Int J Clin Exp Med 2016;9(8):16006-16015
www.ijcem.com /ISSN:1940-5901/IJCEM0032366

Original Article

Efficacy and safety comparison between intravenous and oral voriconazole: a systematic review and meta-analysis

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Received May 17, 2016; Accepted July 11, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: The primary objective of this study was to investigate whether the efficacy and safety of oral and intravenous voriconazole were comparable in different populations, including adults, children and patients with kidney or hepatic impairment. Two independent reviewers searched Medline, Embase, and Cochrane databases, three Chinese literature databases and one clinical trial registry platform. The inclusion criteria were the studies that evaluated fungal infections-related mortality, treatment success, renal, hepatic, neurologic dysfunction, visual disturbance incidence, steady-state trough concentration or attainment rate of target concentration between oral and intravenous voriconazole with label recommended dose. Two prospective and five retrospective cohort studies were included in this study. Results suggest higher success rate of anti-fungal therapy (RR = 0.66, 95% CI 0.47-0.92, P = 0.01) and lower steady-state trough concentration (MD = 1.17, 95% CI 0.28-2.06, P = 0.01) in oral group for adults. Renal dysfunction incidence was found increase in intravenous group for adults, but with no significant difference (RR = 2.25, 95% CI 0.30-16.71, P = 0.43). There were limited studies included for children, and steady-state trough concentration was found not significantly different between two formulations (MD = 0.15, 95% CI -0.66-0.95, P = 0.72). No eligible literature was found for the patients with renal or hepatic dysfunction. This meta-analysis highlights the need for high-quality studies to confirm and update the findings.

Keywords: Voriconazole, oral formulation, intravenous formulation, systematic review

Introduction

Voriconazole is a triazole antifungal agent, available as oral and intravenous formulations, with broad-spectrum antifungal activity against *Aspergillus*, *Candida* and *Fusarium* species [1-5]. Voriconazole label approved by U.S. Food and Drug Administration indicates the pharmacokinetics is comparable between intravenous and oral formulations with recommended dose in adults. However, it is frequently confounded by multiple factors in practical clinical settings, such as CYP2C19 genotype of the patient, drug-drug interactions and multiple diseases, which may have impacts upon clinical pharmacokinetics and outcomes [6]. Therefore, it is not clear whether the label recommended dose of intravenous and oral formulation could extrapolate to clinic efficacy and safety of voriconazole.

Furthermore, it is more indefinite to make sure whether the comparability is similar in different populations, such as children and kidney or hepatic impairment patients. It was reported the pharmacokinetics is significantly different between children and adults [7, 8]. Pharmacokinetics of voriconazole is proved to be linear in pediatrics, but nonlinear in adults [9, 10]. The oral bioavailability of voriconazole for pediatric patients is about 44.6%, which is significantly lower compared with about 96% in adults [8]. Accordingly, the efficacy and toxicity may display discrepantly between intravenous and oral

voriconazole in children. As we known, sulphobutylether-β-cyclodextrin (SBECD), as solubilizing agent, is contained in the voriconazole intravenous formulation [3, 11], which may be accumulated in patients with impaired renal function and induce kidney toxicity [11, 12]. Fortunately, no renal damage was found in patients with impaired renal function (CLcr<50 mL/min) in many clinical trials [2, 12, 13], which is inconsistent with label. Moreover, voriconazole is extensively metabolized by the liver, thus patients with hepatic impairment may have altered pharmacokinetics due to saturation of voriconazole metabolism [14]. It is reported that oral administration of the loading dose of voriconazole might result in a greater potential of liver damage due to higher portal vein concentrations [15]. Therefore, whether these two formulations can be substituted in renal and hepatic impaired patients remains unclear.

The objective of this study was to systematically investigate whether the clinical efficacy and safety were comparable between oral and intravenous voriconazole in different populations, including adults, children and kidney or hepatic impairment patients.

Methods

Data sources

Three English literature databases (MEDLINE, EMBASE, Cochrane Library), three Chinese literature databases (CNKI, Wanfang and CBM) and one clinical trial registry platform (Clinicaltrials.gov) were searched from the inception to March 4th, 2015. The search term was the combination of Medical Subject Headings term and text free term "voriconazole" in all databases and Clinicaltrials.gov.

