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Relationship between exposure to treosulfan and its monoepoxytransformer – An insight from population pharmacokinetic study in pediatric patients before hematopoietic stem cell transplantation

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ABSTRACT

Treosulfan (TREO), a structural analog of busulfan, is currently studied as a myeloablative agent in conditioning regimens before hematopoietic stem cell transplantation in pediatric patients. High exposure to TREO (> 1650 mg∗h/mL) might be related to early toxicity, especially skin toxicity and mucositis. The aim of the present study was to investigate a potential relationship between exposure to TREO and its monoepoxytransformer (S,S-EBDM), as well as variability of the pharmacokinetics of these entities by means of a population pharmacokinetic approach with a non-linear mixed-effects analysis.

The study included data from 14 children with malignant and non-malignant diseases treated with TREO in daily doses 10–14 g/m^2. The parent-metabolite population pharmacokinetic model was developed in NONMEM 7.3 software. Upon the constructed model, an extensive simulation was performed to assess the correlation between exposure to TREO and S,S-EBDM.

It was found that TREO and S,S-EBDM pharmacokinetics was best described with 2-compartmental and 1-compartmental linear models, respectively. The vast majority (> 65%) of TREO was transformed to S,S-EBDM. Overall, a considerable interpatient variability of pharmacokinetic parameters was observed, especially the clearance of S,S-EBDM. A weak correlation was found between the exposure to TREO and S,S-EBDM ($r = 0.1681$, $p < 0.0001$). Also, patients with an exposure to TREO above 1650 mg∗h/mL were most likely to have also a high exposure to S,S-EBDM (35.38 μM∗h vs. 43.14 μM∗h, $p < 0.0001$).

In summary, a parent-metabolite population pharmacokinetic model for TREO and S,S-EBDM was developed for the first time. It was shown that there is a weak correlation between exposure to TREO and S,S-EBDM. Therefore therapeutic drug monitoring of not only prodrug but also its active epoxide might be needed.

1. Introduction

Since its introduction in 1980s for treatment of ovarian cancer, treosulfan (TREO) has gained much interest in modern medicine. This alkylating agent is currently being investigated as an alternative to busulfan in conditioning regimens prior to hematopoietic stem cell transplantations (HSCT) in pediatric patients (Wachowiak et al., 2011). TREO itself is a prodrug that undergoes two-step hydrolysis (Feit et al., 1970). This highly temperature- and pH-dependent reaction renders two entities. In the first step, an intermediate monoepoxytransformer ((2*S*,3*S*)-1,2-epoxybutane-3,4-diol-4-methanesulfonate; S,S-EBDM) is formed and in the second step a final diepoxide product ((2*S*,3*S*)-1,2:3,4-diepoxybutane, S,S-DEB) is obtained. These products, predominantly S,S-DEB, have an ability to alkylate DNA, mostly in the N_7 position of guanine (Millard et al., 2006). Therefore, interstrand and intrastrand cross-links are formed and, as a consequence, cytotoxic activity is observed (Park et al., 2005).

According to several clinical studies, TREO is generally well tolerated by the patients conditioned for HSCT and its main adverse effects comprise of mucositis, skin toxicity, hepatic toxicity and neurological toxicity (Główka et al., 2010). Noteworthy, contrary to busulfan, the rate of sinusoidal obstruction syndrome appears to be lower in patients treated with TREO than in those treated with busulfan (Slatter et al., 2011). Still, the results from the ongoing head-to-head clinical trial are

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yet to be published (ClinicalTrials.gov, 2015). Another advantage of TREO over busulfan is its dosing regimen. TREO is administered once daily on three consecutive days prior to the transplant procedure, while busulfan requires up to 4 portions of the drug administered on four consecutive days (Główka et al., 2010). However, the pharmacokinetics of TREO in pediatric patients, especially in infants, and its relation to the potential toxicity of the drug is not fully understood. Recently, a pivotal paper was published which described a relationship between a high exposure to TREO and early toxicity of this drug (van der Stoep et al., 2017). However, the authors focused solely on the prodrug and no data were provided on the concentrations of epoxytransformers. Therefore, the aim of the present study was to investigate the potential relationship of the exposure to TREO and its active transformer, S,S-EBDM, as well as variability of the pharmacokinetics of these entities by means of a population pharmacokinetic approach with a non-linear mixed-effects analysis.

2. Material and methods

2.1. Patients' characteristics and sampling protocol

The study included 14 pediatric patients, recruited in years 2007–2011 from the Department of Oncology, Hematology and Pediatric Transplantation at the Poznan University of Medical Sciences and the Department of Pediatric Hematology, Oncology and Bone Marrow Transplantation at the Wroclaw Medical University, with malignant and non-malignant diseases. Detailed patients' characteristics are presented in Table 1. Conditioning regimens prior to HSCT included TREO administered as a 1 h or 2 h infusion at daily doses of 10, 12 or 14 g/m^2.

