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Busulphan conditioning

Accidental busulfan overdose during conditioning for stem cell transplantation

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Summary:

High dose busulfan is widely used in preparative regimens for bone marrow transplantation. We describe three cases of accidental busulfan overdosing. Two adults received a single dose of 8 and 18 mg/kg busulfan, respectively. Doses of 9 × 4 mg/kg were ingested by a 14-year-old girl, who experienced seizures. In all cases, no severe liver toxicity including veno-occlusive disease was observed. Plasma samples were obtained from two patients. Busulfan plasma concentrations were far above published values after high-dose busulfan treatment. Busulfan was eliminated by a first-order process. All patients survived these high doses of busulfan and successful transplantation was possible. Two patients died from refractory GvHD on days 91 and 80 after transplantation. One patient is alive in remission after an observation time of 18 months. These cases show that busulfan overdosing may occur and pharmacokinetic evaluation is warranted to estimate risk of early and late toxicity.
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Busulfan (1,4-bis(methanesulfonyloxy)butane), alkylating by two terminal high-reactive functions, is widely used as a component of the preparative regimen for bone marrow transplantation (BMT). Administered at a total dose of 16 mg/kg in divided daily doses, the immediate toxicity of busulfan is moderate. Several studies have investigated the correlation of busulfan plasma levels and toxicity. One of the most frequently observed complications after administration of busulfan is veno-occlusive disease (VOD) of the liver.[1,2] The incidence of severe VOD is estimated to be 15% and depends on overall intensity of the conditioning regimen and pretreatment.[3] Some study groups found a correlation between calculated values of the area under concentration (AUC) of busulfan and manifestation of VOD, while other studies did not confirm these results.[4,5] Murphy *et al*[6] described generalized seizures after high-dose therapy with busulfan. However, these complications and other adverse reactions such as skin changes or mucositis were observed after high-dose busulfan administration.[7–9] Busulfan overdosing has been reported as cumulative overexposure after long-term treatment with low-dose busulfan, usually resulting in severe bone marrow aplasia.[10,11]

Apart from these publications, we found a small number of reports on errors in drug administration of high-dose busulfan.[12–14] Detailed reports on busulfan overdosing in two infants and the results of a survey about overdoses of high-dose chemotherapy including two sketchily described cases with busulfan have been published.

In the past 4 years, we were aware of three cases, one occurring at our institution, with accidental busulfan overdosing during the conditioning for stem cell transplantation. Higher than usual daily doses of busulfan in two adults and a 14-year-old girl are described.

Methods

Plasma levels were measured with a modified HPLC method based on a precolumn derivation of busulfan to 1,4-diiodobutane, followed by a postcolumn photochemical dissociation of iodide anions for UV detection. The chromatographic system consisted of a Waters 626 pump (Waters, Eschborn, Germany) and a gradient controller 600S (Waters) connected to a 717plus autosampler (Waters). Detection was conducted with a Spectra-Focus LC spectrometer (Spectra-Physics, Darmstadt, Germany). Acquired data were processed using Maxima Software (Waters). Solvent was degassed online by a vacuum membrane degasser (Spectra Physics). Separation was performed on a Lichrospher 100 RP-18 (5 μm) (LiChroCART HPLC Cartridge system 125 × 4 mm; Merck, Darmstadt, Germany), protected with a LiChrospher 100 RP-18 (5 μm) guard column (LiChroCART, 4 × 4 mm, Merck). The isocratic solvent system consisted of methanol and water (70:30; v/v) at a flow rate of 1.2 ml/min. The detection wavelength was 226 nm.

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Case 1

A 59-year-old man with acute myelogenous leukemia, evolving from myelodysplastic syndrome, failed to respond to induction chemotherapy, consisting of cytarabine and mitoxantrone. An allogeneic blood stem cell transplant from an HLA-matched sibling donor was planned. He was scheduled for a dose-reduced conditioning regimen containing busulfan 4 mg/kg p.o. in divided daily doses for 2 days (total dose: 8 mg/kg, similar to a protocol published by Slavin *et al*[15]).

