Optimización de la dosis de **BUSULFÁN intravenoso** en el acondicionamiento previo al TPH

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Laura, **2 años**, 14 kg, 87 cm
Mucopolisacaridosis
Objetivo mieloablativo: 85.000-95.000 ng/ml x h
Dosis inicial: **4,8 mg/kg**

Protocolo
Busulfán
Ciclofosfamida
Timoglobulina

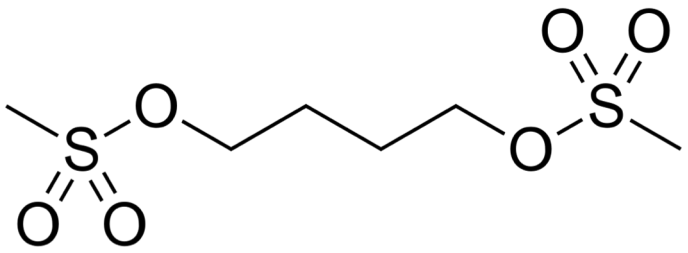
Guille, **16 años**, 82 kg, 174 cm
Leucemia aguda linfoblástica
Objetivo mieloablativo: 80.000-85.000 ng/ml x h
Dosis inicial: **3,2 mg/kg**

Protocolo
Busulfán
Tiotepa
Fludarabina

Daniel, **4 meses**, 3,6 kg, 48 cm
Síndrome de Omenn
Intensidad reducida: 55.000-65.000 ng/ml x h
Dosis inicial: **3,5 mg/kg**

Protocolo
Busulfán
Fludarabina
Timoglobulina

Busulfán



- Tratamiento neoplasias mieloproliferativas (2 mg- 6 mg/d VO)
  - Leucemia mieloide crónica
  - Policitemia vera
  - Trombocitosis esencial

- **Acondicionamiento previo al trasplante de progenitores hematopoyéticos (dosis altas)**

  + agentes linfotóxicos (ciclofosfamida o fludarabina)

  + fármacos con acción anti-tumoral (tiotepa, melfalán, clofarabina)

Monitorización farmacocinética busulfán

¿Por qué?

¿Cuánto?

¿Cómo?

Biol Blood Marrow Transplant 22 (2016) 1915–1925

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Guideline

Personalizing Busulfan-Based Conditioning: Considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee

Jeanne Palmer [1,*], Jeannine S. McCune [2,†], Miguel-Angel Perales [3], David Marks [4], Joseph Bubalo [5], Mohamad Mohty [6], John R. Wingard [7], Angelo Paci [8], Moustapha Hassan [9], Christopher Bredeson [10], Joseph Pidala [11], Nina Shah [12], Paul Shaughnessy [13], Navneet Majhail [14], Jeff Schriber [15], Bipin N. Savani [16], Paul A. Carpenter [17]