Inclusion and exclusion criteria

Both interventional and observational studies comparing clinical outcomes of oral and intravenous voriconazole were eligible. There was no restriction in study population. Initial dosing regimen of voriconazole was restricted to label recommended dose to improve clinical feasibility of our results. For adults, the intravenous and oral doses were 3-4 mg/kg and 200 mg every 12 hours, respectively. For children, the intravenous doses were 7-8 mg/kg every 12 hours, and the oral doses were between 200 mg and 9 mg/kg (maximum 350 mg) every 12 hours. Reviews, letters, editorials, guidelines, case reports and pre-clinical studies were excluded. Language was restricted to English and Chinese.

Outcomes

The primary efficacy outcomes were defined as fungal infections-related mortality and treatment success. The primary safety outcomes included renal, hepatic, neurologic dysfunction incidence and visual disturbance incidence. Since it has been found that steady-state trough plasma concentration of voriconazole is related to its clinical efficacy and safety, steady-state trough concentration and attainment rate of target concentration were regarded as our secondary outcomes [16-19].

Literature screening

This study was a part of Practice Guideline for Individualized Medication of Voriconazole, which had been registered on the international clinical practice guidelines registry platform (registration number IPGRP-2015CN001). Literatures were divided into six parts, and reviewed by two members respectively according to the relevance with the guideline. The relevant studies were further examined by two reviewers (A.P.W and K.C) independently based on the inclusion criteria of this review through titles and abstracts. Last, full text of all studies that were potentially relevant was retrieved and reviewed. Disagreements were resolved by discussion with the third reviewer (C.Z).

Data extraction and quality assessment

Following data were extracted from identified studies: study design, setting, characteristics of patients, intervention and comparison (formulation, dosage, administration route and treatment duration), sample size, length of follow-up, time of sampling and relative definitions. Quality of randomized controlled trials (RCTs), pharmacokinetic interventional studies including cross-over randomized controlled trials and single arm before-and-after studies, and cohort studies were assessed using Cochrane risk of bias tool, modified risk-of-bias tool (Table S1) and Newcastle-Ottawa scales (NOS), respectively [20, 21]. With regard to the

Table 1. The characteristics of included studies

Reference	Study design, country	Populations	Sample size		Age		Gender (Male)		Weight (kg)		Follow-up time (d)	Time of sampling after initial therapy (d)
			IV	PO	IV	PO	IV	PO	IV	PO		
Bartelink 2013*	Retrospective cohort study, Netherlands	Children and young adults who received an allogeneic HSCT	33	9	2-12		58%		20 (11-50)[a]		NR	At least 3
Bruggemann 2011*	Retrospective cohort study, Netherlands	Children with hematological malignancy	3	5	3.67±1.15[b] (3-5)	5.20±2.95[b] (2-8)	1	2	16.17±2.06[b]	21.22±7.76[b]	NR	5 (3.0-19.5)[a]
Driscoll 2011	Single arm before-and-after study, USA	Immunocompromised children	36	33	5.4 ±3.0[b] (2-11)		NR	NR	22.9 ±12.2[b] (10.8-54.5)		30 after the last dose	7
		Healthy adults	33	34	35.3±7.8[b] (22-55)		NR	NR	75.1±11.2[b] (49.0-97.0)			
Imataki 2008	Retrospective cohort study, Japan	Patients with hematological malignancy	8	12	54.75±16.14[b]	56.42±15.42[b]	7	9	NR	NR	14	NR
Mori 2015	Single arm before-and-after study, Japan	Immunocompromised pediatric patients	14	14	7.7 (3-11)[a]	7.7 (3-11)[a]	NR	NR	25.3 (11.5-43.0)[a]	25.3 (11.5-43.0)[a]	30 (±7) after last dose	7
Okuda 2008	Retrospective cohort study, Japan	Patients with deep mycosis	7	21	58.2±23.2[b] (18-85)		NR	NR	51.8±8.97[b] (40-63)		NR	5
Wang 2014	Retrospective cohort study, China	Proven or probable IFI, use voriconazole >14 d	39	61	67.90±19.17[b] (18-99)	59.84±20.80[b] (18-95)	30	45	59.72±5.61[b]	58.69±8.50[b]	NR	8 (3-51)[a] after first dose

[a]Median (range); [b]Mean ± SD; *Maintenance doses were adjusted based on results of TDM after initial administration. HSCT: Hematopoietic stem cell transplantation; IFI: Invasive fungal infection; NR: Not reported.

