic Studies

Two other studies were identified that evaluated unique pharmacodynamic properties of isavuconazole and are briefly summarized here. Kovanda et al. studied the pharmacokinetic–pharmacodynamic relationship between isavuconazole dose, exposure, and the time course of galactomannan index (GMI) from patient data obtained during the SECURE trial [23]. Overall findings showed an association of GMI with clinical outcomes (importantly, day-7 GMI increases of >0.25 units significantly increased risk of death compared to those with no increase or increases <0.25 [hazard ratio, 9.766; 95% CI 4.356–21.9, $p<0.001$). A total of 78 patients treated with isavuconazole had plasma concentrations and serial GMIs available for pharmacokinetic–pharmacodynamic analysis. A one-compartment model with an absorptive compartment resulted in an adequate fit for the data obtained. No relationships between minimum concentrations or exposure with clinical response or survival were documented. Findings showed an AUC:EC_{50} (half maximal effective concentration) of 108.6 or more resulted in a GMI <0.5 at end of treatment. No relationship was noted between average exposure and GMI change at day 7 or GMI at end of treatment. Therefore, further study is required to determine if isavuconazole pharmacokinetics can have a predictable impact on GMI and any associated clinical outcomes.

Keirns et al. reported results of a Phase I study in addition to an analysis of safety data from the SECURE trial to evaluate cardiac-related adverse effects of isavuconazole [24]. In the Phase I study, subjects were randomized to receive oral isavuconazole at regular dosing (200 mg three times daily for 2 days, then 200 mg daily for 11 days), oral isavuconazole at supratherapeutic dosing (200 mg three times daily for 2 days, then 600 mg daily for 11 days), placebo, or placebo for days 1–12, then oral moxifloxacin 400 mg on day 13. No prolongation of QTc interval was documented and isavuconazole was concluded to shorten the QTc interval in a dose-dependent manner. In SECURE, a shortened interval was also documented. Clinical implications of QTc shortening by isavuconazole are unknown but should be monitored in patients with cardiac-related disorders.

9 Implications for Therapeutic Drug Monitoring

The role of therapeutic drug monitoring for isavuconazole is currently unclear. A post hoc analysis from the SECURE trial analyzed trough levels to determine the extent of intra-subject variability [25]. Findings showed that intra-subject variability was less than 30%, which suggests isavuconazole demonstrates predictable pharmacokinetics and argues against the need for therapeutic drug monitoring. It was also found that trough levels, when grouped into quartiles, were not correlated with clinical success. In consideration of these findings and others, the literature is inconclusive about the utility of isavuconazole therapeutic drug monitoring as a whole [26]. Further research is required to explore any potential role; however, the relatively predictable pharmacokinetics may preclude utility in the general population.

10 Summary

Isavuconazole is a new triazole antifungal with official indications for invasive fungal infections caused by *Aspergillus* and *Mucormycosis*. It also demonstrates efficacy against a variety of other fungal pathogens. To date, no major safety concerns have emerged from preclinical and clinical trials but the safety profile will be better understood with use of the agent in practice. It has a pharmacokinetic profile that allows for convenient dosing (once daily during maintenance period), minimal drug interactions, and appears to allow for regular dosing in renal and hepatic dysfunction.

Table 3 Summaries of studies reporting pharmacokinetic parameters with hepatic, renal, and gastric impairment

