INTRODUCTION

Busulfan is a chemotherapeutic drug that is used in conditioning regimens for hematopoietic stem cell transplantation (HSCT). The drug is administered once daily in a three hour infusion according to the following scheme:

<table>
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<th>Body weight</th>
<th>Myeloablative target AUCday0-4 90mg*h/L 4 days, 1dd, mg/kg</th>
<th>Non-myeloablative target AUCday0-3 60mg*h/L 3 days, 1dd, mg/kg</th>
<th>JMML target AUCday0-4 75 mg*h/L 4 days, 1dd, mg/kg</th>
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<tbody>
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<td>kg</td>
<td>Dose (mg) Dose (mg/kg)</td>
<td>Dose (mg) Dose (mg/kg)</td>
<td>Dose (mg) Dose (mg/kg)</td>
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<td>10.1 3.4</td>
<td>9 3.2</td>
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<td>24 4.7</td>
<td>21.0 4.2</td>
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<td>31.7 4.5</td>
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<td>36.9 4.6</td>
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</table>

A total exposure of 90 mg*h/L relates to 21.6 mM*min total, or 5400 μM*min/day.

Optimal exposure to busulfan in combination with fludarabine (90 mg*h/L in 4 days for myeloablative and 60 mg*h/L for non-myeloablative) leads to an optimal (event free) survival. When busulfan is combined with another alkylating agent (cyclophosphamide, thiotepa, melphalan) an exposure of 75 mg*h/L is advised. This exposure can be achieved by drawing blood samples on the first day of busulfan treatment and adjust the dose of busulfan on the second day of treatment based on the results of therapeutic drug monitoring (TDM). During intravenous administration of busulfan it is very important to draw blood samples exactly according to protocol. In these samples concentrations of busulfan in plasma will be measured and the 4-day-cumulative area under the curve (cAUC) will be calculated using pharmacokinetic (PK) software and a PK-model.
AIM
Correct and uniform administration and blood sampling of busulfan to estimate exposure (cAUC) based on TDM.

PREPARATION
Inform the patient and parents about the procedure.

1. Administration of busulfan
   - Busulfan is administered on 3 or 4 consecutive days. Blood samples must be drawn on day 1 and are measured by the laboratory on day 2. Administration of busulfan on day 2 will take place only after TDM is performed and the advised dose is calculated and communicated to the treating physician.
   - The pharmacy department compounds the busulfan solution by diluting Busilvex 6 mg/ml with NaCl 0,9% to a fixed concentration of 0,6 mg/ml. This solution is stable for 8 hours at room temperature (including infusion time). A cytostatic connector (Connect Z, Codan) filled with NaCl 0,9% is connected to the infusion bag to prevent contact with the busulfan solution when connecting to the infusion system.
   - Use NaCl 0,9% for flushing the infusion system before and after administration of busulfan.
   - For administration use an infusion system with cytostatics adapter and follow the general rules for the administration of cytostatics.
   The complete infusion system is described in appendix 1.

Tools:
- Syringe 10 ml filled with NaCl 0,9%
- Infusion bag (or syringe) with busulfan solution
- Cytostatic drug infusion system (see appendix 1)
- Infusion pump
- Non sterile gauze, with disinfectant (alcohol 70%)
- Non sterile nitril gloves
- If needed: plaster, non sterile gauze

2. Blood sampling management
   - The patient must have a double-lumen central venous catheter (CVC) (usually a Hickman catheter), because administration and drawing blood samples necessitates 2 separate intravenous lines. To the blood sampling lumen a Microclave® is connected.
   - The physician or SCT coordinator provides pre-printed laboratory forms showing date, time of collection and blood sample number. The laboratory forms are available at the UMC laboratory (alternatively: fill out the information at our website, link see below).

