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A retrospective study on the impact of glucocorticoids on the efficacy of posaconazole in the prevention/treatment of invasive fungal infections in patients with hematological malignancies

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ABSTRACT

Background: Posaconazole (PCZ) has been used to prevent and treat invasive fungal infections in immunocompromised patients with hematological malignancies. There is a significant correlation between plasma drug concentration and the efficacy of posaconazole.
Objectives: This study aimed to investigate the effects of glucocorticoid on PCZ C_{min} and on the outcome of PCZ prevention/treatment of invasive fungal infections.
Methods: We conducted a retrospective study at a tertiary hospital, examining patients who were administered posaconazole oral suspension between September 2021 and September 2023, to assess the effect of glucocorticoid on the plasma drug concentration and antifungal effect of posaconazole.
Results: (I) The concomitant usage of glucocorticoid reduced PCZ C_{min} from 1310.00 (648.48 , 2550.00) ng/mL to 1085.00 (529.79 , 1767.50) ng/mL ($p = 0.032$), and the C_{min}/Dose (C/D) decreased from 2.14 (0.98, 4.10) ng/mL/mg to 1.66 (0.86, 2.73) ng/mL/mg ($p = 0.038$). (II) There was a significant difference in PCZ C_{min} between patients on low-dose glucocorticoids and those on medium & high-dose glucocorticoids (1271.14 vs 720.19 ng/mL, $p < 0.001$). (III) PCZ C_{min} was significantly lower in patients with longer glucocorticoid duration than with shorter ($p = 0.013$). (IV) Compared with PCZ alone, the concomitant usage of PPIs, glucocorticoids, and PPIs & glucocorticoids significantly reduced PCZ C_{min} ($p < 0.001$, $p = 0.001$, $p = 0.001$).
Conclusions: The concomitant usage of glucocorticoid can significantly reduce PCZ C_{min}, and this decrease has a correlation with the dose and duration of glucocorticoid. However, glucocorticoid may not affect the clinical outcome of posaconazole in the prevention/treatment of invasive fungal infections.

Introduction

Invasive fungal disease (IFD) occurs when fungi invade human tissues and the bloodstream, causing tissue damage, organ dysfunction, and inflammation. The primary fungi responsible are Candida, a type of yeast, and Aspergillus, a filamentous fungus.[1] Patients with hematological malignancies, such as leukemia, often experience low immune function and agranulocytosis, making them particularly susceptible to IFD. Some of these patients require hematopoietic stem cell transplantation (HSCT) and immunosuppressive therapy, further increasing their IFD risk.[2,3] Research indicates that the incidence of IFD is 26.1 % in acute myeloid leukemia/myelodysplastic syndrome (AML/MDS) and 16.7 % in acute lymphoblastic leukemia (ALL).[4] In critically ill patients, IFD is associated with increased morbidity and mortality.[5] Due to the complexity of the diagnosis, the detection rate of IFD is low. IFD is still the main cause of morbidity and mortality in patients with hematological malignancies at present.[6]

Posaconazole (PCZ), a second-generation triazole antifungal derived from itraconazole, received FDA approval in 2006. It effectively targets a wide range of fungal pathogens. PCZ works by inhibiting lanosterol

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14α-demethylase on the fungal cell membrane, thereby disrupting the biosynthesis of ergosterol, which is essential for fungal cell survival. Currently, PCZ is available in three formulations: oral suspension, delayed-release tablet, and intravenous. PCZ is commonly used to prevent IFD in patients undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT).[7] The Infectious Diseases Society of America (IDSA) recommends PCZ as a first-line prophylactic treatment for IFD during chemotherapy and transplantation in individuals with hematological malignancies.[8] Research suggests a correlation between PCZ minimum plasma concentration (PCZ C_{min}) and IFD incidence. It is generally advised that the concentration for preventing IFD should exceed 700 ng/mL, while for treatment, it should be greater than 1000 ng/mL.[9–11]