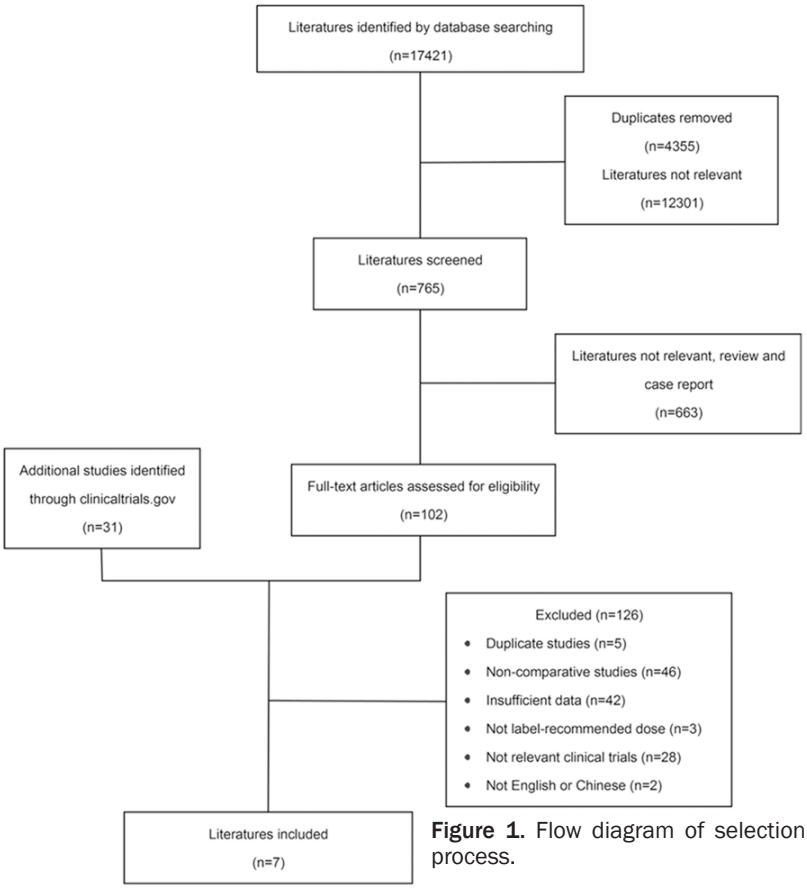

Figure 1. Flow diagram of selection process.

Table 2. Quality appraisal of cohort studies

Reference	1[a]	2[b]	3[c]	4[d]	5A[e]	5B[f]	6[g]	7[h]	8[i]
Bartelink 2013	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes
Bruggemann 2011	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes
Imataki 2008	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes
Okuda 2008	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	Yes
Wang 2014	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes

[a]Indicates exposed cohort truly representative. [b]Non-exposed cohort drawn from the same community. [c]Ascertainment of exposure from a secure record. [d]Outcome of interest not present at start of study. [e]Cohorts comparable on basis of genotype of CYP2C19 and drug-drug interactions. [f]Cohorts comparable on other factors, such as age, weight, etc. [g]Assessment of outcome of record linkage or independent blind assessment. [h]Follow-up long enough for outcomes to occur. [i]Complete accounting for cohorts. NR: Not reported.

fifth item of NOS, the genotype of CYP2C19 and drug-drug interactions were regarded as the most critical indicator that affected comparability between the two cohorts [14, 22]. Two authors (A.P.W and K.C) extracted data and assessed the risk of bias independently. Disagreements were resolved by discussion with the third reviewer (C.Z). We contacted the study's corresponding author for required data if necessary. If specific data couldn't be obtained, the literature was not eligible.