Table 1
Frequently asked questions

Frequently Asked Questions (FAQs)	Summary of Answers
FAQ1. Why does personalized busulfan (BU) dosing need to be considered during hematopoietic cell transplantation (HCT)?	Personalized BU dosing is considered mainly because BU has a narrow therapeutic index and a specific BU exposure have been associated with important clinical outcomes in in HCT patients. Therefore, personalized BU dosing via therapeutic drug monitoring (TDM) needs to be considered to minimize sinusoidal obstruction syndrome, lower graft rejection rates, and lower relapse rates in certain situations.
FAQ2. Is personalized BU dosing always necessary?	No. BU TDM is currently considered to be unnecessary for reduced intensity conditioning (RIC) regimens where the balance of BU toxicity to BU efficacy is favorable. With RIC, data is needed to determine if lower BU doses or lower BU exposure compromise efficacy.
FAQ3. When should conditioning utilize BU TDM?	The first consideration to use BU TDM is when the specific BU exposure is associated with clinical outcome(s) in a homogenous patient population. BU TDM must be used in children receiving high-dose BU before allogeneic HCT to lower the risk of graft rejection. Another significant consideration for personalizing BU is when the regimen was developed with BU TDM.
FAQ4. Is oral or IV BU preferred?	Intravenous (IV) busulfan tends to be preferred on the basis of patient convenience and concerns about intrapatient pharmacokinetic variability because of unpredictable gastrointestinal absorption of oral BU and hepatic first-pass effects.
FAQ5. How should personalized BU dosing be achieved?	Personalized BU dosing should be achieved by using TDM after selecting and administering the initial dose of high-dose BU.
FAQ6. How is the initial BU dose best selected?	The initial IV BU dose should be based on the European Medicines Agency (EMA) nomogram for children with a target area under the curve (AUC) of 1125 μmolar × min. For adults with the same target AUC, the initial IV BU dose should be 0.8 mg/kg every 6 hours or 3.2 mg/kg every 24 hours. The initial IV BU dose may need adjustment for lower or higher target AUC. Oral BU dosing always begins at 1 mg/kg.
FAQ7. What is the optimal dosing frequency of BU?	The available IV BU data for adults do not suggest a significant difference in outcomes between Q6H and daily dosing, likely because BU clearance, volume of distribution and half-life appear to be similar regardless of dosing frequency. In children relevant studies are ongoing. Oral BU should be administered Q6H.
FAQ8. What is the best method for predicting BU clearance?	BU clearance is calculated based on the administered BU dose and an estimate of post-dose BU exposure using validated pharmacokinetic modeling tools (see Technical Appendix). Test dose strategies are not currently recommended.
FAQ9. How do other medications affect BU pharmacokinetics?	Ideally, there would be no changes to medications given concomitantly with BU in order to minimize any drug-drug interactions that alter BU pharmacokinetics. The following medications have affected IV BU clearance: fludarabine, deferasirox, metronidazole; or oral BU clearance: fludarabine, metronidazole, ketobemidone, and itraconazole. Phenytoin affects oral BU clearance but its effect upon IV BU clearance is unclear. By extrapolation, voriconazole or posaconazole would likely decrease BU clearance and should be avoided during conditioning.
FAQ10. Should the initial BU dose be personalized based on genetic polymorphisms?	Pharmacogenomics-based dosing of BU, either IV or oral, is not recommended.

¿Por qué?

RIESGOS SOBRE-EXPOSICIÓN ↑ SOS

ESTRECHO MARGEN TERAPÉUTICO

RIESGOS INFRA-EXPOSICIÓN ↓ Fallo implante, recaídas

↑ Variabilidad interindividual
≠ Objetivo según paciente

- 1989; Grochow LB et al; **Bu VO**; Beneficios TDM
- 1999; Andersson et al; **Bu IV**, Ventajas teóricas

SOS: Síndrome de obstrucción sinusoidal
TDM: *Therapeutic Drug Monitoring*

¿Por qué?

La exposición importa…

- ✓ McCune JS, Gibbs JP, Slattery JT. **Plasma concentration monitoring of busulfan: does it improve clinical outcome?** Clin Pharmacokinet. 2000; 39: 155-165.
- ✓ Bolinger AM, Zangwill AB, Slattery JT, et al. **Target dose adjustment of busulfan in pediatric patients undergoing bone marrow transplantation**. Bone Marrow Transplant. 2001; 28: 1013-1018.

… aunque la evidencia es distinta según la enfermedad de base

- ✓ Baker KS, Bostrom B, DeFor T, Ramsay NK, Woods WG, Blazar BR. **Busulfan pharmacokinetics do not predict relapse in acute myeloid leukemia**. Bone Marrow Transplant. 2000; 26: 607-614.

Beneficios demostrados de la monitorización farmacocinética de busulfán

(Régimen BU/CY)

- Mejora tasas implante en niños
- Disminuye toxicidad hepática en adultos
- Disminuye tasas de recaída en pacientes con LMC no tratada previamente

¿Cuánto?

¿Exposición óptima? → AUC? Css?

- AUC = 900-1350 (+/- 5%) µmolar x min (Q6H)
- Factores: enfermedad de base, riesgo rechazo
- Literatura heterogénea, series limitadas de casos

Ojo unidades
Ojo Q6H

Table 2
BU AUC to CSS Equivalency Table

AUC µMolar × min Q6H dosing	AUC µMolar × min daily dosing	CSS * ng/ mL	AUC† mg/L × h Q6H dosing	AUC mg/L × h daily dosing
877	3508	600	3.60	14.4
900	3800	650	3.90	15.6
1125	4500	770	4.62	18.5
1316	5262	900	5.40	21.6
1500	6000	1026	6.16	24.6

All BU plasma exposures are presented in this manuscript using the units within the original manuscript and, if needed, converted to BU concentration at steady state (CSS). The technical appendix and equations 1 to 3 in FAQ5 explain how to convert between the various BU exposure units.