The pharmacokinetics of posaconazole vary significantly among individuals, influenced by factors such as concomitant medications and patient-specific characteristics, potentially compromising its efficacy for prevention or treatment of IFD. Reviews indicate that body weight, proton pump inhibitors, and the incidence of diarrhea are important dependent variables for PCZ C_{min}.[12] A retrospective study highlighted that proton pump inhibitors and medium & high doses of glucocorticoids (GCS) (GCS $>$ 0.7 mg/kg, daily) can reduce PCZ C_{min}.[13] Given that many patients with hematological malignancies undergo HSCT and are treated with glucocorticoids to suppress immune function, it is crucial to investigate how GCS affects PCZ plasma concentration. At present, few studies examine the interaction between glucocorticoids and posaconazole. Existing research suggests a potential link between glucocorticoids and altered PCZ plasma concentration, as well as adverse reactions, but in-depth analyses are lacking. This study uniquely examines how the GCS affects the clinical outcomes of PCZ in the prevention and treatment of IFD, as well as the impact of varying doses and treatment durations of GCS on the PCZ C_{min}. Additionally, considering previous findings that proton pump inhibitors (PPIs) can reduce PCZ concentration, we compared the effects of GCS and PPIs on PCZ plasma levels. In summary, this study specifically studied the effect of GCZ on the antifungal effect of PCZ, which would provide marked guidance for clinical medication of PCZ.

Methods

Study design

This retrospective observational study was conducted in a tertiary hospital in China from September 2021 to September 2023. Inclusion criteria: (I) Patients with Hematological Malignancies: Participants must have a confirmed diagnosis of a hematological malignancy; (II) PCZ Oral Suspension Usage: Patients must have received posaconazole oral suspension for the prevention or treatment of IFD for at least 7 days; (III) Age: Participants must be at least 13 years old, as posaconazole oral suspension is approved for use in adults and pediatric patients aged 13 and above;[14] (IV) Therapeutic Drug Monitoring (TDM): At least one steady-state PCZ TDM must have been conducted during the administration period. Exclusion criteria: Patients with incomplete, inaccurate, or missing data were excluded from the study. IFD is diagnosed according to the criteria established by the European Organization for Research and Treatment of Cancer and the Mycology Study Group (EORTC/MSG).[15]

Measurement of PCZ plasma concentration

The analytes were extracted from human plasma by protein precipitation. Posaconazole-d4 (Beijing Manhage Biotechnology Co. Ltd, Batch Number: 0034635, Purity: 99.9 %, Molecular Weight: 353.33) was used as the internal standard (IS). The separation was performed on a DEMETER MSCB-2A column (C18 Column, 3.0 mm × 100 mm, 3 μm, ANAX) at 45 °C. The mobile phase was 0.03 % formic acid aqueous solution (solvent A) (Mass Spectrometry Grade, ANAX) and acetonitrile-methanol (5: 1) (solvent B) (Mass Spectrometry Grade, ANAX) at a flow rate of 0.6 mL/min. The gradient elution program was: solvent B 28 % 0–0.50 min, 28 %-90 % 0.50–1.20 min, 90 % 1.20–2.30 min, 28 % 2.30–2.31 min. The concentration of PCZ was determined by ACQUITY ultra-high performance liquid chromatograph (Waters) equipped with a Xevo TQD triple quadrupole tandem mass spectrometer (Waters) in electrospray positive ion (ESI) mode with multiple reaction monitoring (MRM) system. The injection volume was 2 μL, and the ion pairs of posaconazole and internal standard were *m/z* 701.2–127.0 and *m/z* 705.4–127.2, respectively. The methodological validation met the acceptance criteria of the US Food and Drug Administration (FDA).

Groups

A total of 86 patients and 283 plasma samples were included in this study. Fig. 1 illustrates the grouping structure. According to whether or not taking GCS, 86 patients were divided into With GCS (n = 67) and Without GCS group (n = 19). The clinical outcomes of the two groups were compared. Further analysis was conducted within the With GCS group to explore the relationship between the duration of GCS administration and the distribution of PCZ C_{min}. This group was subdivided into three subgroups based on the number of days of GCS administration: 1–4 days (n = 36), 5–10 days (n = 25), and 10–20 days (n = 6).

The 283 plasma samples were categorized into two groups based on the presence of GCS: the With GCS group (n = 207) and the Without GCS group (n = 76). We compared the distribution of PCZ C_{min} between these groups. To examine the relationship between PCZ C_{min} distribution and GCS dosage, the With GCS group were divided into low-dose subgroup (GCS dose $<$ 0.5 mg/kg/d, n = 144) and medium & high-dose subgroup (GCS dose $\geq$ 0.5 mg/kg/d, n = 63), all GCS doses were converted into the equivalent dose of prednisone.