Data synthesis and analysis

Different subpopulations were analyzed separately, including adults (more than 18 years old) and children (2-12 years old) and patients with kidney or hepatic impairment. Meta-analyses were performed using RevMan software, version 5.1 (Nordic Cochrane Centre, The Cochrane Collaboration). Risk ratios (RRs) and mean differences (MD) with 95% confidence intervals (CIs) were calculated to indicate dichotomous and continuous pooled outcomes, respectively. The median and range were converted to mean and standard deviation for further analysis by the method reported by Hozo, *et al* [23]. The Cochrane Q χ^2 test and I^2 statistic were used to assess heterogeneity among studies. $P<0.1$ was considered significant considering the low statistical power of the χ^2 test for heterogeneity. In case that $P<0.1$ as well as $I^2>50\%$, random effect model was used as the analysis model. Otherwise, fixed effect model was used. Subgroup analyses were conducted according to the study design.

Results

Literature selection and study description

The study selection process for inclusion is shown in **Figure 1**. Two pharmacokinetic before-and-after and five cohort studies were included in this systematic review. A summary description of the included studies is presented in **Table 1**. Raw data of each outcome is

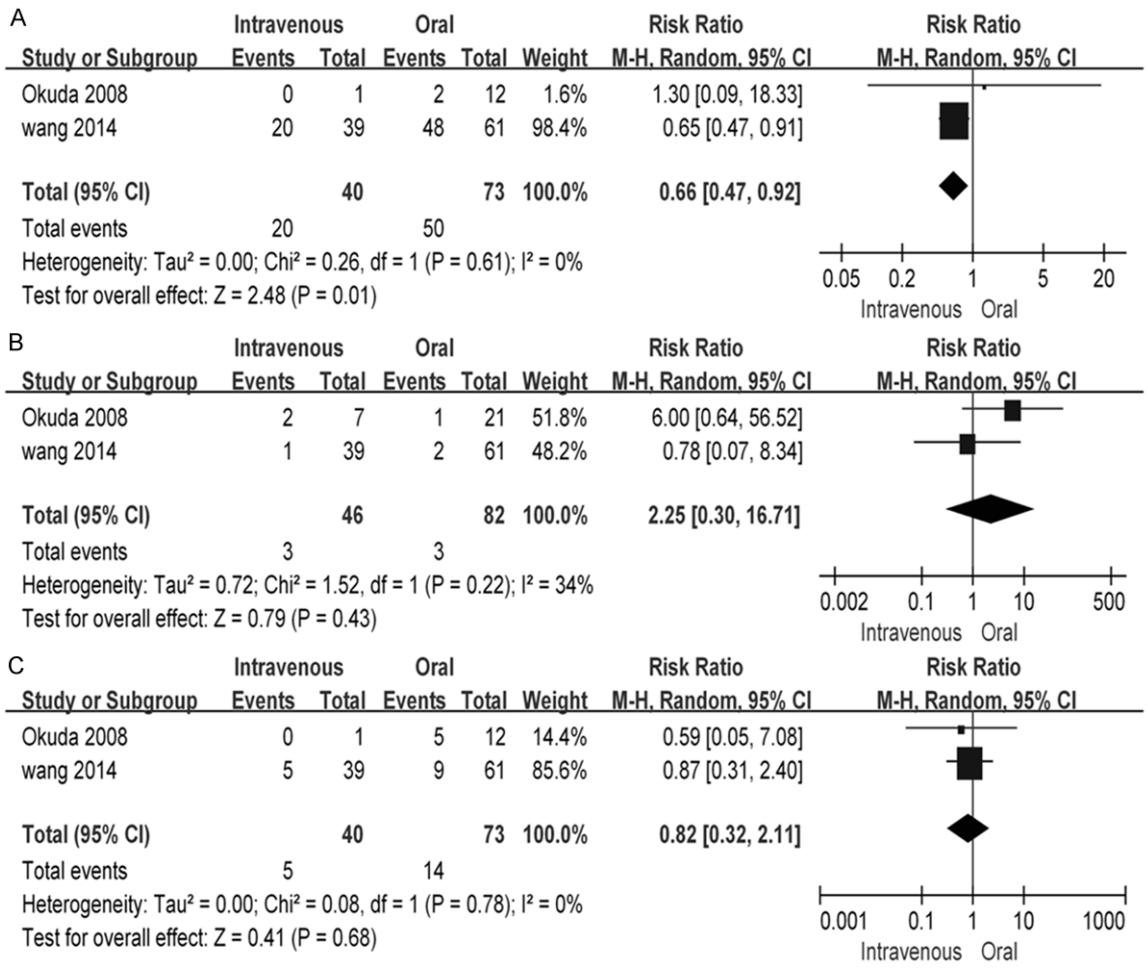