* CSS = AUC divided by the dosing frequency.

† When the AUC is expressed in micromolar (micromoles/L) units, then the BU molecular weight (246.3 g/mol) must be used to calculate the AUC in mg/L units.

AUC global = 60.000 ng/ml x h
Css = 650 ng/ml

AUC global = 90.000 ng/ml x h
Css = 925 ng/ml

INTENSIDAD REDUCIDA

MIELO ABLATIVO

Css = AUC/intervalo posológico

¿Cómo?

¿Qué necesito para monitorizar busulfán?

1 muestra pre-1ª dosis
4 muestras post 1ª dosis

Técnica
Laboratorio de Bioquímica

Conocimiento para estimar la exposición e interpretar los resultados

Método analítico: cromatografía líquida con detección ultravioleta (HPLC-UV) previa derivatización del compuesto con dietilditiocarbamida (Dr. Edgar Zapico)

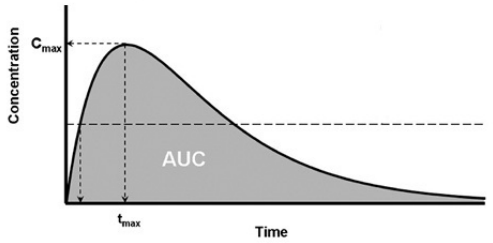
- Grochow LB, Jones RJ, Brundrett RB, Braine HG, Chen TL, Saral R, et al. Pharmacokinetics of busulfan: correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. Cancer Chemother Pharmacol. 1989; 25 (1): 55-61.
- Ehrsson H, Hassan M, Ehrnebo M, Beran M. Busulfan kinetics. Clin Pharmacol Ther. 1983; 34 (1): 86-9.
- Vassal G, Gouyette A, Hartmann O, Pico JL, Lemerle J. Pharmacokinetics of high-dose busulfan in children. Cancer Chemother Pharmacol. 1989; 24 (6): 386-90.
- Vassal G, Deroussent A, Challine D, Hartmann O, Koscielny S, Valteau-Couanet D, et al. Is 600 mg/m2 the appropriate dosage of busulfan in children undergoing bone marrow transplantation? Blood. 1992; 79 (9): 2475-9.
- Regazzi MB, Locatelli F, Buggia I, Bonetti F, Zecca M, Pregnolato M, et al. Disposition of high-dose busulfan in pediatric patients undergoing bone marrow transplantation. Clin Pharmacol Ther. 1993; 54 (1): 45-52.

¿Cómo?

Dosis inicial: según protocolo

¿Cómo se calcula el AUC?

✓ Programa de regresión no lineal (*Software ID3*)



Modelo poblacional busulfán

Ajuste de dosis: según objetivo individualizado +/- nuevo control

✓ Las fórmulas:

- Cl = Dosis administrada/AUC
- **Dosis personalizada = Cl x objetivo AUC**

Seguimiento: profilaxis antiepiléptica, interacciones, analítica, validación…

Nuestra experiencia (2010-2020)

- 43 pacientes pediátricos **BUSULFAN IV**
- 4 meses-16 años; 30 varones/13 mujeres (70/30%)
- 5 intensidad reducida, 38 mieloablativos
- Dosis iniciales: 3,2 mg/kg – 5,1 mg/kg

Sin ajuste	Aumento dosis	Disminución dosis
5 (12%)	14 (32%) Magnitud ↑ 15%	24 (56%) Magnitud ↓ 12%

- ✓ Se repitió monitorización tras la segunda dosis en 13 casos
- ✓ 8 fallos de implante (2 recuperados)
- ✓ 4 síndrome sinusoidal hepático

Conclusiones

La monitorización farmacocinética de busulfán en pediatría…

- Herramienta que puede ayudar a **mejorar los resultados de eficacia y seguridad**.
- Técnica analítica + software + **CONOCIMIENTO**
- **Individualización del objetivo**
- **Seguimiento farmacoterapéutico**

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