Plasma samples were categorized into the combined-GCS group (n = 120), combined-PPIs group (n = 25), combined-PPIs & GCS group (n = 87), and the controls group (n = 51) according to the concurrent use of GCS or PPIs. The distribution of PCZ C_{min} between the four groups was compared.

Data collection

According to the individual clinical status of the patients, PCZ C_{min} was measured routinely approximately one week after administration of PCZ oral suspension. The plasma samples were taken irregularly, and each plasma sample was collected 30 minutes before the next administration. The following demographic and clinical data were extracted from the hospital information system (HIS): age, gender, body mass index (BMI), PCZ C_{min} and C/D, hematological diagnosis, drugs, adverse drug reactions (ADRs) and biochemical indicators [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GT), total bilirubin (TBIL), albumin, C-reactive protein (CRP), procalcitonin (PCT), urea, serum creatinine (SrCr), creatine kinase, serum potassium].

Outcome evaluation

The primary outcome focused on the impact of glucocorticoid on PCZ C_{min}, PCZ C/D, and the outcome of PCZ in preventing and treating IFD. The secondary outcome examined how varying doses or durations of glucocorticoid administration affected PCZ C_{min}.

Statistical analysis

Categorical variables were described by numbers and percentages. The continuous variables of normal distribution were described by the mean and standard deviation (SD), and the non-normal distribution data were described by median and interquartile range (IQR). The *t*-test was used for the comparison of normal distribution data between

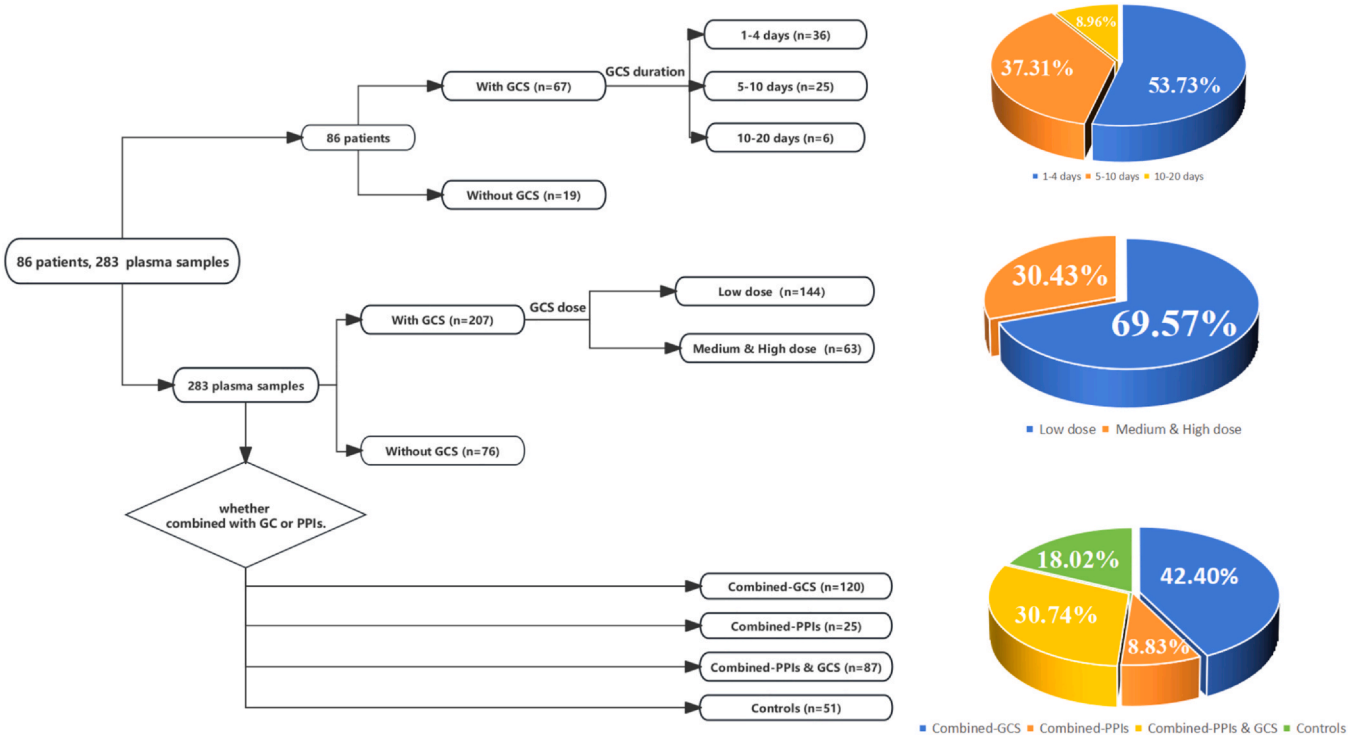

Fig. 1. Groups.

groups, the Mann-Whitney *U* test or Kruskal-Wallis test was used for non-normal distribution data between groups, and the Chi-square test was used for the comparison of categorical data between groups. All statistical analyses were performed in SPSS v22, and graphical representations were generated in Graph Pad Prism 9.5 or Microsoft office Excel 2021.

Results

Patients' demographic characteristics

A total of 86 patients and 283 plasma samples of PCZ were included in this study. The PCZ C_{min} was 1160.12 (590.75, 2000.00) ng/mL. The prophylactic dose of PCZ was 200 mg, 3 times/day, and the therapeutic dose was 200 mg, 4 times/day. Details are shown in Table 1.

The impact of glucocorticoid on PCZ C_{min}

Fig. 2 illustrates that GCS reduced PCZ C_{min} from 1310.00 (648.48 , 2550.00) ng/mL to 1085.00 (529.79 , 1767.50) ng/mL ($p = 0.032$), and the C_{min}/Dose (C/D) from 2.14 (0.98,4.10) to 1.66 (0.86,2.73) ng/mL/mg ($p = 0.038$). For patients using PCZ as a prophylactic measure against IFD, those taking GCS concomitantly experienced a breakthrough prevention incidence of 8.33 % (5/60), while no breakthrough prevention occurred in the group not taking GCS (0/19). In contrast, when PCZ was used for treating IFD, all patients were on GCS, and the treatment failure rate was 28.57 % (2/7). Despite these observations, statistical analysis indicates that the co-administration of GCS may not have a significant correlation with clinical outcomes ($p = 0.142$). Further details are available in Table 2.

We examined how varying doses and duration of glucocorticoids affect PCZ C_{min}. Fig. 3A shows there was a significant difference in PCZ C_{min} between patients with low-dose GCS 1271.14 (750.38 , 2040.00) ng/mL and patients with medium and high-dose GCS 720.19 (305.40 , 1380.00) ng/mL ($p < 0.001$). Meanwhile, Fig. 3B indicates that the PCZ C_{min} of patients with shorter days of GCS was significantly higher than that of patients with longer days (1234.57 vs 1180.00 vs 710.00 ng/mL, $p = 0.013$).

Compared with patients on low-dose glucocorticoids, the proportion of PCZ C_{min} exceeding 700 ng/mL was lower among those on medium/high doses (61.4 % vs 62.5 %, $p = 0.690$). Similarly, when comparing

Table 1
Demographic and clinical characteristics of patients.

Item	Result
Age (years)	54.40 (40.00, 68.00)
Male	49 (57.00 %)
Female	37 (43.00 %)
BMI(kg/m^2)	23.67 (21.04, 26.37)
Average number of patient concentration measurements	2.50 (1.00, 4.25)
Daily dose (mg)	600.00 (600.00, 800.00)
Days of taking medicine	14.00 (8.00, 21.00)
PCZ concentration	
C_{min}(ng/mL)	1160.12 (590.75, 2000.00)
C/D (ng/mL/mg)	1.73 (0.88, 3.20)
Days in hospital	28.50 (21.75, 36.25)
Underlying conditions	
ALL	7 (8.14 %)
MDS	10 (11.63 %)
AML	48 (55.81 %)
Others	21 (24.42 %)
Chemotherapy	49 (56.98 %)
Baseline liver and kidney function	
Albumin	34.00 (30.40, 37.20)
AST	19.25 (15.20, 30.92)
ALT	20.20 (11.77, 36.62)
ALP	75.00 (58.00, 107.50)
AST/ALT	1.05 (0.70, 1.44)
γ-GT	26.50 (19.00, 61.25)
TBIL	11.80 (9.27, 16.65)
Creatinine	56.75 (43.80, 70.10)
Urea	4.86 (3.63, 5.94)
Creatine kinase	33.00 (20.00, 64.00)
K	3.67 (3.37, 3.92)

Note: BMI, body mass index; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transferase; TBIL, total bilirubin.