Figure 2. Risk ratios of success rate of anti-fungal therapy (A), renal (B) and hepatic (C) dysfunction incidence in adults: intravenous versus oral. (A) Test for overall effect: Z = 2.48 P = 0.01; (B) Test for overall effect: Z = 0.79 P = 0.43. (C) Test for overall effect: Z = 0.41 P = 0.68.

presented in Table S2. Diagnosis criteria of invasive fungal infections (IFI) were defined following definition by European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) in three studies [24-26]. Clinical response of voriconazole was defined in three studies [25-27]. Toxicity outcomes were reported in two studies based on Common Terminology Criteria for Adverse Events (CTCAE) (Table S3) [25, 27].

Quality of included studies

Both pharmacokinetic before-and-after studies [28, 29] were under high risk of bias for items of random sequence generation, carry over effect and incomplete outcome data due to absence of control group, wash out period and presence of drop out during latter intervention, respectively. The quality assessments of 5 cohort studies [24-27, 30] were shown in **Table 2**.

Efficacy outcomes

Treatment success

Adults: There were two cohort studies [25, 27] included. Significantly increased treatment success rate was found in oral group (RR = 0.66, 95% CI 0.47-0.92, P = 0.01, **Figure 2A**). No significant heterogeneity was found among these two studies (I^2 = 0%, P = 0.61).

Children: There was only one cohort study [26] included. Two and four children in intravenous (n = 3) and oral (n = 5) groups achieved therapeutic targets, respectively, with no statistical difference.