The entire dose for 2 days, prepared as busulfan powder in gelatine capsules, was handed over to the patient, who misunderstood the instructions and took the entire dose at once. The error was immediately recognized by the nurse and blood samples were taken at 1, 2, 5, 8, 24, 26, and 32 h after ingestion. Figure 1 shows the concentration *vs* time curve ($c \times t$ curve) of busulfan. Measured peak plasma level was 12 151 ng/ml. The busulfan $AUC_{0-\infty}$ was calculated at 78 500 ng h/ml. Both values were far above published data after oral application of 1 mg/kg busulfan as single dose.[5] Compared with our data, after administration of 4 mg/kg busulfan as a single daily oral dose, approximately three times higher peak and AUC values were determined.[16] Plasma half-life was calculated at 2.8 h, within the range of published values for smaller doses.[17]

With the patient in a stable condition, no further measures were taken. Despite these high plasma levels of busulfan no seizures occurred with benzodiazepine prophylaxis (diazepam 20 mg p.o. in divided doses daily in the course of conditioning with busulfan). Liver enzyme levels were in the normal range until day 18 after transplantation. On day 7, slightly elevated bilirubin plasma levels of 41.4 μmol/l were observed. Treatment was continued as scheduled. Considering the Seattle-criteria, no VOD occurred.[1] Neutrophil recovery ($>0.50 \times 10^9$/l) was observed on day 15 after transplantation. Platelets were more than 50×10^9/l without transfusion on day 17. In conclusion, the patient had an uneventful initial course after transplantation.

On day 75 after cessation of immunosuppression, he experienced clinical symptoms of skin and gastrointestinal GvHD, which was confirmed by colonoscopy and histological studies. In addition, hyperbilirubinemia without weight gain or other signs of VOD developed. He died of complications of grade IV acute GvHD on day 91 after transplantation.

Case 2

A 48-year-old woman accidentally took busulfan 18 mg/kg (intended total dose of 16 mg/kg + 2 mg/kg was keeping in reserve in case of vomiting) as a single dose, which was noticed 30 min later. Vomiting could not be induced. A gastric lavage was performed 90 min after ingestion and showed remnants of capsules. Additionally, charcoal was administered. With standard phenytoin prophylaxis, no seizures were observed. The scheduled conditioning regimen containing busulfan and cyclophosphamide (CY) was changed and continued with fludarabine 30 mg/m^2 once daily i.v. for 5 consecutive days (total dose 150 mg/m^2) instead of CY. Plasma samples were collected beginning 4 h after ingestion. The first measured value after 4 h was 6720 ng/ml, which declined with a half-life of 2.0 h to the lower range of published values for smaller doses.[17] Increased metabolism caused by induced enzymes after anticonvulsive prophylaxis with phenytoin is a possible explanation. Additionally, impaired absorption after gastric lavage might reduce the plasma half-life. Figure 2 describes the concentration *vs* time curve of busulfan fitted with TOPFIT software using an one-compartment model.[18] Estimates of AUC depended very much on assumptions about the concentrations before the first measurement. Assuming a theoretical peak concentration at 3 h after ingestion, two times higher AUC than patients after a single daily dose of 4 mg/kg busulfan was calculated.[16] In spite of a probable high peak plasma concentration, no VOD occurred. The patient engrafted and is alive in remission after an observation time of >18 months.

Case 3

A 14-year-old girl with MDS was scheduled for a transplant from an allogeneic sibling donor. A conditioning regimen including busulfan, CY, and melphalan was

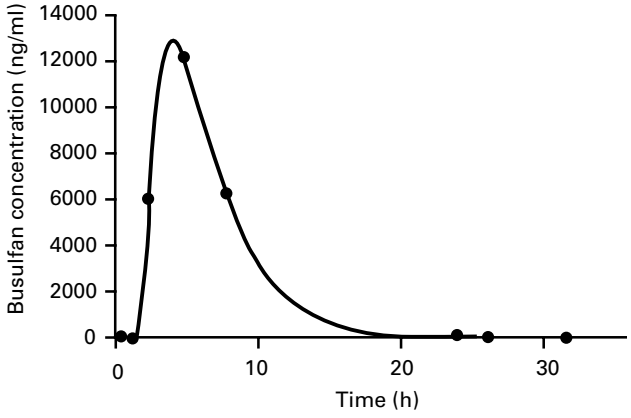

Figure 1 Concentration *vs* time curve (case 1).

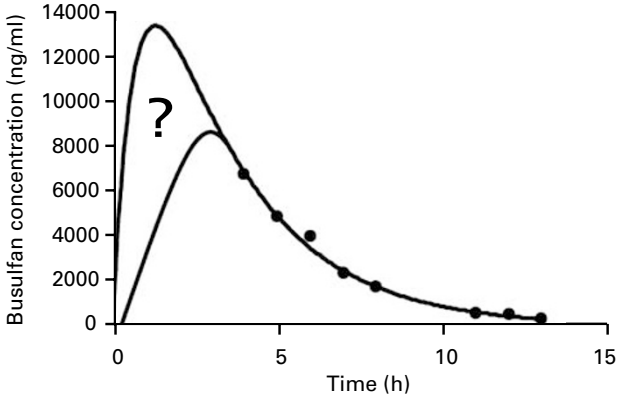

Figure 2 Concentration *vs* time curve (case 2).

planned. Instead of 4 mg/kg busulfan in four daily doses of 1 mg/kg, nine doses of 4 mg/kg in 6 h intervals were inadvertently given. She developed seizures and the dosing error was detected. Generalized seizures were treated with diazepam and clonazepam; no specific pathology was documented in a cranial computer tomography. The treatment regimen was stopped and no further conditioning was given except ATG.

