Factors Influencing the Safety and Efficiency of Antifungal Prophylaxis with Posaconazole in Children with Hematological Diseases: From Genetics to Polypharmacotherapy

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Abstract The aim of this study was to determine the impact of ABCB1 polymorphism, BMI, age and drug co-administration on safety and efficiency of posaconazole (PCZ) oral suspension treatment in children with hematological diseases. Seventy children were included in the study. ABCB1 polymorphism in fifty-eight children was determined using a PCR–RFLP method. A protocol with data on the health condition, treatment and adverse events (AE), as well as a survey on treatment tolerance for the legal guardians was evaluated. Liver function tests were observed for the first 20 days, and AE during the complete medication period. For statistical analysis a $\chi^2$ test with Yates’s correction, a Pearson’s or Spearman’s correlation test was performed ($p < 0.05$). Genetic testing showed 24% CC, 46% CT and 30% of TT variants. PCZ prophylaxis failed in twenty cases, where change in prophylactic treatment was needed. Fifty-two children suffered from at least one mild to moderate adverse event. Sixty-five legal guardians completed the survey, most of them reported the treatment to be well tolerated. ABCB1 polymorphism had no impact on AE occurrence and posaconazole prophylaxis efficiency. Age influenced the number of gastrointestinal ($p = 0.02$), visual ($p = 0.05$), neurological ($p = 0.01$), dermatological ($p = 0.002$) and flu-like ($p = 0.02$) complications. AST ($p = 0.03$) and LDH ($p = 0.008$) activity presented age dependency. The concomitant use of proton pump inhibitors (PPI) had impact on liver health parameters elevation ($p = 0.009$) and circulatory system complications ($p = 0.008$). High incidence of mild to moderate AE, and other factors influencing PCZ pharmacokinetics (PPI co-administration, obesity), suggest a need for careful pediatric onco-hematology patient evaluation.

Keywords ABCB1 protein · Adverse drug event · Children · Posaconazole · Hematology

Introduction

Posaconazole (PCZ) is a triazole antifungal agent. The drug is primarily indicated for molds infection prophylaxis in patients receiving chemotherapy for acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and in patients after allogenic hematopoietic stem cell transplantation (allo-HSCT).

It may also be used for treatment of particular cases of invasive aspergillosis, fusariosis, chromoblastomycosis, coccidioidomycosis and candidiasis [1, 2].

The treatment of children is very specific. Not only from the psychological point of view, also the pharmacokinetic properties of drugs differ from the adult population. Basic alterations are gathered in Table 1 [3, 4].

According to the Food and Drug Administration (FDA) PCZ oral formulation is approved for children older than 13 [2, 3]. Some studies showed that the agent is also safe in children younger than 12 [5]. Although posaconazole has either no grading (in cases of children after allo-HSCT without GVHD) or a BI grade (in children after allo-HSCT with GVHD and in de novo or recurrent leukemias) according to the Recommendations for primary
chemoprophylaxis of invasive fungal diseases in paediatric patients with cancer or haemopoietic stem-cell transplantation of the ECIL-4, it is often used in clinic for antifungal prophylaxis in children with hematological malignances [6].

The pediatric onco-hematology population is particularly exposed to adverse drug reactions (ADR) and adverse events (AE). The effectiveness and safety of PCZ oral suspension is influenced mainly by food intake, gastric pH and motility as well as drug-drug interactions [5, 7, 8]. Posaconazole is a substrate for UDP-glucuronosyltransferase and P-glycoprotein, thus agents having impact on these two clearance pathways must be taken into consideration during PCZ medication [1].

As P-glycoprotein is encoded by the ABCB1 gene, the polymorphism of which is connected with changes in the protein expression, the aim of our study was to determine the impact of ABCB1 polymorphism on the safety and efficiency of posaconazole oral suspension treatment in children. We also took into consideration other agents potentially influencing antifungal prophylaxis (BMI, age, drug co-administration). To our knowledge it is the first of this kind study performed among the Polish pediatric population with hematological diseases.