Tools:
- Adapter with a Microclave® on the bloodsampling lumen of the CVC
- Laboratory form; use 1 form for each blood sample
- EDTA laboratory sampling tube (2 ml)
- Sterile syringes of 2 ml and 5 ml
- Needle
- Syringe 10 ml filled with NaCl 0,9%
PROCEDURE
Check whether the information provided is understood by the patient and parents.
Before and after the procedure hand hygiene is applied.
Gather all the required supplies before starting the procedure.

1. Administration of busulfan in infusion bag
   - Disinfect the connections with alcohol 70%
   - Prepare the infusion bag with busulfan and set the infusion pump to "wait"
   - Connect the bag with busulfan solution with the Connect Z to the cytostatics adapter, close the clamp between the adapter and the flushing fluid and open the clamp of the tubing of the infusion bag with cytostatics.
   - Fill the infusion system at maximum speed with 20 ml busulfan solution.
   - Calculate the infusion rate:
     \[
     \text{infusion rate (in ml/hour)} = \frac{\text{total content infusion bag (X ml) + total volume infusion system (at UMC Utrecht: 35 ml) - volume filling infusion system (20 ml)}}{3 \text{ hours}}
     \]
   - Have a colleague check the calculated infusion rate.
   - After filling the system set the pump to the calculated infusion rate. This is the time of starting infusion busulfan.
   - Have a colleague check the set infusion rate.
   - At the end of the busulfan infusion set the infusion pump to "wait".
   - Close the clamp of the tubing of the infusion bag with busulfan and open the clamp between the adapter and the rinsing solution.
   - Flush with 35 ml NaCl 0,9% at the same infusion rate that was used for infusion of the busulfan solution.
   - When the flushing phase is completed, set the pump back to the infusion rate prior to infusion of busulfan. This is the time point of ending infusion busulfan.

2. Collecting and processing of blood samples
   - On day 1 blood samples are drawn for TDM, in case of dose adjustment of > 25% blood samples are also drawn on day 2 (or 3).
   - Blood collection takes place via the Microclave® which is connected to the second lumen i.e. not the one via which busulfan was administered.
   - Stop all ongoing infusions of all lumens.
   - Draw the blood sample according to the general rules for bloodcollection from a central venous line at the times indicated on the laboratory forms.
     - Sample 1: approximately 5 minutes after end of infusion*
     - Sample 2: approximately 1 hour after end of infusion
     - Sample 3: approximately 2 hours after end of infusion
     - Sample 4: approximately 3 hours after end of infusion
   - * Write down the exact time the sample was drawn on the pre-printed laboratory form
   - Please note on the first form:
     - dosage
     - time of starting and ending the busulfan infusion
   - Restart the pump for both lumens.
   - After every collection please send the blood sample and laboratory form immediately to the laboratory where the samples are placed directly in the freezer.
After the complete procedure please fill out patient details and contact details of the treating physician at our website via the following link: https://www.umcutrecht.nl/subsite/Farmalab/Bepalingen/Bepalingen+A+tm+C/Busulfan/AUC-curve.htm

REFERENCES


For more information, please contact:

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e-mail: E.M.L.vanReij@umcutrecht.nl

This information is based on SOP:

- AFSPRAKEN + LOGISTIEK VOOR BUSULFAN BLOEDAFNAME EN THERAPEUTIC DRUG MONITORING
- Medicijn toedienen - busulfan intraveneus en bloedspiegels afnemen - Kinderen
APPENDIX I: infusion system busulfan

Administration of busulfan in infusion bag:
1. Connect Z (Codan)
2. Cyto-Set Infusomat Space (B. Braun)
3. Infutak 2-weg (Medisize)
4. Extension line 1x3mm, 700cm (Dialex Biomedica)
5. Extension line 1mm, 25cm (Cair), connected with Hickman catheter

Administration of busulfan in syringe:
1a. 2-way connector (Codan)
2a. Extension line 1mm, 200cm (Cair)

APPENDIX II: schedule of busulfan administration and blood sampling

Busulfan infusion in 3 hours

<table>
<thead>
<tr>
<th>Filling system</th>
<th>Busulfan infusion, including flushing</th>
<th>Blood sampling for therapeutic drug monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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