Busulfan Dosing in Children: Body Weight versus Body Surface Area or Allometric Body Weight Dosing

Trame MN1,2,3 · Bergstrand M2 · Karlsson MO2 · Boos J3 · Hempel G1,3

1Department of Pharmaceutical and Medical Chemistry – Clinical Pharmacy - University of Münster, Germany
2Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
3Department of Paediatric Haematology and Oncology, University Children’s Hospital Münster, Germany
Contact e-mail: tramemirj@uni-muenster.de

Background and Objectives

- Busulfan is frequently used in high-dose conditioning regimens prior to bone marrow transplantation in children.
- Aim of this analysis was to evaluate whether the current licensed EMA dosing recommendation of IV busulfan (Busilvex®) according to body weight (BW) is appropriate for dosing busulfan in children and if a more precise dosing recommendation can be suggested.
- Due to the narrow therapeutic index of busulfan with an AUC of 900 – 1500 μM*h it was of particular interest to compare the area under the curve (AUC) of a BW based dosing regimen1 as recommended in the labelling of Busilvex® with other dosing regimens such as a body surface area (BSA) based dosing regimen.

Patients

Model Development Dataset

- 94 children received busulfan prior to bone marrow transplantation.
- Median age 9.2 years (range 0.4 – 18.8 years).
- 48 children received oral busulfan every 6 h.
- 41 received between 13 and 20 mg/kg.
- 46 children received IV busulfan as an infusion.
- first dose was given as a double dose: 1.4 – 2.0 mg/kg over 4 h followed 12 h later by 15 single doses: 0.7 – 1.0 mg/kg every 6 h.

Model Evaluation Dataset

- 34 children, median age 2.6 years (range 0.1 – 18.9 years), received IV busulfan once daily as a 3 h infusion.
- first dose in patients > 1 year: 120 mg/m²
- first dose in patients < 1 year: 90 mg/m²
- followed by doses evaluated through TDM.

Plasma Sample Collection and Analysis

- Plasma samples were drawn during routine drug monitoring in children receiving busulfan.
- 4 – 5 samples per dosing regimen prior to next dose.
- All plasma samples were analysed either by HPLC using postcolumn photolysis or by LC-MS with a LOD of 5 μg/L.

Population Pharmacokinetic Analysis

- Plasma concentration-time data were analysed using NONMEM VI.
- One-compartment model with 1st-order absorption.
- FOCE Interaction
- Residual variability was modelled using a proportional error model.
- Exponential model for IV and IOV.
- Covariates:
  - BSA or BW*0.75 as a covariate on clearance (CL) and BW as a covariate on volume of distribution (V).

Results

- CL values did not reflect the shape of the CL versus weight curve as reported in previous investigations2, in neither the development nor the evaluation dataset (figure 1 a,b). Instead, our data show a 22% higher CL for children < 9 kg of BW and lower CL values (range 30-56%) for children > 9 kg of BW.
- Comparing the CL per BSA (figure 1 c) or per allometric BW (figure 1 d), no difference in the scaled CL between the five weight groups is seen.
- By external model evaluation and simulation using prediction corrected Visual Predictive Checks3 we were able to confirm the models (figure 2).

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Table 1: Population model comparison [Abbreviations: BW body weight, BSA body surface area, CL Clearance, V volume of distribution, V/Cl clearance, % absorption rate constant, F bioavailability, standard errors in brackets, * estimated for a 27.2 kg subject, ** CV% based on simulations and FE(1)mean(FE)] and in squared parentheses shows the variance for the log-transform of F

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base model</th>
<th>BSA model</th>
<th>Allometric BW model</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL [l/h]</td>
<td>3.1 (0.9)</td>
<td>4.8 (1.8)</td>
<td>4.1 kg<em>0.75 (1.8)</em></td>
</tr>
<tr>
<td>V [l]</td>
<td>15.3 (11.0)</td>
<td>18.4 kg<em>0.75 (11.0)</em></td>
<td>18.3 kg<em>0.75 (11.0)</em></td>
</tr>
<tr>
<td>xA [l]</td>
<td>0.66 (0.80)</td>
<td>1.00 (1.00)</td>
<td>0.80 (1.00)</td>
</tr>
<tr>
<td>F (%)</td>
<td>67 (11)</td>
<td>63 (9)</td>
<td>60 (11)</td>
</tr>
<tr>
<td>BW/Cl of xV (%)</td>
<td>3.4 (0.2)</td>
<td>3.2 (0.2)</td>
<td>2.0 (0.2)</td>
</tr>
</tbody>
</table>
| Random effects
| Interindividual variability | 47 (10) | 25 (10) | 21 (10) |
| V (%)     | 56 (10)   | 20 (10) | 24 (10) |
| xA (%)    | 119 (11)  | 65 (11) | 56 (11) |
| F (%)     | 29 (11)   | 24 (11) | 25 (11) |
| Intravariability | 15 (11) | 11 (11) | 11 (11) |
| V (%)     | 29 (11)   | 21 (11) | 22 (11) |
| Residual error
| Proportional [%] | 27 (7) | 27 (7) | 27 (7) |
| Objective function | 1066 | 1066 | 1066 |

Conclusion

- The findings of our analysis provide an alternate dose regimen to the EMA dosing recommendation of Busilvex® in children.
- Dose regimens based on BSA and allometric BW provide AUCs closer to the therapeutic target for a priori and TDM dose adjustments based on our simulations.
- An update to Busilvex® labelling may be warranted.

References