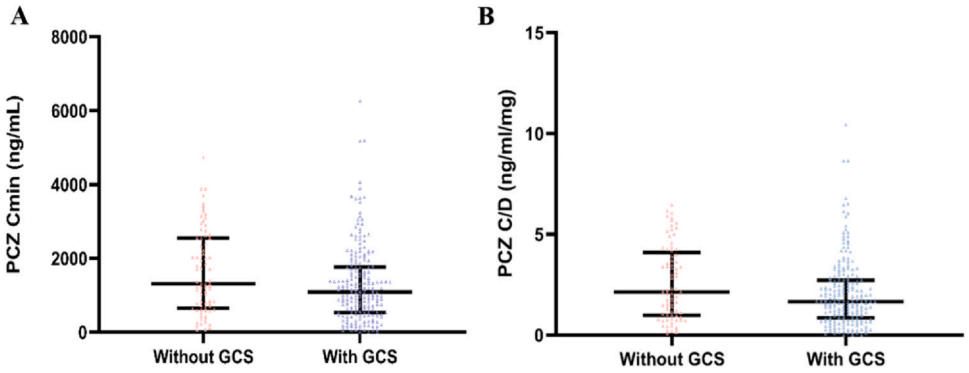

Fig. 2. The distributions of PCZ C_{min} (A) and PCZ C/D (B). Note: the long line in the middle represents the median, the short lines above and below respectively represent the 75th percentile and the 25th percentile, and the red and blue triangles represent the PCZ C_{min} or the PCZ C/D.

Table 2
Clinical outcome of patients with GCS and without GCS.

	Prophylaxis(n,%)		Treatment(n,%)		ALL(n,%)	
	Success	Failure	Success	Failure	Success	Failure
With GCS	55 (69.62 %)	5 (6.33 %)	5 (71.43 %)	2 (28.57 %)	60 (69.77 %)	7 (8.14 %)
Without GCS	19 (24.05 %)	0 (0.00 %)	0 (0.00 %)	0 (0.00 %)	19 (22.09 %)	0 (0.00 %)
Total	74 (93.67 %)	5 (6.33 %)	5 (71.43 %)	2 (28.57 %)	79 (91.87 %)	7 (8.14 %)
χ^2 value	1.690		—		2.161	
P value	0.194		—		0.142	

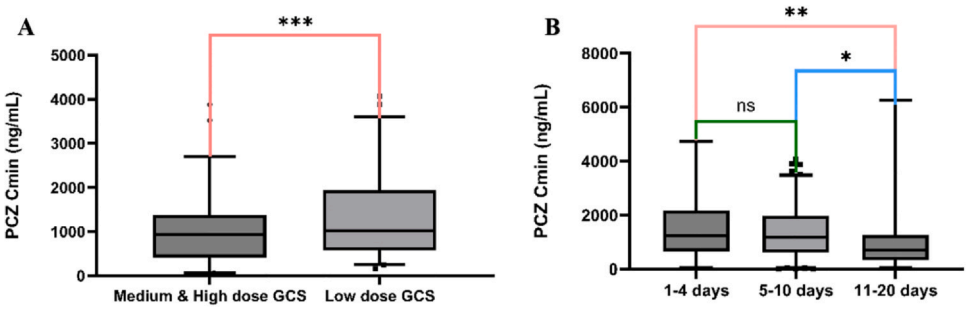

Fig. 3. Box (median and 25th–75th percentiles) and whiskers (5th–95th percentiles) plot of PCZ C_{min} with GCS of different dose (A) and different days (B). Note: ns indicates $p > 0.05$, * indicates $p < 0.05$, * * indicates $p < 0.01$, * ** indicates $p < 0.001$.

to patients with glucocorticoids for 1–4 days, those with glucocorticoids for 10–20 days exhibited a lower proportion (51.3 % vs 73.2 %, $p = 0.009$). Further details can be found in Fig. 4.

The impact of PPIs or glucocorticoid on PCZ C_{min}

The PCZ C_{min} in the Combined-PPIs, Combined-GCS, and Combined-GCS & PPIs groups were significantly lower compared to the control group ($p < 0.001$, $p = 0.001$, $p = 0.001$). Notably, the Combined-PPIs group exhibited the lowest PCZ C_{min} among all groups. Further details can be found in Table 3.

