Busulfan Pharmacokinetics Using a Single Daily High-Dose Regimen in Children With Acute Leukemia

By Peter J. Shaw, Christa E. Scharping, Russell J. Brian, and John W. Earl

The pharmacokinetics of busulfan, given as a single daily dose (either 4 mg/kg or 150 mg/m²), was determined in 22 children undergoing bone marrow transplantation for acute leukemia. The single daily dose regimen showed similar pharmacokinetics to previously reported regimens of 4 x 1 mg/kg, except for fourfold higher mean peak plasma levels and negligible trough levels. Daily systemic exposure for single dose regimens based on weight (4 mg/kg) or surface area (150 mg/m²), respectively, were very similar to regimens of (4 x 1 mg/kg) or (4 x 37.5 mg/m²). Dose (milligrams per kilogram), peak plasma levels, and area under the curve (AUC) were all higher in 12 children treated with 150 mg/m² busulfan than in 9 children treated with 4 mg/kg. AUC was age dependent for the 4 mg/kg dose but not for the 150 mg/m² dose. The use of a 150 mg/m² dose allows escalation of the dose above 4 mg/kg, eliminating the tendency for younger children to receive lower systemic exposure. Little toxicity was observed in this study. Clearance and distribution volume correlated negatively with age, and AUC correlated positively with dose (milligram per kilogram). Administration of busulfan as crushed rather than whole tablets reduced the delay time for appearance of busulfan in plasma but had no effect on absorption or other pharmacokinetic parameters.

Most patients received initial chemotherapy according to an Australian & New Zealand Children's Cancer Study Group (ANZ CCGS) protocol for AML. The study, including sampling for pharmacokinetics and dose escalation of Bu, was approved by the Children's Hospital Ethics Committee.

A total of 22 children between 1 and 14 years of age were involved in this study, 19 with AML and 3 with ALL. Table 1 gives details of the clinical data and the chemotherapy conditioning regimens for these children. Bu was given as whole or crushed tablets in a single dose on each of four mornings. A normal diet was offered on each day of Bu administration. Nine patients were given a single daily dose of Bu for 4 days at 4 mg/kg/d. Two of these patients, who were recipients of unrelated transplants, had melphalan at 140 mg/m² after Bu. Thirteen patients were administered a single daily dose for 4 days at 150 mg/m²/d. Bu (10 mg/kg) was followed by 2 days of cyclophosphamide at 60 mg/kg/d. All patients received anti-convulsant prophylaxis. None received phenytoin; two patients already on carbamazepine continued this drug; the others all received clonazepam, 0.05 mg/kg twice daily orally from the day before to the day after Bu administration.

The Bu dose was administered during the day, before 1 pm in 19 of 21 patients with the mean starting time of 11:00 hours (range: 9:00 to 14:30 hours). Thus, the effects of diurnal variation on Bu pharmacokinetics was minimized. Heparinized whole blood samples (1 mL) were collected from central venous lines. The first sample was collected before Bu was administered and the remainder at 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after the dose. Occasionally an 18-hour sample was also collected. Plasma samples were separated by centrifugation for 10 minutes at 4°C at 3,000 rpm, then frozen and stored at −20°C until analysis.

Bu was determined in plasma samples using a modified version of a previous method by conversion to the 1,4-dihydroxybutane derivative and measurement by Gas Chromatography with Electron Capture. An aliquot of plasma (0.2 mL) was added to acetone (0.1 mL) and 1 mol/L sodium phosphate buffer, pH 7.0 (0.1 mL), in a screw

From the Departments of Biochemistry and Oncology, Royal Alexandra Hospital for Children, Camperdown, Australia.

Submitted October 7, 1993; accepted June 9, 1994.

C.E.S. is supported by the Leukaemia Research & Support Fund. Address reprint requests to Peter J. Shaw, FRACP, Oncology Unit, Royal Alexandra Hospital for Children, Camperdown, Sydney, NSW 2050 Australia.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1994 by The American Society of Hematology.

