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The effectiveness and safety of posaconazole enteric-coated tablet versus oral suspension in invasive fungal infections

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Posaconazole enteric-coated tablet and oral suspension are two oral drugs in the treatment of invasive fungal infections (IFIs). This study compared the effectiveness and safety between posaconazole enteric-coated tablet and oral suspension, and provided a real world basis for the clinical practice. A retrospective cohort study was performed on IFIs patients treated with posaconazole enteric–coated tablet or oral suspension. The primary endpoints were in-hospital mortality, treatment discontinuation rate and clinical effective rate. The secondary endpoints were adverse events incidence (liver dysfunction, renal dysfunction and hypokalemia). One hundred and forty-four patients were totally included and divided into enteric-coated tablet group ($n = 46$) and oral suspension group ($n = 98$). There was no significant difference in effectiveness and safety between two groups. The female (OR = 0.130, $P = 0.018$) and diabetes mellitus (OR = 4.242, $P = 0.003$) were independently associated with combined in-hospital mortality/treatment discontinuation rate. The renal replacement therapy (OR = 10.071, $P = 0.006$), hypoalbuminemia (OR = 6.646, $P = 0.002$) and posaconazole duration (OR = 1.119, $P = 0.002$) were risk factors for liver dysfunction. The posaconazole enteric-coated tablet has comparable effectiveness and safety with oral suspension in IFIs, which need large-scale cases studies to confirm in the future.

Keywords Posaconazole enteric-coated tablet, Posaconazole oral suspension, Invasive fungal infections, Effectiveness, Safety

Invasive fungal infections (IFIs) refer to the diseases in which fungi invades and grow in the human body, then causes inflammatory reaction and tissue damage[1]. IFIs are mostly found in immune compromised patients such as hematological diseases, malignancies and hematopoietic stem cell transplantation leading to the prolonged hospital stay and increased total treatment costs and mortality[1]. The incidence of IFIs in China patients with hematologic tumors is 8.3%, which may be lower than the actual value due to missed diagnosis[2,3]. Voriconazole, posaconazole and isavuconazole are the first-line recommended drugs for invasive aspergillosis[4–6]. As a second-generation triazole antifungal drug, posaconazole has broad-spectrum antifungal activity against most Aspergillus, Candida and Mucor[7]. At present, there are three available formulation of posaconazole in China including enteric-coated tablet listed in 2018, oral suspension listed in 2013 and injection listed in 2021.

Due to large individual pharmacokinetic differences, the plasma concentration of posaconazole oral suspension is influenced by various factors leading to the potential therapeutic failure[8]. The bioavailability of posaconazole oral suspension is greatly affected by foods, gastric pH and gastrointestinal motility, whereas enteric-coated tablet avoids these limitations[9–12]. Studies have reported that patients receiving posaconazole enteric-coated tablet reached higher plasma concentrations than those receiving oral suspension[13–17]. However, there is still lack of real world data comparing clinical effectiveness and safety between posaconazole enteric-coated tablet and oral suspension, which causes confusion in clinical practice. Therefore, the objective of this study was to retrospectively evaluate the effectiveness and safety of posaconazole enteric-coated tablet and oral suspension in patients with IFIs, and to provide evidence-based basis for clinical application.

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Methods

Study design and participants

This study was a retrospective cohort study conducted in The First Affiliated Hospital of Shandong First Medical University, a tertiary university hospital in China. We screened patients of IFIs from June 2021 to March 2024. The data of this study was collected from Shandong Provincial Qianfoshan Hospital Healthcare Big Data Platform (SPQHHBDP). The SPQHHBDP integrates multi-source data from hospital information system (HIS), electronic medical records (EMR), laboratory information management system (LIS), picture archiving and communication system (PACS), nursing information system. The encrypted personal identification number was used as a unique identifier to interlink each person's data information in the above-mentioned database. Patients inclusion criteria: (1) inpatients who meet the criteria for probable and proven diagnosis of IFIs[18]; (2) patients were administered with posaconazole enteric-coated tablet or oral suspension during hospitalization; (3) posaconazole duration more than 3 days. Patients exclusion criteria: (1) posaconazole enteric-coated tablet and oral suspension were used during the same hospitalization; (2) incomplete clinical information, such as absence of important laboratory tests; (3) pregnant and lactating patients.