Blood samples after busulfan ingestion were not available. Using the mean absorption and elimination constant published by Shaw *et al*,[19] plasma levels of busulfan can be estimated to have reached between 2000 and 6500 ng/ml over 72 h.

The patient engrafted with neutrophils $>0.50 \times 10^9$/l on day 14 and platelets $>50 \times 10^9$/l on day 17 after transplantation. Initially, no relevant hepatotoxicity was observed. On day 20, the patient experienced acute GvHD grade 2, which was successfully treated with prednisolone. She was readmitted on day 75 after transplantation with hyperbilirubinemia. Histology of the liver biopsy provided evidence of GvHD and cytomegalovirus infection. There was no indication of VOD. She died of multiorgan failure caused by sepsis almost 5 months after busulfan conditioning.

Discussion

Several studies have reported medical errors. Nonoperative treatment errors are often caused by incorrect drug administration.[20] Mistakes in application of chemotherapeutic agents may particularly lead to fatal outcomes.[21–23] We report three cases of busulfan overdosing. Contrary to expectation and in spite of the high peak plasma levels of busulfan, no VOD was seen. Seizures were observed in one patient only, who probably had high plasma levels of busulfan during the whole treatment time of 72 h. Although we only have measurements of concentrations in the early absorption phase in one of these patients, circumstantial evidence suggests that up to a certain degree, excessively high peak levels do not seem to be associated with higher toxicity. For overall toxicity of busulfan conditioning, overall duration of treatment or the AUC seem to be more relevant. This theory is supported by calculated elimination parameters. Despite the unusually high doses of busulfan, the measurements showed drug elimination by a first-order process. The measured plasma levels 24 h after ingestion were lower than 100 ng/ml, just slightly higher than values after ingestion of busulfan 4 mg/kg once daily.[16]

These results are comparable with published reports on accidental busulfan overdosing in infants. Petersen *et al*[12] described a case of a higher than usual dose of busulfan within a preparative regimen before BMT being given to a 2-year-old boy. The patient inadvertently received single doses of busulfan of approximately 2 mg/kg instead of 1 mg/kg, resulting in a total dose of 23.3 mg/kg. After discovering the error, the regimen was modified. Apart from vomiting, no further adverse effects were seen.

An accidental busulfan overdose with three consecutive doses of 4 mg/kg at intervals of 6 h administered to a 4.6 kg infant with Wiskott–Aldrich syndrome was described by Stein *et al*.[14] Hemodialysis was performed to enhance clearance of busulfan. No severe busulfan toxicity was noted.

Several reports have attempted to analyze drug administration errors and have made suggestions for preventing adverse events in treatment with chemotherapeutic agents.[24–26] Chen *et al*[13] published the results of a questionnaire to evaluate chemotherapy practices in the US. Overdoses of high-dose chemotherapy including two cases of busulfan overdose were investigated and recommendations for safeguards were proposed. Many errors were caused by inexperience of clinicians or by insufficient controls. In our cases, several reasons led to busulfan overdosing. In the first case, the patient misunderstood the nurse's instructions. To prevent this, only single doses of chemotherapeutic drugs have been handed out to the patients since this incident. The third case was the result of a physician and pharmacy error. Different control mechanisms may reduce these mistakes.

Another point is to manage problems after errors. Recognizing errors early gives more possibilities of action.[12] Obtaining plasma samples may help to calculate the AUC and make a decision about further treatment. In two of the cases described, the planned conditioning regimen was changed to reduce toxicity. Furthermore, hemodialysis seems to enhance drug clearance and decrease acute toxicity of busulfan.[14]

In the situation of an accidental overdose, information about other cases may be of crucial importance for management decisions. On the other hand, fear of litigation and loss of reputation for the institution involved may constitute reasons, for refraining from making pharmacokinetic measurements and publishing the experience. We would therefore like to encourage all oncologists to report all (hopefully rare) similar experiences. Standard operation procedures for the administration of cancer drugs need to be checked frequently, to recognize possible loopholes for errors.

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