Blood, Vol 84, No 7 (October 1), 1994: pp 2357-2362

2357
and the mixture was vortexed for 20 seconds then heated at 70°C for 40 minutes with brief vortexing every 10 minutes. The hexane layer was transferred to a crimp sealed autosampler vial and molL potassium iodide (1.6 mL) and hexane (0.5 mL) was injected into the gas chromatograph. A Hewlett Packard 5730A diameter (id.) packed column of 2% OV101 on 100-120 mesh High linear electron capture detector and a 0.61 Gas Chromatograph was used, equipped with a extracted, derivatized, and analyzed by GC as described for the plasma samples. The peak height (millimeters) was plotted against concentration time of 6.8 minutes. 7WC, 250°C, and 25°C, respectively. 1,4-Diiodobutane had a retention isothermally with oven, detector, and injector port temperatures of Performance Chromosorb W. The within-day coefficients of variation were 2.6% for a Bu concentration of 6.8 pmol/L (n = 7). Another patient (126) also had trisomy 21, but did not have atypical pharmacokinetics, so the cause of the atypical pharmacokinetics in patient 113 remains unknown.

Means and standard deviations were calculated for the various pharmacokinetic parameters and compared by the Wilcoxon Rank Sum test using the Statistical Package for Interactive Data Analysis (SPIDA) version 6.04 (The Statistical Computing Laboratory, Macquarie University, NSW, Australia). Pharmacokinetic parameters from literature sources were taken from the published figures and, if necessary, converted to micromoles per liter or converted to a different time unit, in order to allow direct comparisons. In some cases published data tables were used to calculate means and standard deviations, elimination and absorption constants being first converted to half-lives.

RESULTS

A semi-logarithmic plot of the disposition of Bu from a single daily oral dose of Bu administered at 4 mg/kg or 150 mg/m² is shown in Fig 1. Mean plasma Bu levels and 95% confidence intervals for the two groups of patients are shown for a 24-hour period. There was a short delay time after the dose was administered before Bu appeared in the plasma. Bu reached a peak in plasma after about 2 hours and was almost completely eliminated by 24 hours as 17 of 21 patients had 24-hour trough-levels below the 0.1 µmol/L limit of detection and the remaining 4 were below 0.4 µmol/L. None of the patients vomited on the day that Bu pharmacokinetics was performed.

In 9 of 21 patients a 4 mg/kg single dose per day regimen was used and the remaining 12 patients had a 150 mg/m²
busulfan pharmacokinetics in leukemia

Fig 1. Semi-logarithmic plot of the mean disposition of busulfan in children on the 4 mg/kg and 150 mg/m² dosing regimens.

From www.bloodjournal.org by guest on October 26, 2017. For personal use only.
and the remainder four times per day. We found a negative correlation between clearance and age in the whole group of 21 patients (Fig 3B), showing that younger children had higher Bu clearance. A previous study also showed that clearance was significantly higher in younger children. There was also a negative correlation between volume of distribution and age (Fig 3C), indicating that younger children in our study had higher distribution volumes than older children.

Younger children in the study were given crushed tablets of Bu whereas the older children were given whole tablets. Patients taking crushed tablets had a significantly shorter delay time (Table 3), but there was no significant difference in absorption, elimination, AUC, or dose (milligrams per kilogram). The mean delay time was 40 minutes for whole tablets compared with 8 minutes for crushed tablets. The possibility was previously raised6 that the form of drug administration (crushed tablets or capsule) may affect absorption, but we have shown that the form of drug administered affects delay time rather than absorption.

Toxicity and outcome are summarized in Table 1. One patient suffered a brief convulsion after the third dose of Bu. She was on carbamazepine and after loading with oral clonazepam the fourth dose of Bu was given uneventfully. Definite VOD occurred in one patient at the 4 mg/kg dose and another had possible VOD with the 150 mg/m² dose (124), but this is uncertain as she also had skin, gut, and liver graft-versus-host disease. Interstitial pneumonitis of unknown etiology requiring ventilator support also occurred in this patient. The pharmacokinetic profiles of the patients who developed VOD or pneumonitis did not differ from the rest of the group, but the numbers are small.