Treatment and grouping

All patients were treated with posaconazole enteric-coated tablet or oral suspension according to clinical guidelines[4–7]. Patients were divided into posaconazole enteric-coated tablet group (POS-Tab group) and oral suspension group (POS-OS group). This study met the hospital ethics standards and had been approved by the Medical Ethics Committee of the First Afliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital) (approval number: YXLL-KY-2023 (097)). The study is retrospective in nature, therefore the requirement for informed consent was waived by the Medical Ethics Committee of the First Afliated Hospital of Shandong First Medical University (Shandong Provincial Qianfoshan Hospital). And all procedures were conducted by the principles of the Declaration of Helsinki.

Evaluation of effectiveness and safety

The baseline characteristics, disease prognosis and laboratory tests were collected. The effectiveness endpoints of this study included in-hospital mortality, treatment discontinuation rate, combined in-hospital mortality/treatment discontinuation rate and clinical effective rate. In-hospital death was defined as the death due to disease deterioration or other reasons during hospitalization and death discharge diagnosis[19]. Treatment discontinuation was defined as the discontinue treatment due to the continuous disease aggravation[20]. Clinical effectiveness was defined as the recovery to normal, the improvement of clinical symptoms, microbiological examination and laboratory examination including white blood cell count, C-reactive protein and procalcitonin.

The safety endpoints of this study included liver dysfunction [elevations of alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin and γ-glutamyl transpeptidase (γ-GT)], renal dysfunction (elevations of blood creatinine and urea nitrogen) and hypokalemia. The evaluation criteria of safety endpoints referred to the adverse event evaluation criteria of CTCAE 5.0 version[21]。 The multivariate logistic regression analyses were performed to correct and eliminate the impact of baseline difference on the effectiveness and safety. At the same time, univariate and multivariate logistic regression analyses were used to evaluate the influencing factors of combined in-hospital mortality/treatment discontinuation rate and liver dysfunction.

Statistical analysis

In this study, SPQHHBDP (based on R programming language) was used for statistical analysis. Continuous data were presented as mean and standard deviation (The independent-samples T test was used) if normally distributed otherwise median and range (The Wilcoxon rank-sum test was used). Categorical data were presented as numbers and percentages (The chi-square test was used).

Results

In this study, 494 patients were administered with posaconazole enteric-coated tablet or oral suspension more than 3 days during hospitalization. 144 patients with probable diagnosis and proven diagnosis of IFIs were finally included. In all included patients, 46 cases received posaconazole enteric-coated tablet (POS-Tab group) and 98 cases received posaconazole oral suspension (POS-OS group). The baseline characteristics of all included patients were shown in Table 1. The differences of age, leukemia, transplant status, diabetes mellitus, mechanical ventilation, neutropenia, combined immunosuppressant of cyclosporine and methotrexate, mean hospital stay and posaconazole daily dose between two groups were significant ($P < 0.05$).

Effectiveness outcomes

The total in-hospital mortality was 4.2% (6/144), including 4 cases in POS-Tab group and 2 cases in POS-OS group. The total treatment discontinuation rate was 12.5% (18/144), including 6 cases in POS-Tab group and 12 cases in POS-OS group. In total, the combined in-hospital mortality/treatment discontinuation rate was 16.7% (24/144). The total clinical effective rate was 54.2% (78/144).

After the multivariate logistic regression analysis correction, the in-hospital mortality, treatment discontinuation rate, combined in-hospital mortality/treatment discontinuation rate and clinical effective rate between the two groups showed no significant difference ($P < 0.05$) (Table 2).

The results of univariate and multivariate logistic regression analysis showed that female (OR = 0.130, $P = 0.018$) and diabetes mellitus (OR = 4.242, $P = 0.003$) were independently associated with combined in-hospital mortality/treatment discontinuation rate ($P < 0.05$) (Table 3).

