Title: Models of Asparaginase and Asparagine Pharmacokinetics and Pharmacodynamics in Pediatric Acute Lymphoblastic Leukemia

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Objectives: Asparaginase (ASP) is an anticancer drug which is especially important for acute lymphoblastic leukemia (ALL) [1-9]. It’s mechanism of action is to reduce levels of asparagine by hydrolyzing it to aspartic acid and ammonia. Since leukemic cells do not synthesize adequate asparagine, they rely on serum asparagine for protein synthesis. Therefore, ASP selectively starves leukemia cells. There are currently three preparations of ASP available: E-coli (Elspar™); PEG (Oncospar™); and Erwinia (Erwinase™). The goal of this study is to assess the pharmacokinetics and pharmacodynamics of ASP using both descriptive and mechanistic models.

Methods: A cohort of 38 patients enrolled on St. Jude R16 protocol for relapsed ALL was used in this study. Patients were randomly assigned to receive either Elspar (10,000 IU/m², thrice weekly for 12 doses over 26 days) or Oncospar (2,500 IU/m² weekly for 4 doses over 21 days) during induction therapy. Five patients who had a hypersensitivity reaction to these preparations were switched to Erwinase. ASP pharmacokinetic samples were collected on days 8 and 29 of induction therapy. Additionally, serial plasma and CSF asparagine samples, serum samples for anti-ASP antibodies, and toxicity data (hypersensitivity to ASP) were collected over the 29 day treatment period. A mechanistic pharmacokinetic/pharmacodynamic model was developed which describes the plasma disposition of ASP and the enzymatic reaction between ASP and asparagine, including the endogenous formation of asparagine. This model was used to quantitatively describe the current data set, and to simulate the effects of variations to ASP dose, schedule, and preparation, along with other relevant model parameters on asparagine depletion.

Results: The clearance of ASP was significantly higher (p=0.001) for Elspar compared to Oncospar validating the dosing of Elspar every 2 to 3 days compared to the dosing of Oncospar every 7 days. Furthermore, there was significantly higher clearance of Oncospar (p=0.004) in patients that were positive for antibodies to Oncospar. Next, the pharmacodynamic effects of ASP on asparagine were assessed. We observed differences in CSF asparagine depletion according to ASP preparation and anti-ASP status. Specifically, patients who were positive for antibodies had attenuated depletion of plasma and CSF asparagine compared to those who were negative for antibodies (p=0.01 and p=0.04 respectively). Additionally, there was a trend to greater depletion (p=0.1) in CSF asparagine due to Elspar compared to Oncospar. Patients with hypersensitivity reactions to either Elspar or Oncospar and were switched to Erwinase had no significant reduction in their CSF asparagine from day 8 to day 29 (p=0.25). Our mechanistic model showed that the two factors which most influenced plasma asparagine levels were the maximum inhibitory effect parameter ($V_{MAX}$) and the rate of endogenous asparagine production. The model also showed that changes in ASP pharmacokinetics or dose (over the clinically relevant range) had little effect on the CSF asparagine dynamics. Instead, the transport of asparagine between the plasma and CSF has the highest impact on CSF asparagine levels.

Conclusions: The data shows that there are significant pharmacokinetic differences between the two preparations of ASP. Additionally, the ASP preparation along with antibody status affects the pharmacodynamics of asparagine. The mechanistic model developed helps us understand these differences and simulate the effects of various changes in the treatment.

References:


