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Pharmacokinetics of treosulfan and its active monoepoxide in pediatric patients after intravenous infusion of high-dose treosulfan prior to HSCT

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ABSTRACT

Pro-drug treosulfan (TREO) is currently evaluated in randomized phase III clinical trials as a conditioning agent prior to HSCT. In the present paper pharmacokinetics of both TREO and its biologically active monoepoxide (S,S-EBDM) was investigated in pediatric patients for the first time. The studies were carried out in 16 children (median age 7.5 years) undergoing TREO-based preparative regimen prior to HSCT, who received 10, 12 or 14 g/m^2 of the drug as a 1 h or 2 h intravenous infusion. Plasma concentrations of TREO as well as S,S-EBDM were determined using the validated HPLC–MS/MS method. The changes in S,S-EBDM concentration over time followed TREO levels. The area under the curve (AUC) of TREO was 100-fold higher than AUC of S,S-EBDM. No statistically significant dependency of the dose-normalized AUC of either TREO or S,S-EBDM on the patients' age and body surface area was stated. Moreover, plasma C_{max} as well as AUC of S,S-EBDM demonstrated linear correlation with the C_{max} and AUC of TREO, respectively. The biological half-lives of TREO and S,S-EBDM were similar. This indicates that S,S-EBDM was completely eliminated from the patients' blood within relatively short time, comparable to TREO.

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1. Introduction

Treosulfan ((2S,3S)-butane-1,2,3,4-tetraol-1,4-bismethanesulfonate, TREO), a structural analog of busulfan (BU), is an anticancer drug registered in several European countries for treatment of advanced ovarian carcinoma (Gropp et al., 1998). Since 2000 the drug has been applied in preparative regimen prior to hematopoietic stem cell transplantation (HSCT). The basis of using high-dose TREO in this procedure is its strong myeloablative action and lower organ toxicity in comparison to BU. Owing to such properties TREO has been an efficient myeloablative agent in many conditioning regimens before HSCT in adults as well as pediatric patients (Baronciani et al., 2008; Beelen et al., 2005; Beier et al., 2013; Casper et al., 2010, 2012; Główka et al., 2008; Greystoke et al., 2008; Hilger et al., 1998, 2000; Holowiecki et al., 2008; Michallet et al., 2012; Nemecek et al., 2011; Ruutu et al., 2011; Scheulen et al., 2000; Schmidt-Hieber et al., 2007; Shimoni et al., 2012; Wachowiak et al., 2011). Nowadays, randomized phase III clinical trials are conducted to compare TREO/fludarabine regimen with BU/fludarabine that currently constitutes a standard medical treatment (ClinicalTrials.gov.).

TREO is a pro-drug of two biologically active epoxy-derivatives. The process of its activation is non-enzymatic but depends on pH and temperature and it is stopped at pH < 5.0. The activation pathway consists of two consecutive reactions of intramolecular nucleophilic substitution (Fig. 1). In the first step of the transformation the monoepoxide ((2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate, S,S-EBDM) is formed and then it converts to (2S,3S)-1,2:3,4-diepoxybutane (S,S-DEB). The formed epoxy-transformers are responsible for the DNA alkylation, which causes inhibition of a replication and transcription (Feit et al., 1970; Główka et al., 2012; Hartley et al., 1999).

Despite increasing clinical use of TREO as a myeloablative agent before HSCT, so far only pharmacokinetic studies of the parent drug have been carried out. After intravenous infusion of high-dose

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TREO to adults as well as children prior to HSCT the drug demonstrated linear pharmacokinetics and its plasma concentrations were best fitted by a two-compartment model. Parameters of TREO such as biological half-life ($t_{0.5}$), volume of distribution (V_{ss}) and total clearance (Cl_{tot}) were independent of the dose (Beelen et al., 2005; Główka et al., 2008; Nemecek et al., 2011; Scheulen et al., 2000). Currently only one paper presents plasma concentrations of S,S-EBDM after iv TREO administration to two leukemia pediatric patients undergoing TREO-based preparative regimen (Główka et al., 2012). Moreover, up till now pharmacokinetic parameters of the epoxy-transformers of TREO after administration of the parent drug have not been published. Therefore, in this paper we described the results of investigation of the pharmacokinetics of TREO and S,S-EBDM performed in sixteen pediatric patients who received three different iv doses of TREO within a conditioning prior to HSCT.

2. Patients and methods

2.1. Materials

TREO was kindly supplied by medac GmbH (Hamburg, Germany). Formic acid, ammonium formate and codeine were obtained from Sigma–Aldrich (St. Louis, MO, USA). Citric acid of analytical grade was purchased from P.O.Ch. (Gliwice, Poland). Acetonitrile (Merck KGaA, Darmstadt, Germany) was of HPLC gradient grade. Demineralised water at a conductivity of 0.1 μS/cm, prepared in deionizer (Simplicity UV, Millipore, USA) and filtered through a 0.45 μm cellulose membrane filter (Sartorius, Germany), was used.