Baseline characteristics	POS-Tab ($n=46$)	POS-OS ($n=98$)	Total ($n=144$)	*P* value
Population characteristics				
Age(years)/M (P25, P75)	55.0(17.0,67.0)	37.5(13.0,53.5)	39.0(14.5,58.0)	0.003
Male/case (%)	31(67.4%)	54(55.1%)	85(59.0%)	0.162
Concomitant disease/case (%)				
Leukemia	9(19.6%)	61(62.2%)	70(51.4%)	< 0.001
Lymphadenoma	1(2.2%)	4(4.1%)	5(3.5%)	0.924
Myelodysplastic syndrome	/	3(3.1%)	3(2.1%)	0.551
Solid tumor	6(13%)	3(3.1%)	9(6.2%)	0.053
Transplant status	18(39.1%)	58(59.2%)	76(52.8%)	0.025
Diabetes mellitus	15(32.6%)	14(14.3%)	29(20.1%)	0.011
GVHD(graft versus host disease)	9(19.6%)	34(34.7%)	43(29.9%)	0.064
Concomitant status/case (%)				
Renal replacement therapy	6(13.0%)	3(3.1%)	9(6.2%)	0.053
Mechanical ventilation	10(21.7%)	4(4.1%)	14(9.7%)	0.002
Hypoalbuminemia (< 30 g/L)	6(13.0%)	12(12.2%)	18(12.5%)	0.893
Neutropenia($< 1.5\times10^9$/L)	7(15.2%)	64(65.3%)	71(49.3%)	< 0.001
Infection site/case (%)				
Pulmonary infection	45(97.8%)	85(86.7%)	130(90.3%)	0.073
Bloodstream infection	8(17.4%)	24(24.5%)	32(22.2%)	0.339
Abdominal infection	1(2.2%)	3(3.1%)	4(2.8%)	> 0.999
Urinary infection	2(4.3%)	2(2%)	4(2.8%)	0.809
Culture of the pathogen/case (%)				
Aspergillus	30(65.2%)	63(64.3%)	93(64.6%)	0.913
Mucor	5(10.9%)	10(10.2%)	15(10.4%)	> 0.999
Combined antifungals/case (%)				
Caspofungin	11(23.9%)	16(16.3%)	27(18.8%)	0.277
Micafungin	/	6(6.1%)	6(4.2%)	0.205
Amphotericin B Liposome	5(10.9%)	3(3.1%)	8(5.6%)	0.129
Amphotericin B Cholesteryl Sulfate	/	4(4.1%)	4(2.8%)	0.398
Flucytosine	3(6.5%)	1(1%)	4(2.8%)	0.184
Combined immunosuppressant				
Methylprednisolone	17(37.0%)	31(31.6%)	48(33.3%)	0.527
Prednisone	6(13.0%)	8(8.2%)	14(9.7%)	0.535
Cyclosporin	4(8.7%)	47(48%)	51(35.4%)	< 0.001
Tacrolimus	4(8.7%)	6(6.1%)	10(6.9%)	0.830
Lucotinib	3(6.5%)	10(10.2%)	13(9.0%)	0.684
Methotrexate	2(4.3%)	27(27.6%)	29(20.1%)	0.001
Rituximab	1(2.2%)	11(11.2%)	12(8.3%)	0.131
Therapeutic regimen				
Posaconazole duration (Days)/M(P25, P75)	7.5(4.2,11.5)	10.0(5.2,16.0)	9.0(5.0,15.0)	0.073
Mean hospital stay (Days)/M(P25, P75)	16.0(7.0,28.0)	26.0(11.0,36.0)	22.5(9.0,33.0)	0.027
Posaconazole daily dose (mg)/M(P25, P75)	300.0(200.0,300.0)	600.0(541.9,800.0)	591.7(300.0,638.1)	< 0.001
Number of therapeutic drugs monitored patients	8(17.4%)	12(12.2%)	20(13.9%)	0.405

Table 1. The baseline characteristics of patients in the two groups. POS-Tab: posaconazole enteric-coated tablet; POS-OS: posaconazole oral suspension.

Safety outcomes

In this study, the total liver dysfunction rate was 20.8% (30/144), including 8 cases in POS-Tab group and 22 cases in POS-OS group. The total renal dysfunction rate was 11.8% (17/144), including 7 cases in POS-Tab group and 10 cases in POS-OS group. The total hypokalemia rate was 20.8% (30/144), including 7 cases in POS-Tab group and 23 cases in POS-OS group. There was no significant differences in safety endpoints between two groups ($P > 0.05$). In addition, the multivariate logistic regression analysis correction obtained the same statistical results (Table 4).