Materials and Methods

The study was performed according to the Declaration of Helsinki and with approval of the Bioethics Committee of the Wroclaw Medical University (KB-657/2012). It is a single center, non-randomized retrospective analysis of seventy pediatric patients who received posaconazole oral suspension for antifungal prophylaxis.

| Absorption                          | Distribution          | Metabolism                          | Excretion                     |
|-------------------------------------|-----------------------|-------------------------------------|-------------------------------|
| ↓ Surface of gastrointestinal tract | ↑ Total body water    | ↓ CYP3A7 after birth, barely measurable in adults |
| ↓ HCl secretion                     | ↑ Extracellular water | ↓ CYP2D6 (20% of adult activity at 1 month of postnatal age, adult competence—3–5 years of age) |
| ↓ Motility and peristalsis          | ↓ Fat content         | ↓ CYP2C9, CYP2C19 (low activity during the first week of life, adult activity—6 months of age) |
| ↓ Gastric emptying                  | ↑ Body water: fat ratio | ↓ CYP1A2 (adult levels—4 months of age, in children 1–2 years of age may be exceeded) |
| ↓ Bile secretion                    | ↓ Protein serum levels, especially albumins | ↓ CYP3A4 (low activity in the first month of life, adult levels—6–12 months postnatally) |
| Immature enzymes                    | ↓ 3, Glycoprotein concentration | ↓ N-acetyltransferase 2 (NAT2) (adult activity 1–3 years of age) |
| Thinner stratum corneum             | ↓ Protein binding     | ↓ Uridine diphosphoglucuronyltransferase (UDP-GT) (adult activity—6–18 months of age) |
| ↑ Hydration of epidermidis           | ↑ Permeability of brain-blood barrier |                               |
| Variable skeletal muscle blood flow |                       |                                     |                               |

Patients Characteristics

The included children were patients of the Paediatric Bone Marrow Transplantation, Oncology and Hematology Unit, of the Wroclaw Medical University Hospital, aged between 2 months and 19 years. The median PCZ dose was 8 mg per kg of body weight, two times a day according to the algorithm evaluated by Welzen et al. [9]. Most important data on patients enrolled is presented in Table 2.

Table 2 Patient characteristics

| Characteristic | Number of patients (%) |
|----------------|------------------------|
| Gender         |                        |
| Male           | 43 (61.4)              |
| Female         | 27 (38.6)              |
| Age (median) [years] – median (25Q–75Q) | 7 (2.0–14.0) |
| < 6            | 32 (45.7)              |
| 7–11           | 14 (20)                |
| > 12           | 24 (34.3)              |
| Diagnosis      |                        |
| ALL            | 23 (32.8)              |
| AML            | 18 (25.7)              |
| SAA            | 8 (11.4)               |
| WAS            | 4 (5.7)                |
| Other hematological diseases | 16 (24.4) |
| BMI [kg/m²] – median (25Q–75Q) | 16.4 (14.3–18.6) |
| < 18.5         | 51 (72.8)              |
| 18.5–25        | 17 (24.3)              |
| > 25           | 2 (2.9)                |

ALL acute lymphoid leukemia, AML acute myeloid leukemia, SAA serious aplastic anemia, WAS Wiskott-Aldrich Syndrome.
Patients’ Protocol and Survey

A protocol with most important data on patients health condition, underlying diseases, allo-HSCT performance, previous infections, treatment and adverse events was evaluated. As posaconazole may lead to hepatic impairment we also monitored biochemical parameters of liver function. Those were aspartate aminotransferase (AST), alanine transaminase (ALT), activated partial thromboplastin time (APTT), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH) activity, albumin and fibrinogen concentrations at three time points (before, at the seventh, and the twentieth day) of PCZ prophylaxis.

Drug-drug interactions are also factors influencing PCZ pharmacokinetics and inducing AE occurrence. So, we tried to determine, on the basis of patients treatment history, drugs potentially interacting with the antifungal agent. We monitored AE during the complete posaconazole conducted medication period.

In addition a survey on treatment tolerance and observed adverse events was evaluated and performed among the legal guardians of the examined children. Sixty-five of them completed the questionnaire.

The survey consisted of five parts: first—connected with basic information (body weight (BW), age, height), second—with information on previous fungal infections (occurred before hospital admission), third—potential food supplement administration, fourth—adverse events observed during posaconazole treatment (we intentionally listed AE possibly occurring during PCZ therapy) and fifth—concerning the treatment satisfaction in a 0–5 score scale. On this scale 0 meant no opinion, 1-no satisfaction (serious fungal infection occurred despite posaconazole prophylaxis), 2-low satisfaction (local fungal infection in more than one body area occurred), 3-moderate satisfaction (local fungal infection occurred), 4-satisfaction (no fungal infection, but adverse events occurred), 5-full satisfaction (no fungal infection and good tolerance).