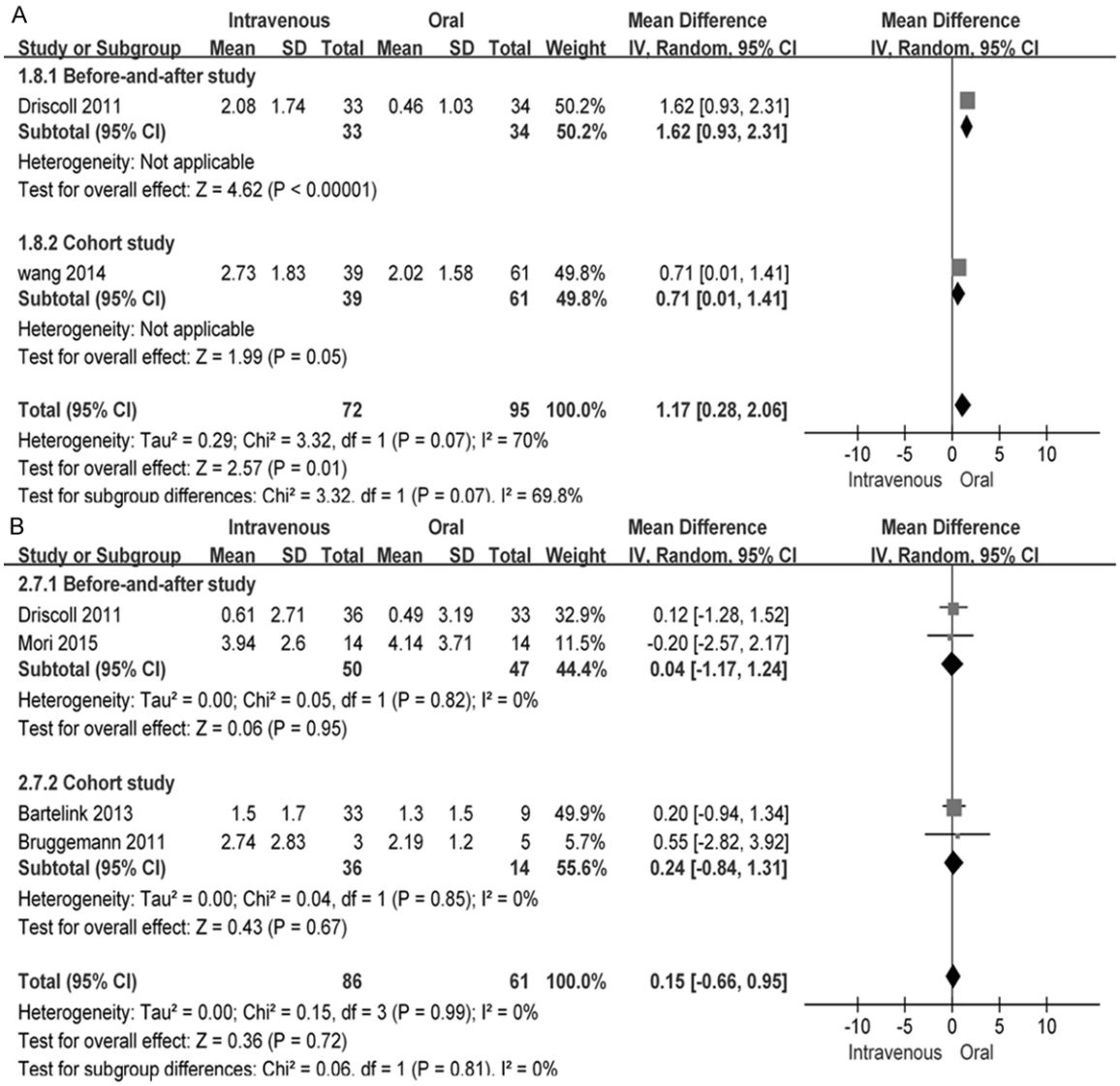

Figure 3. Mean difference of steady-state trough concentration in adults (A) and children (B) (subgroup analysis by study design): intravenous versus oral. (A) Test for overall effect: Z = 2.57 P = 0.01; test for overall effect in before-and-after studies: Z = 4.62 P<0.00001; test for overall effect in cohort studies: Z = 1.99 P = 0.05; (B) Test for overall effect: Z = 0.36 P = 0.72; test for overall effect in before-and-after studies: Z = 0.06 P = 0.95; test for overall effect in cohort studies: Z = 0.43 P = 0.67.

Safety outcomes

Renal dysfunction incidence: For adults, there were two cohort studies [25, 27] included. Increasing trends of renal dysfunction incidence was observed in intravenous group, but no significant statistic difference was found (RR = 2.25, 95% CI 0.30-16.71, P = 0.43, **Figure 2B**). No significant heterogeneity was detected among these two studies (I^2 = 34%, P = 0.22).

Hepatic, neurologic dysfunction and visual disturbance: There were two [25, 27], one [27] and one [30] cohort studies included to compare hepatic, neurologic dysfunction and visual disturbance in adults, respectively. And one cohort study [26] was found to compare these three safety outcomes in children. No statistical difference was found between intravenous and oral formulations for these three outcomes in adults and children, separately (**Figure 2C** and Table S2).

Secondary outcomes

Steady-state trough concentration: There were one before-and-after study [28] and one cohort study [25] included to compare steady-state trough concentration in adults. Significantly higher steady-state trough concentration was found in intravenous group (MD = 1.17, 95% CI 0.28-2.06, P = 0.01, **Figure 3A**), and significant heterogeneity was found between these two studies (I^2 = 70%, P = 0.07).

With regards to children, there were two before-and-after studies [28, 29] and two cohort studies [30, 31] included. No significant difference was found between intravenous and oral groups (MD = 0.15, 95% CI -0.66-0.95, P = 0.72, **Figure 3B**). No significant difference was shown between intravenous and oral groups through analysis of before-and-after studies (MD = 0.04, 95% CI -1.17-1.24, P = 0.95, **Figure 3B**) and cohort studies separately (MD = 0.24, 95% CI -0.84-1.31, P = 0.67, **Figure 3B**). No significant heterogeneity was found among these four studies (I^2 = 0%, P = 0.99).