The results of univariate and multivariate logistic regression analysis showed that renal replacement therapy (OR = 10.071, $P = 0.006$), hypoalbuminemia (OR = 6.646, $P = 0.002$) and posaconazole duration (OR = 1.119, $P = 0.002$) were independently associated with liver dysfunction (Table 5).

Effectiveness/ case (%)	POS-Tab ($n=46$)	POS-OS ($n=98$)	Total ($n=144$)	*P* Value	Correction for the multivariate logistic regression analysis		
					OR	95%CI	*P* value
In-hospital mortality	4(8.7%)	2(2.0%)	6(4.2%)	0.157	1.785	0.068 ~ 85.503	0.739
Treatment discontinuation rate	6(13.0%)	12(12.2%)	18(12.5%)	0.893	0.451	0.101 ~ 1.765	0.268
Combined in-hospital mortality/ treatment discontinuation rate	10(21.7%)	14(14.3%)	24(16.7%)	0.263	0.539	0.126 ~ 2.015	0.375
Clinical effective rate	24(52.2%)	54(55.1%)	78(54.2%)	0.742	1.699	0.657 ~ 4.561	0.281

Table 2. Comparison of effectiveness between two groups and correction for multivariate logistic regression analysis. POS-Tab: posaconazole enteric-coated tablet; POS-OS: posaconazole oral suspension.

Influencing factors	Univariate analysis		Multivariate logistic regression analysis		
	χ^2/w value	*P* value	OR	95%CI	*P* value
Age (years)/M (P25, P75)	988.500	0.016	0.985	0.951 ~ 1.016	0.369
Female	4.830	0.028	0.130	0.017 ~ 0.572	0.018
Leukemia	4.359	0.037	1.952	0.519 ~ 8.234	0.334
Diabetes mellitus	9.983	0.002	9.021	1.692 ~ 59.975	0.014
Renal replacement therapy	41.813	< 0.001	1462509268.657	0 ~ NA	0.991
Mechanical ventilation	25.319	< 0.001	4.339	0.492 ~ 32.542	0.149
Aspergillus	6.612	0.010	0.850	0.237 ~ 3.250	0.805

Table 3. Univariate and multivariate logistic regression analyses influencing the combined in-hospital mortality/treatment discontinuation rate.

Safety/case (%)	POS-Tab ($n=46$)	POS-OS ($n=98$)	Total ($n=144$)	*P* value	Correction for the multivariate logistic regression analysis		
					OR	95%CI	*P* value
Liver dysfunction	8(17.4%)	22(22.4%)	30(20.8%)	0.486	0.561	0.152 ~ 1.936	0.367
Elevations of ALT	5(10.9%)	8(8.2%)	13(9%)	0.829	0.699	0.105 ~ 3.884	0.688
Elevations of AST	2(4.3%)	7(7.1%)	9(6.2%)	0.782	0.716	0.062 ~ 6.088	0.765
Elevations of total bilirubin	5(10.9%)	5(5.1%)	10(6.9%)	0.359	1.051	0.154 ~ 7.355	0.959
Elevations of γ-GT	3(6.5%)	17(17.3%)	20(13.9%)	0.080	0.202	0.029 ~ 1.045	0.073
Renal dysfunction	7(15.2%)	10(10.2%)	17(11.8%)	0.385	0.238	0.045 ~ 1.027	0.068
Elevations of blood creatinine	3(6.5%)	5(5.1%)	8(5.6%)	> 0.999	0.235	0.027 ~ 1.494	0.148
Elevations of urea nitrogen	5(10.9%)	7(7.1%)	12(8.3%)	0.666	0.308	0.053 ~ 1.547	0.166
Hypokalemia	7(15.2%)	23(23.5%)	30(20.8%)	0.256	0.476	0.125 ~ 1.676	0.257

Table 4. Comparison of safety between two groups and correction for multivariate logistic regression analysis. POS-Tab: posaconazole enteric-coated tablet; POS-OS: posaconazole oral suspension.