DNA Isolation and Genetic Testing

We collected seventy samples (one from each patient) of whole blood drawn on EDTA. The samples were stored at -20 °C.

DNA was isolated using the QIAamp® DNA Blood Mini Kit according to the manufacturer instruction, in a laminar flow cabinet.

For ABCB1 polymorphism determination, an adapted Siegmund et al. [10] polymerase chain reaction-restriction length polymorphism (PCR–RFLP) method was used.

Statistical Analysis

We performed statistical analysis on the collected data. For every group the number of cases (N), median (M), range (min–max), upper and lower quartile (25Q–75Q) was calculated. The hypothesis on the equality of median values of the groups was verified using the Kruskal–Wallis test.

For discrete parameters the frequency of features in the groups was analyzed using the Chi squared test with Yates’s correction, with an adequate number of degrees of freedom df (df = (m − 1) * (n − 1)).

For chosen pairs of parameters a Pearson’s or Spearman’s correlation test was performed.

p values less than 0.05 were considered statistically significant. p values between 0.05 and 0.1 were considered as tendency. The statistical analysis was performed using the EPIINFO program (Ver. 7.1.1.14, 2013, USA).

Results

Seventy patients of the Paediatric Bone Marrow Transplantation, Oncology and Hematology Unit, of the Wroclaw Medical University Hospital were included in our study. The median BMI was 16.4 kg/m², two children were overweight. During the observation period 21 (30%) children suffered from acute GVHD, seven of them further developed a chronic form of the disease.

Fifty-eight legal guardians agreed for genetic testing of their children. The performed C3435T genetic testing for ABCB1 polymorphisms showed that 24% (N = 14) of patients presented the CC, 46% (N = 27) the CT, and 30% (N = 17) the TT variant.

Posaconazole oral formulation prophylaxis failed in 20 cases, where a change in treatment was needed according to suspected IFI development.

Fifty-two children suffered from at least one mild to moderate adverse event during invasive fungal infection prophylactic treatment. However according to the performed survey legal guardians reported the treatment to be well tolerated by their children (number of completed surveys 65; score 5 N = 21, score 4 N = 21, score 3 N = 10, score 2 N = 2, score 1 N = 0, score 0 N = 11). There was no need to discontinue posaconazole prophylaxis due to adverse events in any case. The occurrence of AE among different systems is presented in Fig. 1.

Increased AST activity was observed in 35 cases, ALT activity increased in 42, GGT in 28 cases. Nine children presented higher bilirubin values. Most frequent gastrointestinal disturbances were vomiting (N = 29), nausea (N = 25), loss of appetite (N = 22), diarrhea (N = 21), constipation (N = 20) and abdominal pain (N = 20). Dermatological complication manifested as mouth ulceration.
(N = 24) and rash (N = 11). Nervous system disorders showed as headache (N = 10), insomnia (N = 7) and tremor (N = 5). Ophthalmological disorders most often were connected with blurred vision (N = 9) whereas cardiovascular disorders with hypertension (N = 6). Renal disorders manifested as blood urea concentration increase in 5 and hemorrhagic cystitis in 2 cases.

Drug-drug interaction analysis led to determination of agents potentially inducing AE occurrence during PCZ treatment, having impact on its pharmacokinetic properties. Drugs and number of children treated are presented in Table 3.

Statistical analysis showed that ABCB1 polymorphism has no impact on overall adverse event occurrence and posaconazole prophylaxis efficiency as presented in Table 4. However two patients with good tolerance to posaconazole, who did not suffer from any adverse event during antifungal treatment presented the CC variant. We found a tendency for APTT prolongation during treatment in individuals presenting the TT variant ($p = 0.07$, $\chi^2 = 8.45$). After twenty days of posaconazole treatment the APTT prolonged in four patients presenting the CT variant (N = 27, 14.8%), one patient with CC variant (N = 14, 0.07%) and in 7 patients presenting the TT variant (N = 17, 41.2%).

The age of children influenced the number of gastrointestinal, visual, neurological, dermatological and flu-like complications. The older the child the more often mentioned AE occurred. Furthermore AST and LDH activity presented age dependency especially in the first week of PCZ treatment.

Children with higher BMI values were more susceptible for visual and skin disturbances ($p = 0.057$, $H = 3.61$) as well as increased LDH activity during the first week of IFI prophylaxis.