DISCUSSION

High-dose therapy with Bu has customarily been based on body weight as a dose of 1 mg/kg four times daily. We have used a single daily dose of 4 mg/kg and found the

<table>
<thead>
<tr>
<th>Table 3. Crushed or Whole-Tablet Dose Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter (units)</td>
</tr>
<tr>
<td>Age (mo)</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Delay (min)</td>
</tr>
<tr>
<td>Time peak Bu (min)</td>
</tr>
<tr>
<td>K (abs) (h⁻¹)</td>
</tr>
<tr>
<td>T/2 (abs) (min)</td>
</tr>
<tr>
<td>K (elim) (h⁻¹)</td>
</tr>
<tr>
<td>T/2 (elim) (min)</td>
</tr>
<tr>
<td>AUC (µmol/L, h)</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
</tr>
</tbody>
</table>
regimen well tolerated, with little toxicity. As our regimen of 4 mg/kg/d was well tolerated but associated with an appreciable relapse rate following autologous BMT, it was logical to consider dose escalation. One approach was to use a dosing regimen based on body surface area. Pharmacokinetic studies showed that a surface-area based single dose of 150 mg/m² Bu in children was on average 35% higher than the weight-based 4 mg/kg dose and produced a 63% increase in the AUC indicating considerably higher systemic exposure was achieved. This higher dose was also well tolerated with little toxicity.

A comparison between our results for the 4 mg/kg and 150 mg/m² regimens with previously reported Bu pharmacokinetics is shown in Table 4. The values we obtained for mean delay time, absorption half-life, elimination half-life, clearance, distribution volume, and time to peak Bu compared well with the results obtained by other centers. The mean peak plasma level for our 4 mg/kg dose was found to be 14.0 μmol/L, which was 4.2-fold higher than the value reported by Vassal et al² using a 1 mg/kg dose. Although only 2.6-fold higher than the value reported by Hassan et al³ for a 1 mg/kg dose.

For our 150 mg/m² group we found a 4.8-fold higher mean AUC than that found by Vassal et al⁴ using a 37.5 mg/m² dose and a 6.7-fold higher mean AUC than that found by Yeager et al⁵ in children on a 38.9 mg/m² dose. The comparisons show that systemic exposure on a single daily dose weight-based regimen (1 × 4 mg/kg) is equivalent to a qid regimen (4 × 1 mg/kg) and that the systemic exposure for a single daily dose surface-area based regimen (1 × 150 mg/m²) is the same or greater than qid (4 × 37.5 mg/m² or 4 × 38.9 mg/m²) regimens.

We observed that AUC increased with age for a weight-based regimen confirming that younger children have a relatively reduced systemic exposure to Bu on this commonly used regimen. Younger children received equivalent systemic exposure to the older children when the dose was based on body weight.

The relatively high relapse rate in autologous BMT patients,¹⁶ and past data,¹⁵ suggested that children achieved lower systemic exposure than adults. We have now confirmed this by our observation that systemic exposure to Bu changes with age and is lowest in the younger patients when the dose is based on body weight. It has been proposed that higher clearances¹⁰ and larger volumes of distribution,¹⁰ may lower systemic exposure in younger children. The higher clearance and larger volume of distribution
in younger children observed in this study and in a previous study\(^5\) may be the cause of the relatively lower systemic exposure in younger children.

When considering escalation of the dose of Bu, our hypothesis was that escalation of a single daily dose may provide additional antileukemic activity without a prohibitive increase in toxicity, through avoiding prolonged high trough levels. It is still too early for us to comment on the toxicity of the higher dose of Bu. The incidence of VOD was too low in this series of patients for us to determine whether a relationship exists between VOD and AUC or peak Bu levels. Convulsions have not been a problem with clonazepam prophylaxis. Because of the low toxicity encountered in our patients, we cannot comment on any possible relationship between Bu pharmacokinetics and the complications of therapy or the relapse rate. However, continued pharmacokinetic monitoring of patients in trials designed to establish a target AUC may give us this information in the future. Our experience to date would confirm the appropriateness of increasing the dose of Bu in children to produce dosing equivalent to that used in adults. We are continuing to recruit patients at the 150 mg/m\(^2\)/dose before we consider further intensification of therapy.

ACKNOWLEDGMENT

We thank Dr Gilles Vassal from the Pediatric Oncology Department, Institut Gustav-Roussy, Villejuif, France, for his critical reading of the manuscript and the nursing staff of the Oncology Unit for the collection of all the blood samples. We are also grateful for the assistance of Rogan McNeil, the Children’s Hospital statistician.

REFERENCES


Busulfan pharmacokinetics using a single daily high-dose regimen in children with acute leukemia

PJ Shaw, CE Scharping, RJ Brian and JW Earl