Discussion

IFIs can lead to serious damage of body and function, and even serious life-threatening[22,23]. The triazole antifungals, especially posaconazole, play an important role in antifungal therapy and reduce the mortality of IFIs without increasing the risk of adverse reactions[24]. Compared to posaconazole oral solution, posaconazole solid formulations including tablets and capsules yielded higher mean blood concentration and oral bioavailability through increasing the intestinal solubility of posaconazole under fasted and fed conditions[25]. It has been shown that the overall mortality of IFIs can reach 30% after antifungal therapy alone[26]. Maertens et al. reported that the 6-week mortality of IFIs after posaconazole treatment was 15%, which was close to the combined in-hospital mortality/treatment discontinuation rate (16.7%) in this study[27]. In addition, the total clinical effective rate of posaconazole in this study was 54.2% and consistent with the reported result[9,27]. The clinical effective rate of posaconazole enteric-coated tablet and oral suspension was similar, which verified the excellent clinical efficacy of different posaconazole formulations.

Influencing factors	Univariate analysis		Multivariate logistic regression analysis		
	χ^2/w value	*P* value	OR	95%CI	*P* value
Renal replacement therapy	4.952	0.026	10.071	1.885 ~ 56.519	0.006
Hypoproteinemia	12.728	< 0.001	6.646	2.004 ~ 23.168	0.002
Combination with methylprednisolone	4.737	0.030	1.025	0.335 ~ 3.008	0.964
Posaconazole duration	860.000	< 0.001	1.119	1.045 ~ 1.209	0.002
Mean hospital stay	1018.500	0.001	1.017	0.984 ~ 1.051	0.302

Table 5. Univariate and multivariate logistic regression analyses influencing the liver dysfunction.

In this study, the female and diabetes mellitus were independently correlated with poor prognosis. The combined in-hospital mortality/treatment discontinuation rate in female patients was lower than that in male patients. This is consistent with the results of recent studies that male was one of the risk factors for incidence and mortality of IFIs[28,29]. The diabetes mellitus has been verified as a risk factor for IFIs[30–32]. Based on the above results, the concomitant disease, especially diabetes mellitus, should be paid more attention to timely improve treatment measures and prognosis of IFIs.

Liver dysfunction is one of the most common adverse effect of posaconazole and the focus of attention during clinical treatment[33]. Maertens et al. reported that the incidence of elevated ALT, AST and total bilirubin were 8%, 6% and 3%, respectively[27]. Many studies showed that there was no significant difference in elevated ALT, AST and total bilirubin between posaconazole extended-release tablet and oral suspension[15,34]. In this study, there was also no significant difference in the liver dysfunction incidence between posaconazole enteric-coated tablet and oral suspension. The univariate and multivariate logistic regression analysis revealed that renal replacement therapy, hypoproteinemia and posaconazole duration were risk factors for liver dysfuntion of posaconazole. For patients with hypoproteinemia, elevated blood concentration of posaconazole is more likely to cause liver dysfunction[35]. In addition, excessive posaconazole duration will further aggravate the metabolic burden and increase the risk of liver dysfunction. Therefore, the liver function and blood concentration should be monitored to adjust posaconazole dose.

As a result of mainly fecal excretion, posaconazole rarely lead to renal dysfunction[27]. In this study, the incidence of renal dysfunction caused by posaconazole was low in the two groups. Another common adverse reaction of triazole antifungal drugs is hypokalemia, which may be related to pseudoaldosteronism[36]. The hypokalemia incidence of posaconazole can be up to 22%[37]. In this study, the overall incidence of hypokalaemia was 20.8%. The incidence of hypokalaemia between two groups was similar. This suggests that patients treated with posaconazole should focus on the monitoring of blood potassium and intervening as soon as possible.

Nonetheless, there are some limitations in our study. First, single-center retrospective study cannot represent real clinical situation in prospective studies because of research bias. Second, the sample size of posaconazole enteric-coated tablet was small due to the short application time in our hospital.

Conclusion

In conclusion, the posaconazole enteric-coated tablet has comparable effectiveness and safety with oral suspension in patients with IFIs. The male and diabetes mellitus are independent risk factors for treatment prognosis. The renal replacement therapy, hypoproteinemia and posaconazole duration are high risk factors for liver dysfunction of posaconazole. Additional large sample and multi-center studies are need in the future.

Data availability

The datasets supporting the findings during current study are available upon reasonable request from the corresponding author.

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Author contributions

Y.Y. and R.Y. wrote the main manuscript text. Q.Y. processed the data. Y.H. and Y.L. prepared Tables 1, 2, 3, 4 and 5. All authors reviewed the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Additional information
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