Gender did not influence AE frequency.

The concomitant use of proton pump inhibitors (PPI) had great impact on parameters for liver health elevation and circulatory system complications during PCZ prophylaxis. Most important findings on variables influencing adverse events during posaconazole conducted prophylaxis and their statistical significance are presented in Table 5.

**Discussion**

The aim of this investigation was to determine the impact of ABCB1 polymorphism, BMI, age and drug co-administration on safety and efficiency of posaconazole oral suspension treatment in children with hematological diseases.

In our study the frequencies of ABCB1 C3435T genetic variants (24% for CC, 46% for CT and 30% for the TT variant) were comparable with other research performed among the Polish hematology population [11, 12].
We evaluated the influence of ABCB1 polymorphism on adverse event occurrence in children with hematological malignances treated with PCZ oral suspension. We found no statistical correlation, however a tendency for APTT prolongation during treatment was observed. This finding is completely new and to our knowledge has not been observed in any research before.

What is also interesting in our study, is that patients with good tolerance to posaconazole and with proper prophylactic response (N = 2) presented the CC variant. This may be connected with higher activity of P-gp in patients with this ABCB1 genetic polymorphism, that was previously reported in patients with B cell chronic lymphocytic leukemia, and what comes along with the increased active transport of drugs out of cells, suggesting and supporting the thesis of a protective role of the C3435C variant [12].

We didn’t find a correlation between ABCB1 polymorphism and efficiency of PCZ prophylaxis measured as success or failure of prophylactic treatment. To our knowledge we were the first to evaluate this problem.

During posaconazole pharmacotherapy relatively high incidence of mild to moderate adverse events occurred. Most frequent were gastrointestinal, visual, neurological, dermatological and flu-like complications. The observations are concise with those from other studies. Lehrnbecher et al. [13] reported fever, nausea and/or vomiting, abdominal pain, diarrhea, headache, and skin eruptions as most common during PCZ treatment. Gastrointestinal and skin adverse events, according the observations of Döring et al. [5], were the most common complications.

The elevation of liver function tests namely transaminase activity and LDH activity is a well-known adverse drug reaction caused by triazole antifungal agents [1, 5, 13–15]. What is a new finding, and as to our knowledge was not observed in any of the previous studies in children, is a statistically significant correlation between age and mentioned AE. The older the child the more often described adverse events occurred. A similar tendency was observed for adults, where a reduction in the apparent volume of distribution, and 11% higher average plasma posaconazole concentration were observed according to older age [16]. However as children generally have different pharmacokinetics than adults, this finding cannot be directly extrapolated into the pediatric population.

The concomitant use of proton pump inhibitors (omeprazole, pantoprazole) had impact on parameters for liver health and circulatory system complications during PCZ prophylaxis. The influence of concomitant PPI administration with posaconazole is well established for the adult population and was also evaluated in children [7, 16–19]. Although in general the PPI co-administration is connected with lower posaconazole serum

| Table 4 Influence of ABCB1 polymorphism on adverse events occurrence during posaconazole prophylaxis |
|---------------------------------------------------------------------------------------------------|
| Adverse event | CT N = 27 (46%) | TT N = 17 (30%) | CC N = 14 (24%) | P (χ²) |
|---------------|----------------|----------------|----------------|-------|
| Gastrointestinal disturbances | 7 | 20 | 5 | 12 | 4 | 10 | 0.964 (0.0724) |
| Ophthalmological disturbances | 22 | 5 | 16 | 1 | 13 | 1 | 0.369 (1.99) |
| Elevation of liver function parameters | 3 | 24 | 3 | 13 | 4 | 9 | 0.313 (2.32) |
| Neurological disturbances | 16 | 11 | 11 | 6 | 10 | 4 | 0.741 (0.600) |
| Dermatological changes | 16 | 11 | 9 | 8 | 9 | 5 | 0.812 (0.416) |
| Renal function changes | 25 | 2 | 15 | 2 | 12 | 2 | 0.770 (0.522) |
| General symptoms | 17 | 10 | 10 | 7 | 10 | 4 | 0.762 (0.543) |
| Cardiovascular disturbances | 21 | 6 | 13 | 4 | 12 | 2 | 0.790 (0.472) |
| Invasive fungal infection | 21 | 6 | 13 | 4 | 7 | 7 | 0.148 (3.821) |