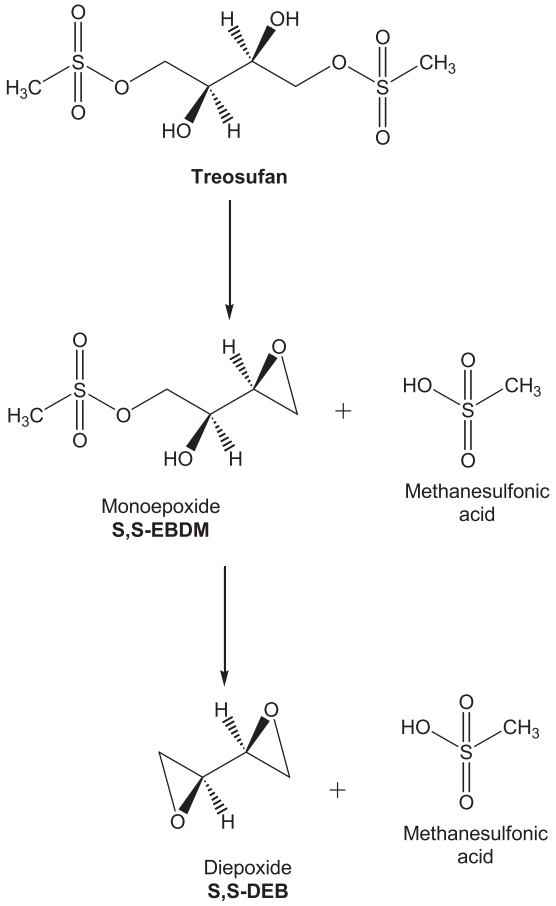

Fig. 1. Activation pathway of TREO to its biologically active epoxides.

2.2. Pediatric patients

Sixteen children (four girls and twelve boys) aged between 0.4 and 18 years (median age 7.5) with hematologic malignancies and nonmalignant diseases 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 were enrolled in the study (Table 1). TREO was administered as a conditioning agent prior to HSCT as a 1 h or 2 h intravenous infusion at daily doses of 10 g/m^2 (1 course in 1 patient), 12 g/m^2 (18 courses in 8 patients) and 14 g/m^2 (8 courses in 7 patients). Before the infusion the drug was dissolved in sterile water for injection to obtain the solution at concentration of 50 mg/mL. The study was approved by the Ethical Committee at the Poznan University of Medical Sciences. Parents of the young patients were informed in writing about all aspects of the study and their permission had to be received prior to the investigation.

2.3. Plasma collection

In the patients No. 1 and 7–15 the blood samples were drawn on a single day at following times: before infusion and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, and 12.0 h after the start of TREO infusion. From the patients No. 2–6 the blood samples were collected on three consecutive days, and from the patient No. 16 on two consecutive days at the limited time points: before infusion and at 0.5, 1.0, 3.0, 4.0, 6.0, and 8.0 h after the infusion start. The collected blood samples were immediately adjusted to pH below 5.0 by addition of 1 M citric acid (50 μL per 1 mL of blood) to avoid the artificial *ex vivo* activation of TREO and then they were centrifuged to obtain plasma. The resulting plasma was kept frozen at −20 °C until the analysis.

2.4. HPLC–MS/MS method

Concentrations of TREO and S,S-EBDM were determined by the HPLC method with tandem mass spectrometry detection. The LC 1200 Series chromatograph was coupled to 6410B Triple Quad mass spectrometer with the MassHunter workstation software for data processing (all from Agilent Technologies, USA). The compounds were separated on the Zorbax Plus C18 column (100 mm × 2.1 mm, 3.5 μm) (Agilent Technologies, USA) at a temperature of 40 °C. The mobile phase was composed of acetonitrile and ammonium formate–formic acid buffer pH 4.0 (5:95, v/v) and the flow was set to 0.4 mL/min. Codeine was used as an internal standard (IS). A volume of 5 μL of the prepared samples was injected to the HPLC system. The eluent from HPLC column was introduced directly to MS using electrospray ionization with positive mode. MS parameters were as follows: capillary voltage 4000 V, nebulizer gas (nitrogen) pressure 40 psi (275.8 kPa), drying gas (nitrogen) flow 10 L/min and drying temperature 300 °C. The following mass transitions were monitored using the multiple reaction monitoring (MRM) mode: TREO **296.0 → 279.1**, 296.0 → 183.1, 296.0 → 87.1, S,S-EBDM **200.1 → 87.1** and codeine 300.0 → 215.0, **300.0 → 165.0** (transitions for quantification are shown in bold). Fragmentor voltage for TREO and S,S-EBDM was 50 V and for codeine 130 V. Collision energies for TREO were 5, 5, and 9 eV, for S,S-EBDM 5 eV and for codeine 25 and 45 eV, respectively.

Plasma samples were prepared for determination of concentrations of TREO and S,S-EBDM according to the procedure described in Romański et al. (2014). Briefly, 52.5 μL of the acidified patient plasma was spiked with 50 μL of water and 10 μL of 0.5 mM solution of the IS. Thereafter, the sample was transferred into a centrifugal filter AmiconUltra-0.5 mL (cut-off 30 kDa) and centrifuged at 14,000*g* at 20 °C over 20 min. Two aliquots of the obtained plasma

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