The blood samples were drawn on a single day from all of the patients, at the first day of the conditioning. Two different sampling protocols were applied. A more intense sampling protocol, in which full blood samples were drawn at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 8 and 12 h after the start of the drug infusion, included 8 children. From the remaining 6 patients, the samples were drawn at 0.5, 1, 3, 4, 6 and 8 h after the beginning of the infusion. Any deviations from the sampling times were carefully noted. The study protocol was approved by the local Ethical Committee at the Poznan University of Medical Sciences and was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. An informed consent was obtained from the parents prior to initiating the study.

Table 1
Characteristics of pediatric patients included in the study. Continuous data are presented as means with standards deviations, and with a minimum-maximum range in brackets. Categorical data are presented as counts.

Characteristic	Value
Age [years]	7.7 ± 5.0 (0.4–15)
Body weight [kg]	28.3 ± 15. (7.7–52)
Body surface area [m^2]	0.98 ± 0.43 (0.25–1.63)
Boys/girls [*n*]	11/3
Total daily treosulfan dose and infusion length (*n*)	
10 g/m^2 – 1 h	1
12 g/m^2 – 1 h	3
12 g/m^2 – 2 h	4
14 g/m^2 – 2 h	6
Creatinine clearance [mL/min] (*n* = 8)	123 ± 60 (71–239)
Diagnosis	
Hematological malignancies	
ALL	4
AML	1
CML	1
Solid tumors	
ES	2
NBL	2
Non-malignant disorders	
SCN	1
WAS	1
X-ALD	2

ALL – acute lymphoblastic leukemia; AML – acute myeloid leukemia; CML – chronic myeloid leukemia; ES – Ewing's sarcoma; NBL – neuroblastoma; SCN – severe congenital neutropenia; WAS – Wiskott-Aldrich syndrome; X-ALD – adrenoleukodystrophy.

Immediately after blood collection the sample was treated with 50 µL of 1 M citric acid per 1 mL of full blood, to avoid ex vivo transformation of TREO to its epoxides. Subsequently, the samples were centrifuged and the obtained plasma was stored at −20 °C until the analysis.

2.2. Determination of TREO and S,S-EBDM

Concentrations of TREO and S,S-EBDM were determined by a validated high performance liquid chromatography method with triple quadrupole mass spectrometer (HPLC-MS/MS). The method validation and preliminary pharmacokinetic analysis were published in details elsewhere (Główka et al., 2015; Romański et al., 2014). The applied method allowed a simultaneous determination of TREO and S,S-EBDM in the plasma samples prepared by ultrafiltration through regenerated cellulose membrane filters with a 30 kDa cut-off. The method was linear in ranges 0.2–5720 µM and 0.9–175 µM, for TREO and S,S-EBDM, respectively. The lower limit of quantitation (LOQ) was 0.2 µM for TREO and 0.9 µM for S,S-EBDM. The method was validated according to the requirements of the European Medicines Agency and was proved to be adequately precise and accurate. Precision expressed as coefficient of variation, and accuracy, expressed as a relative error, were studied between the days by analyzing the samples at the whole concentration range, including LOQ. The coefficient of variation of the analyte determination was 1.8–11.5% and 0.2–13.9%, for TREO and S,S-EBDM, respectively. The relative error of TREO determination was 0.02–11.8%, while for S,S-EBDM the error was 0.8–9.2%.

2.3. Population pharmacokinetic modeling

2.3.1. Software and methods

Population pharmacokinetic modeling was performed in NONMEM software package (version 7.3.0, ICON Development Solutions, Hanover, MD, USA). Diagnostic plots were generated with the R program (version 3.1.2, Foundation for Statistical Computing, Vienna, Austria) and Xpose (version 4.5.3, Uppsala University, Sweden). Visual predictive check (VPC) and model validation were performed with scripts implemented in the Perl Speaks NONMEM (PsN, version 4.4.0) (Lindbom et al., 2004, 2005). All modeling and simulations were run through a Pirana graphical user interface (version 2.9.2) (Keizer et al., 2013).

For linear models, ADVAN5 subroutine was used. First-order conditional estimation method with interaction (FOCE-I) was applied for parameter estimation and determination of associated variability, as well as obtaining individual parameter estimates. An improvement in the model fit was evaluated with the likelihood ratio test. A difference in the objective function value (OFV) of 3.84 ($p < 0.05$) between nested models was considered significant. Visual examination of the diagnostic plots was used to assess the fit of the model. For each tested model following plots were inspected: individual (IPRED) and population-predicted (PRED) concentrations versus observed concentrations, IPRED and PRED concentrations versus time, weighted (WRES) and conditional-weighted residuals (CWRES) versus predicted concentrations, WRES and CWRES versus time and the distribution of CWRES.

The pharmacokinetic parameters were assumed to be log-normally distributed, therefore the interindividual variability (IIV) elements were applied exponentially. Since the dataset comprised of pediatric patients, an allometric scaling of clearance and volume of distribution parameters was applied, according to the following equation (Anderson and Holford, 2008):