Outcomes for patients with kidney or hepatic impairment

Though systematic literature-screening process had been performed according to the inclusion and exclusion criteria, none of the literature was eligible to compare clinical efficacy with safety outcomes in the patients with kidney or hepatic impairment.

Discussion

To our knowledge, this is the first systematic review to compare the efficacy and safety of voriconazole between oral and intravenous formulations in different populations. In our study, it is unexpected to find that the success rate of anti-fungal therapy in oral group was significantly higher only in adults, but not in children. This result may be related to the difference of genetic polymorphism of CYP2C19 and drug-drug interactions of voriconazole. Studies had shown that CYP2C19 enzyme was chiefly responsible for the metabolism of voriconazole [1, 32], and it had been found that the genetic polymorphism of CYP2C19 might affect voriconazole plasma levels [5, 31]. Besides, pharmacokinetic concentrations of voriconazole, especially trough concentrations, might affect clinical response and adverse events [6, 33]. Based on the polymorphism of CYP2C19, individuals can be classified into ultra-rapid metabolizers (*1/*17), extensive metabolizers (*1/*1), intermediate metabolizers (*1/*2, *1/*3), and poor metabolizers (*2/*2, *2/*3, *3/*3) [25]. For ultrarapid and extensive metabolizers, considerably lower voriconazole levels had been found than poor metabolizers, thus potentially leading to therapeutic failure and clinical deterioration [6, 34, 35]. Moreover, drug-drug interaction is another factor which may contribute to the result. The metabolic pathway of voriconazole involves CYP2C19, with CYP2C9 and CYP3A4 being involved to a lesser extent [36]. As such, it has the potential for numerous drug interactions in clinical settings [36, 37]. If combined medication were not well controlled, the comparability of clinical outcomes between two formulations may be affected.

Steady-state trough concentration was indicated to be an indicator of clinical efficacy and toxicity of voriconazole [16-19]. However, in this analysis, it was surprised to find that higher steady-state trough concentration was coupled with lower success rate of therapy in intravenous group. These contradictory results illustrated that steady-state trough concentration may not accurately reflect the efficacy and toxicity of voriconazole [6]. And it was indicated that minimal inhibitory concentration (MIC) should be considered as a powerful impact upon exposure-response relationships, which showed that free trough/MIC ratio was associated with a higher probability of clinical response [6, 38, 39]. That is, if higher MIC is encountered in intravenous group, a lower success rate of therapy may be expected.

In this systematic review, we found more renal dysfunction incidence in adult when administering intravenous voriconazole compared with oral administration, but no statistical significance was found. This may be explained by the fact that SBECD is a second-generation cyclodextrin, which does not significantly concentrate in the intracellular tissues of the kidney compared with first-generation unmodified cyclodextrins, thus attenuating the potential to harm the kidney [40]. Though, close monitoring is still demanded when intravenous voriconazole is used, especially for the patients with impaired renal function.

In this study, we supposed to further compare the efficacy and safety outcomes between oral and intravenous voriconazole in different populations. However, only limited data were found in children, and no eligible data were obtained in patients with kidney or hepatic impairment. More studies are needed to be developed to identify the comparability of clinical efficacy and safety for intravenous and oral voriconazole in these specific populations.

Some limitations should be considered when managing our results. Limited studies were found and all included studies were not randomized and controlled, of which the patient's CYP2C19 genotype, illness condition, potential drug-drug interactions and other factors between intravenous and oral groups may not comparable.

Conclusions

The present systematic review and meta-analysis demonstrates a significant higher success rate of anti-fungal therapy in oral group for adults, however, coupled with a lower steady-state trough concentration. There were limited studies included for children, and steady-state trough concentration was found not significantly different between two formulations. Future high-quality studies that clearly define the study population, age, weight, dose and administration route, genotype of CYP2C19 and drug-drug interactions are needed to confirm and update the findings.