0—no adverse event occurred
1—adverse event occurred
Table 5  Most important findings on variables influencing adverse events during posaconazole treatment and their statistical significance

| Variable potentially influencing adverse event occurrence during PCZ treatment | Age |
|---|---|
| Impact on safety of PCZ treatment | Yes |
| Number of patients tested (%) | 70 (100%) |
| Test | Spearman’s r = 0.45 |
|  | *p* value = 0.00009 |

| Variable | Number of patients (%) | Spearman’s r | *p* value |
|---|---|---|---|
| Age | 70 (100%) | | |
| BMI | 70 (100%) | Spearman’s r = 0.24 | *p* value = 0.47 |

| Additional information on adverse events |  |  |  |
|---|---|---|---|
| Higher AST activity during first week of treatment | 18 (26%) | – 0.27 | 0.036 |
| Higher LDH values during first week of treatment | 13 (19%) | – 0.35 | 0.008 |

| The older the child the more often following adverse events occur |  |  |  |
|---|---|---|---|
| Gastrointestinal | 20/50 | 3.15 (1.42–8.50) | 9.00 (3.70–15.0) | 5.06 | 0.0244 |
| Neurological | 44/26 | 5.90 (1.73–11.0) | 13.0 (6.0–15.4) | 5.71 | 0.0168 |
| Dermatological | 42/28 | 4.25 (1.10–11.0) | 12.5 (6.5–15.4) | 9.32 | 0.0023 |
| Flu-like | 45/25 | 4.50 (1.70–13.0) | 10.0 (6.0–15.2) | 4.74 | 0.0295 |
| Visual | 62/8 | 6.50 (1.90–14.0) | 13.5 (9.50–15.4) | 3.72 | 0.0536 |

| Variable potentially influencing adverse event occurrence during PCZ treatment | Concomitant PPI administration |
|---|---|
| Impact on safety of PCZ treatment | Yes |
| Number of patients tested (%) | 64 (91%) |
| Test | Spearman’s r = 0.24 |
|  | *p* value = 0.47 |

| Additional information on adverse events |  |  |  |
|---|---|---|---|
| Increased LDH activity during first week of treatment | 13 (19%) | – 0.35 | 0.01 |

| Variable potentially influencing adverse event occurrence during PCZ treatment | ABCB1 polymorphism |
|---|---|
| Impact on safety of PCZ treatment | No |
| Number of patients tested (%) | 58 (83%) |
| Test | | |
|  |  |  |  |
| Additional information on adverse events |  |  |  |
| Tendency for APTT prolongation in patients presenting the TT variant | 7 (41%) | 8.45 | 0.076 |
concentrations, during our study we observed that adverse events occurred more often in patients receiving omeprazole or pantoprazole. This could be connected with other drugs used for hematological malignancy treatment. PPI—especially the older representatives (omeprazole, pantoprazole) are CYP2C19 substrates, and therefore might affect pharmacokinetics of other drugs metabolized through CYP2C19 [20].

We observed that children with higher BMI values are more susceptible for visual and skin disturbances as well as increased LDH activity during the first week of IFI prophylaxis conducted with posaconzole. This problem was not evaluated for the pediatric population receiving PCZ in oral suspension formulation. However there is one study describing the experience from using posaconazole in form of extended released tablets. In obese adult patients (BMI > 30 kg/m², and body weight > 90 kg) the antifungal agents serum levels were lower during the tablet formulation treatment [21]. Our observations are not concise with this finding. This could be due to alterations of pharmacokinetic properties of both formulations and both populations (e.g. in children the glucuronidation potential is not as high as in adults, thus it cannot be increased in childhood obesity, as it is the case in the adult population).

Conclusion

ABCB1 polymorphism has no impact on the efficiency and safety of posaconazole treatment in children with hematological malignancies. However the relatively high incidence of mild to moderate adverse events during prophylaxis, and occurrence of other factors potentially influencing PCZ pharmacokinetics such as PPI co-administration or obesity, suggest a need for careful patient evaluation and probable TDM (therapeutic drug monitoring) enrollment in onco-hematological pediatric patients receiving antifungal prophylactic treatment conducted with posaconazole oral suspension formulation.

What is certainly a limitation of our study is the relatively small group of patients and lack of posaconazole serum concentration measurement. However the aim of our retrospective research was to evaluate potential causes of AE occurrence, and prophylaxis failure during PCZ treatment. As our findings were partially new there is certainly a need for larger studies to evaluate the problem in the future.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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