Use of a Water-Soluble Busulfan Formulation—Pharmacokinetic Studies in a Canine Model


In a canine model we investigated the toxicity and pharmacokinetics of a water soluble busulfan preparation. Busulfan was dissolved in dimethylsulfoxide (DMSO) and administered either orally or intravenously in a single dose of 1 mg/kg. The application in either preparation was well tolerated. In seven dogs, peak levels in the range of 730 ng/mL to 1,000 ng/mL were measured after intravenous injection with an area under curve (AUC) of 75 ng·h/kg·mL to 146 ng·h/kg·mL. It was of note that even the oral administration of the same busulfan preparation resulted in AUC values in the same range as observed after parenteral application. The absorption rate of busulfan tablets in our model was as unpredictable as documented in clinical trials. On the basis of the present study, clinical trials using busulfan dissolved in DMSO given either intravenously or orally appear warranted. This approach should lead to predictable blood levels, reduced toxicity, and increased efficacy of busulfan-containing regimens.

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Table 1. Pharmacokinetic Parameters of Busulfan Administration to Seven Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>Administration</th>
<th>Peak AUC (ng·h·kg⁻¹·mL⁻¹)</th>
<th>AUC (ng·h·kg⁻¹·mL⁻¹)</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BU/DMSO i.v.</td>
<td>1,000</td>
<td>100</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>BU/DMSO p.o.</td>
<td>740</td>
<td>100</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>BU tablets</td>
<td>120</td>
<td>16</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>BU/DMSO i.v.</td>
<td>730</td>
<td>93</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>BU/DMSO p.o.</td>
<td>910</td>
<td>101</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>BU/DMSO i.v.</td>
<td>1,010</td>
<td>138</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>BU tablets</td>
<td>720</td>
<td>137</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>BU/DMSO i.v.</td>
<td>910</td>
<td>103</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>BU/DMSO p.o.</td>
<td>570</td>
<td>103</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>BU/DMSO i.v.</td>
<td>940</td>
<td>112</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>BU tablets</td>
<td>72</td>
<td>6</td>
<td>0.6</td>
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<tr>
<td>7</td>
<td>BU/DMSO i.v.</td>
<td>1,102</td>
<td>146</td>
<td>1.0</td>
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<tr>
<td></td>
<td>BU/DMSO p.o.</td>
<td>746</td>
<td>104</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Abbreviations: BU, busulfan; i.v., intravenously; p.o., per os.

GmbH, Aschheim, Germany, and Gynkotek, Germering, Germany enabled the detection of the busulfan-derivative at 226 nm with a retention time of 16.5 minutes. The method described has a high selectivity. The coefficient of variation at a concentration of 250 ng/mL was 2.7%, the detection limit for busulfan in plasma was 50 ng/mL.

Pharmacokinetic parameters were determined by use of the TOPFIT program and AUC was calculated by use of the trapezoidal rule for the first 6 hours. The bioavailability was obtained by comparing AUCs for oral and intravenous administration.

RESULTS

The application of busulfan in either preparation was well tolerated. No clinical side effects or significant changes in blood cell values were detected with the given dose of 1 mg/kg.

Pharmacokinetic results are summarized in Table 1. After bolus intravenous injection of busulfan, peak levels in the range of 730 ng/mL to 1,010 ng/mL were measured (Fig 1). The AUC ranged from 78 ng·h·kg⁻¹·mL to 146 ng·h·kg⁻¹·mL. Both compartmental and noncompartmental fitting showed elimination half-lives between 0.6 and 1.5 hours (median, 0.6 hours). Volume of distribution ranged from 0.8 to 1.4 L/kg (median, 1 L/kg).

In five of the seven dogs, the same busulfan solution used intravenously was also administered orally. Peak plasma levels occurred 0.5 to 1.5 hours after dosing and ranged from 540 ng/mL to 910 ng/mL (Fig 2). AUCs differed by less than 10% in four of five cases from the values achieved after intravenous application.

In three dogs given oral busulfan tablets, the peak levels were 72, 120, and 720 ng/mL, respectively (Fig 2). The corresponding AUC values were less than 20% of those achieved after intravenous application in two dogs and 99% in the third animal.

DISCUSSION

This study shows that busulfan dissolved in DMSO and further diluted in sodium chloride can safely be administered intravenously to dogs. It was of note that in contrast with the unpredictable absorption rate after oral administration of tablets, well documented clinically and observed in the present study in at least two dogs, the oral administration of a busulfan solution (rather than in tablet form) resulted in a high and rather stable absorption rate and in plasma levels comparable with those observed with intravenous administration. This observation points toward a major role of physico-chemical problems of tablet dispersion and not to variations in drug uptake or extraction rate in the liver during first pass as causes of the high intrapatient and interpatient variability of oral busulfan. Another explanation of the higher absorption rate of the oral solution would be the involvement of lymphatic drainage bypassing the liver.

In a recent publication on the bioavailability of busulfan, Hassan et al used intravenous bolus administration of busulfan dissolved in a solution containing propylene glycol, ethanol, and DMSO at a low dose of 0.2 mg/kg. In this
study, the bioavailability of oral busulfan given as tablets ranged from 0.22 to 1.20 in children, and 0.47 to 1.03 in adults. With the intravenous preparation, given at doses of 0.2 mg/kg, AUC values clearly below levels desirable in clinical studies were reached. However, the authors pointed out that it was not advisable to administer this preparation at higher doses based on the poor stability of the preparation, low solubility and potential toxicity of bolus injections. The approach described here allows to circumvent the problems by using fresh preparations of the solution and by diluting it in sodium chloride to allow 0.1 for a 1-hour infusion. However, even bolus injections were well tolerated in dogs.

Dimethylbusulfan (DMB), a better soluble derivative of busulfan and more potent on a weight basis, had been used dissolved in DMSO as an intravenous preparation in earlier studies in animals and in clinical trials. The limited supply of DMB prevented a more extensive clinical evaluation and the drug is currently not available. Nevertheless it is of note that the administration of DMB in DMSO intravenously was not associated with prohibitive toxicity. Also DMSO is used successfully as cryoprotectant in BMT and has found other clinical uses in oncology and internal medicine, not associated with unacceptable side effects.

On the basis of those data and the results obtained in the present study, it appears warranted to perform clinical trials using an intravenous preparation of busulfan. Such an approach is easier for the patient, assures high patient compliance and is likely to lead to more predictable blood levels and reduced toxicity of busulfan-containing regimens.

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