Acknowledgements

We thank all members who participate Chinese Practice Guideline for Individualized Medication of Voriconazole for their whole-hearted cooperation.

Disclosure of conflict of interest

None.

Authors' contribution

Conceived and designed the experiments: SDZ, CZ, APW, KC; Performed the experiments: APW, KC, HYJ; Analyzed the data: APW, KC; Contributed reagents/materials/analysis tools: KC, HYJ; Wrote the paper: APW; Revised the manuscript: APW, KC, CZ; Approved the final version of the manuscript: APW, KC, HYJ, SDZ, CZ.

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Table S1. Modified risk-of-bias tool for pharmacokinetic before-and-after studies

Item	Description
1. Random sequence generation	Describe the method used to generate the allocation sequence insufficient detail.
2. Carry-over effect	Evaluate the carry-over effect and provide relevant information.
3. Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis.
4. Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
5. Comparability	Evaluate the baseline comparability between the comparisons.
6. Pharmacokinetic design	Evaluate the method used to calculate pharmacokinetic parameters and conduct pharmacokinetic studies.
7. Other sources of bias	Describe other possible sources of bias introduced to the study.

Table S2. The outcomes of included studies

Reference	IFI related mortality		Clinical response		Renal dysfunction		Hepatic dysfunction		Neurologic dysfunction		Visual disturbance		Steady-state trough concentration (μg/ml)		Rate of target concentration achievement	
	IV	PO	IV	PO	IV	PO	IV	PO	IV	PO	IV	PO	IV	PO	IV	PO
Bartelink 2013	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.5±1.7 (n = 33)	1.3±1.5 (n = 9)	NR	NR
Bruggemann 2011	NR	NR	2/3	4/5	NR	NR	1/3	1/5	0/3	0/5	0/3	0/5	2.74±2.83 (n = 3)	2.19±1.20 (n = 5)	NR	NR
Driscoll 2011	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.61±2.71 (n = 36)	0.49±3.19 (n = 33)	NR	NR
	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2.08±1.74 (n = 33)	0.46±1.03 (n = 34)	NR	NR
Imataki 2008	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0/8	6/12	NR	NR	NR	NR
Mori 2015	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3.94±2.60 (n = 14)	4.14±3.71 (n = 14)	NR	NR
Okuda 2008	NR	NR	0/1*	2/12*	2/7	1/21	0/1	5/12	0/1	1/12	NR	NR	NR	NR	NR	NR
Wang 2014	NR	NR	20/39	48/61	1/39	2/61	5/39	9/61	NR	NR	NR	NR	2.73±1.83 (n = 39)	2.02±1.58 (n = 61)	NR	NR

*β-d-glucan assay was used to assess the response to treatment. IFI: Invasive fungal infection; IV: intravenous; PO: oral; NR: Not reported.

Table S3. Definition of outcomes for included studies

Reference	IFI diagnosis criteria	Clinical response	Renal dysfunction	Hepatic dysfunction	Neurologic dysfunction	Visual disturbance
Bartelink 2013	EORTC/MSG	NR	NR	NR	NR	NR
Bruggemann 2011	EORTC-MSG	EORTC-MSG	NR	NR	NR	NR
Driscoll 2011	NR	NR	NR	NR	NR	visual questionnaire, distance visual acuity testing, and color vision testing; visual fixation
Imataki 2008	Possible or probable IFI was defined	NR	NR	NR	NR	NR
Mori 2015	NR	NR	NR	NR	NR	NR
Okuda 2008	NR	Either of the β-D-glucan or Aspergillus antigen decreased below the standard	CTCAE v 3.0	CTCAE v 3.0	CTCAE v 3.0	CTCAE v 3.0
Wang 2014	EORTC/MSG	Success and lack of response were defined	CTCAEv.4.03	CTCAEv.4.03	CTCAEv.4.03	CTCAEv.4.03

IFI: Invasive fungal infection; EORTC/MSG: European Organization for Research and Treatment of Cancer/Mycoses Study Group; CTCAE: Common Terminology Criteria for Adverse Events; NR: Not reported.