Discussion

Posaconazole (PCZ) is known for its broad antifungal activity, high tissue concentration, and structural advantages, which enhance its

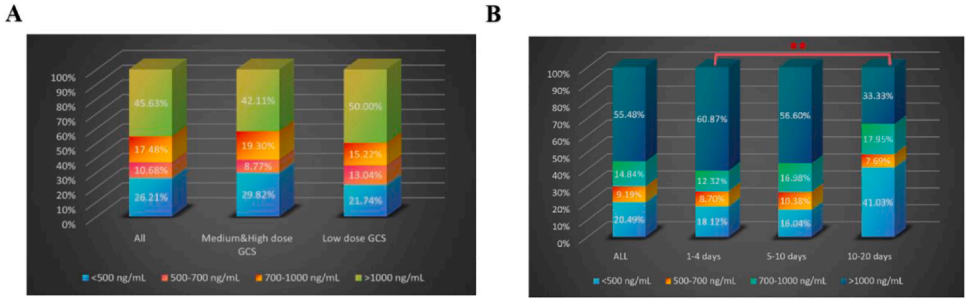

Fig. 4. The frequency distribution of effective concentration for each group. Note: * * indicates statistically significant differences in PCZ $C_{min} > 700$ ng/mL frequency distribution between the 1–4 days group and 10–20 days group.

Table 3
PCZ C_{min} with CGS or PPIs.

	PCZ C_{min}	*P*
Controls	1850.00(1110.00, 2630.00)	
Combined-GCS	1140.06(505.00, 1885.00)	0.001
Combined-PPIs	636.96(401.46, 1178.71)	< 0.001
Combined-GCS & PPIs	1080.00(600.00, 1750.00)	0.001

Note: *P*: Comparison with Controls.

binding to the target enzyme CYP51. This makes it effective even against some azole-resistant fungi. The efficacy and safety of PCZ are significantly correlated with its plasma concentration. However, PCZ can interact with various medications, potentially lowering its plasma concentration below optimal levels. For instance, proton pump inhibitors and H_2 receptor blockers can change the pH in the stomach and reduce the solubility of PCZ. Gastrointestinal prokinetic agents may decrease its gastric residence time, hindering absorption.[16–20] Rifampicin induces P-glycoprotein transporters and increases the clearance rate of PCZ.[21,22] Recent findings also suggest that glucocorticoid (GCS) combinations can decrease PCZ C_{min},[13,23] necessitating further investigation into drug interactions affecting PCZ levels.

In this article, we concretely studied the impact of glucocorticoids on the efficacy of posaconazole in the prevention and treatment of invasive fungal infections in patients with hematological malignancies. Initially, we compared the PCZ C_{min} distribution between the GCS group and without GCS group. which showed that GCS significantly lowered the PCZ C_{min}. This was consistent with the results of Pier Giorgio Cojutti, Zhang S, et al.[13,23]

Unlike earlier studies, our study explored whether the PCZ C_{min} reduction caused by GCS influenced clinical outcomes in preventing or treating fungal infections and found no significant effect. Actually, there was no final consensus reached about posaconazole target concentration for prophylactic use to date. Jang et al. and the FDA have suggested a target of 0.7 mg/L,[24] while the 4th European Conference on Infections in Leukemia (ECIL-4) recommends 0.5 mg/L at steady state.[25] A Chinese prospective study recommended PCZ C_{min} > 0.47 μg/mL after chemotherapy or HSCT to avoid the occurrence of IFD.[26] Glucocorticoids may reduce the concentration of posaconazole, but the proportion of cases where it drops below 0.5 mg/L is not so high (22.33 %), thus minimizing its impact on clinical outcomes. Nevertheless, this interaction warrants attention, as it could still pose infected risks.

It is worth noting that we found that there was a significant difference in the effect of different doses of GCS on PCZ C_{min} ($p < 0.001$). Additionally, PCZ C_{min} was observed to decline with prolonged GCS use ($p = 0.013$). A real-world study showed that the use of PCZ oral suspension for antifungal prophylaxis in patients with hematological diseases for ≥ 4 days, the overall IFD breakthrough rate was 1.6 %.[27] Consequently, when GCS is administered concurrently with PCZ, particularly over extended periods or in high doses, healthcare providers should closely monitor PCZ plasma concentrations and adjust the treatment regimen as necessary.