References	Population	Dosing	Pertinent pharmacokinetic–pharmacodynamic results	Clinical efficacy	Clinical safety
[20]	$N = 48$ adult subjects (16 healthy volunteers, 16 with mild liver impairment, 16 with moderate liver impairment)	Subjects randomized to receive BAL8557 (prodrug of isavuconazole) orally or intravenously at a single dose of 100 mg	Increased concentrations of isavuconazole observed beyond 8 h in impaired patients vs. healthy controls (both IV and PO) Cl was decreased ($p < 0.05$) and half-life increased ($p < 0.05$) in impaired subjects vs. healthy controls No difference between mild and moderate impairment in PK parameters	NA	4 adverse events reported that were all not attributed to drug (right bundle branch block, upper abdominal pain, high blood pressure, hyperhydrosis)
[21]	$N = 19$ completed part 1 (healthy controls versus ESRD) and $N = 29$ completed part 2 (healthy controls versus mild, moderate, and severe renal impairment)	Single intravenous dose of isavuconazonium sulfate (equivalent to 200 mg isavuconazole). ESRD patients received 2 doses of 200 mg intravenous isavuconazole (1 h post-dialysis and prior to dialysis	No major differences were found for ESRD patients versus healthy controls aside from an expected increased elimination half-life (204.5 vs. 125.5 h, respectively) and V (735.6 vs. 386.2 l, respectively) No major differences were found for any pharmacokinetic parameter in part 2 (AUC, T_{max}, half-life, C_{max}, Cl, or V). Dosage adjustments likely not needed in patients with renal impairment	NA	No severe or serious adverse drug reactions reported
[22]	$N = 1$ patient with previous Roux-en-Y gastric bypass surgery requiring isavuconazole for invasive *Mucormycosis*	200 mg orally three times daily, then 200 mg daily On day 17, dosing increased to 200 mg twice daily	Day 7 concentrations (standard dosing): Trough: 1.05 mg/l 2 h post-dose: 2.32 mg/l 4 h post-dose: 2.42 mg/l 8 h post-dose: 1.85 mg/l Day 27 concentrations (after dose increase): Trough: 4.43 mg/l 2 h post-dose: 6.06 mg/l 4 h post-dose: 5.75 mg/l 8 h post-dose: 5.41 mg/l	Treatment success deemed after 4 months of therapy	NR

IV intravenous, *PO* orally, *Cl* clearance, *PK* pharmacokinetics, *NA* not applicable, *ESRD* end stage renal disease, *AUC* area under the curve, C_{max} maximum plasma concentration, *V* volume, *NR* not reported

The pharmacokinetic and pharmacodynamic studies summarized above are of high quality and are largely based on data arising from diseased patients treated clinically with isavuconazole. This is important, as disease processes may alter pharmacokinetic parameters observed in healthy volunteers. One limitation of the literature, however, is that it is largely based on data from only two Phase III trials, SECURE and VITAL. Although these are the major landmark studies that the drug was approved from, the patient populations were limited in terms of number and type. Further study is therefore required to better understand the pharmacokinetic and pharmacodynamic properties in other populations and to determine the influence of comorbidities and concurrent use of medications on clinical outcomes.

Compliance with Ethical Standards

Conflict of interest Dr. Kyle Wilby reports no conflicts of interest.

Funding No funding was received for this manuscript.

References

1. World Health Organization. The top 10 causes of death. Global Disease Burden. World Health Organization. 2017. http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 14 Sept 2017.
2. Enoch DA, Ludlam HA, Brown NM. Invasive fungal infections: a review of epidemiology and management options. J Med Microbiol. 2006;55:809–18.
3. Pfaller MA, Pappas PG, Wingard JR. Invasive fungal pathogens: current epidemiological trends. Clin Infect Dis. 2006;43:S3–14.
4. Rybak JM, Marx KR, Nishimoto AT, Rogers PD. Isavuconazole: pharmacology, pharmacodynamics, and current clinical experience with a new triazole antifungal agent. Pharmacotherapy. 2015;35:1037–51.
5. Kim S, Kwon J, Park C, Han S, Yim D, Choi J, et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether B-cyclodextrin in haematological patients with renal impairment. Mycoses. 2016;59:644–51.
6. Moore JN, Healy JR, Kraft WK. Pharmacologic and clinical evaluation of posaconazole. Expert Rev Clin Pharmacol. 2015;8:321–34.
7. Natesan SK, Chandrasekar PH. Isavuconazole for the treatment of invasive *Aspergillosis* and *Mucormycosis*: current evidence, safety, efficacy, and clinical recommendations. Infect Drug Resist. 2016;9:291–300.
8. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387:760–9.
9. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR III, et al. Isavuconazole treatment for *Mucormycosis*: a single-arm open-label trial and case–control analysis. Lancet Infect Dis. 2016;16:828–37.
10. Thompson GR III, Rendon A, Riberio dos Santos R, Queiroz-Telles F, Ostrosky-Zeichner L, et al. Isavuconazole treatment of *Cryptococcosis* and dimorphic mycoses. Clin Infect Dis. 2016;63:356–62.
11. Viljoen J, Azie N, Schmitt-Hoffmann AH, Ghannoum M. A phase 2, randomized, double-blind, multicenter trial to evaluate the safety and efficacy of three dosing regimens of isavuconazole compared with fluconazole in patients with uncomplicated esophageal candidiasis. Antimicrob Agents Chemother. 2015;59:1671–9.
12. Jacobs SE, Saez-Lacy D, Wynkoop W, Walsh TJ. Successful treatment of allergic bronchopulmonary aspergillosis with isavuconazole: care report and review of the literature. Open Forum Infect Dis. 2017;4:ofx040.
13. Schmitt-Hoffmann A, Roos B, Heep M, Schleimer M, Weidekamm E, Brown T, et al. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 mg) and oral administrations (100, 200, and 400 mg) of its prodrug, BAL8557, in healthy volunteers. Antimicrob Agents Chemother. 2006;50:279–85.
14. Schmitt-Hoffmann A, Roos B, Maares J, Heep M, Spickerman J, Weidekamm E, et al. Multiple-dose pharmacokinetics and safety of the new antifungal triazole BAL4815 after intravenous infusion and oral administration of its prodrug, BAL8557, in healthy volunteers. Antimicrob Agents Chemother. 2006;50:286–93.
15. Townsend R, Kato K, Hale C, Kowalski D, Lademacher C, Yamazaki T, et al. Two phase I, open-label, mass balance studies to determine the pharmacokinetics of 14C-labeled isavuconazonium sulfate in healthy male volunteers. Clin Pharmacol Drug Dev. 2017;. https://doi.org/10.1002/cpdd.376.
16. Cornely OA, Bohme A, Schmitt-Hoffmann A, Ullmann AJ. Safety and pharmacokinetics of isavuconazole as antifungal prophylaxis in acute myeloid leukemia patients with neutropenia: results of a phase 2, dose escalation study. Antimicrob Agents Chemother. 2015;59:2078–85.
17. Kovanda LL, Marty FM, Maertens J, Desai AV, Lademacher C, Engelhardt M, et al. Impact of mucositis on absorption and systemic drug exposure of isavuconazole. Antimicrob Agents Chemother. 2017;61:1–10.
18. Desai A, Kovanda L, Kowalski D, Lu Q, Townsend R, Bonate PL. Population pharmacokinetics of isavuconazole from phase 1 and phase 3 (SECURE) trials in adults and target attainment in patients with invasive injections due to *Aspergillus* and other filamentous fungi. Antimicrob Agents Chemother. 2016;60:5483–91.
19. Kovanda LL, Desai AV, Lu Q, Townsend RW, Akhtar S, Bonate P, Hope WW. Isavuconazole population pharmacokinetic analysis using nonparametric estimation in patients with invasive fungal disease (results from the VITAL study). Antimicrob Agents Chemother. 2016;60:4568–76.
20. Schmitt-Hoffmann A, Roos B, Spickermann J, Heep M, Peterfai E, Edwards DJ, Stoeckel K. Effect of mild and moderate liver disease on the pharmacokinetics of isavuconazole after intravenous and oral administration of a single dose of the prodrug BAL8557. Antimicrob Agents Chemother. 2009;53:4885–90.
21. Townsend RW, Akhtar S, Alcorn H, Berg JK, Kowalski DL, Mujais S, Desai AV. Phase I trial to investigate the effect of renal impairment on isavuconazole pharmacokinetics. Eur J Clin Pharmacol. 2017;73:669–78.
22. Knoll BM. Pharmacokinetics of oral isavuconazole in a patient after Roux-en-Y gastric bypass surgery. J Antimicrob Chemother. 2014;69:3441–3.
23. Kovanda LL, Kolamunnage-Dona R, Neely M, Maertens J, Lee M, Hope WW. Pharmacodynamic of isavuconazole for invasive mold disease: role of galactomannan for real-time monitoring of therapeutic response. Clin Infect Dis. 2017;64:1557–63.
24. Keirns J, Desai A, Kowalski D, Lademacher C, Mujais S, Parker B, et al. QT interval shortening with isavuconazole: in vitro and in vivo effects on cardiac repolarization. Clin Pharmacol Ther. 2017;101:782–90.
25. Kaindl T, Engelhardt M, Townsend R, et al. Intra-subject variability and exposure-response relationship of isavuconazole in the phase 3 SECURE study in patients with invasive mould disease caused by *Aspergillus* spp. and other filamentous fungi. Abstract O424. Presented at European Society of Clinical Microbiology and Infectious Diseases (ECCMID) 26th Congress, 9–12 April 2016, Amsterdam, Netherlands.
26. Schwartz IS, Wiederhold NP. Update on therapeutic drug monitoring of antifungals for the prophylaxis and treatment of invasive fungal infections. Curr Fungal Infect Rep. 2017;11:75–83.