In this study, we compared the PCZ C_{min} of combined-GCS group, combined-PPIs group, combined-PPIs & GCS group, and the controls group. Interestingly, the combined PPIs group exhibited the lowest PCZ C_{min}, which deviates somewhat from the findings of Pier Giorgio Cojutti et al. We hypothesize that PPIs reduce the dissolution of PCZ by inhibiting gastric acid secretion and increasing gastric pH, while GCS can stimulate gastric acid secretion.[28,29] This interaction suggests that GCS might mitigate the impact of PPIs on reducing PCZ plasma concentrations, highlighting the complexity of these drug interactions.

The precise mechanism by which GCS affect PCZ C_{min} remains unclear. Hyeon Jeong Suh et al. found that Ugt1A4 * 3 gene polymorphism is associated with low PCZ plasma concentration in patients with hematological malignancies.[30] Pier Giorgio Cojutti et al. speculate that GCS may up-regulate the activity of UGT1A4 and increase the clearance rate of PCZ.[13] Considering drug transporters, it's plausible that GCS could influence PCZ C_{min} through effects on P-glycoprotein (P-gp). P-gp is a transmembrane protein found in various tissues such as the placenta, blood-brain barrier, intestinal mucosa, and renal proximal tubule. It relies on ATP to mediate the efflux of a variety of endogenous substances and lipophilic exogenous substances.[31–33] Since PCZ is a P-gp substrate, its pharmacokinetics may be altered when patients concomitantly take drugs affecting P-gp. For instance, phenytoin sodium, which induces UDP-glucuronidase and P-gp, significantly reduces maximum concentration (C_{max}) and area under the curve (AUC) of PCZ by 41 % and 50 %, respectively. Steroids, including glucocorticoids, may influence P-gp expression. Various studies have shown that sex steroids like estrone, estriol, and ethinyl estradiol can induce P-gp expression at both protein and mRNA levels in vitro.[34,35] Dexamethasone and hydrocortisone can induce the expression of P-gp in the blood-brain barrier of rats. Human T lymphocytes and human colon adenocarcinoma cells (LS-180 cells) can also enhance the expression of P-gp under the induction of dexamethasone.[36–38] Thus, GCS might increase PCZ clearance by inducing P-gp expression, resulting in enhanced efflux and decreased PCZ C_{min}. Whether the mechanism involves the UGT1A4 pathway, the P-gp pathway, or another route, further prospective studies are necessary to confirm these interactions.

We acknowledge several limitations in this retrospective study. Firstly, the limited sample size may make the generalizability pessimistic. Additionally, the study focused only on dexamethasone sodium phosphate injection as the type of glucocorticoid analyzed, which restricts our ability to assess the impact of varying types of GCS on PCZ C_{min}. Future research will aim to address these gaps by exploring a broader range of GCS and increasing the sample size for more comprehensive analysis. Nonetheless, our findings offer a reference point for the clinical application of PCZ and underline the importance of monitoring drug interactions in patients receiving concurrent treatments.

Conclusions

The concomitant usage of GCS can significantly reduce PCZ C_{min}, with the reduction becoming more pronounced as the duration and dose of GCS increase. However, glucocorticoid may not have a significant effect on the clinical outcome of PCZ prevention/treatment of IFD. Given that PCZ C_{min} is closely linked to its effectiveness in IFD prevention and treatment, it is crucial for healthcare providers to monitor drug concentrations closely during treatment.

Declarations

Not applicable.

Authors' contributions

S. Yuan: Writing – review and editing, writing – original draft, visualization, project administration, methodology, investigation, formal analysis, data curation, and conceptualization. S. Liu: Writing – review and editing, writing – original draft, visualization, project administration, methodology, investigation, formal analysis, data curation, and conceptualization. Y. Zhao: Project administration, methodology, and investigation. Z. Wang: Project administration, methodology, and investigation. Y. Liu: Supervision, resources, project administration, and funding acquisition. J. Yu: Supervision, resources, project administration, and funding acquisition.

Ethics approval and consent to participate

This retrospective study was approved by the Hospital Ethics Committee (Approval No.: 20200638).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declarations of Competing interests

The authors declare that they have no competing interests.

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Authors' other information

Not applicable.

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