Low Blood-to-Cerebrospinal Fluid Passage of Sorbitol After Intravenous Infusion

Roland Nau, DrMed; Torsten Dreyhaupt, DrMed; Herbert Kolenda, DrMed; and Hilmar W. Prange, DrMed

Background and Purpose: Compared with mannitol, the osmotherapeutic agent sorbitol is less prone to accumulate in the blood and the same quantity may be infused in a smaller volume. Because of these advantageous characteristics, we studied the pharmacokinetics of sorbitol in serum and cerebrospinal fluid.

Methods: Six patients (five women and one man; age range, 46–70 years) with an external ventriculostomy and suffering from brain edema due to cerebrovascular disease received sorbitol as part of their therapy. Before and after the first dose of 50 g infused over 20 minutes, sorbitol concentrations in serum and cerebrospinal fluid were determined repeatedly using an enzymatic procedure.

Results: Maximal sorbitol concentrations ranged from 2,705 to 5,821 (median, 3,227) mg/l in serum compared with 6.7–130.7 (median, 19.5) mg/l in cerebrospinal fluid. Cerebrospinal fluid maxima were observed 0.17–3 hours after the end of the infusion. Sorbitol elimination in serum was adequately described by a two-compartment pharmacokinetic model (distribution half-life, 0.05–0.14 hour; elimination half-life, 0.23–0.61 hour). Elimination in cerebrospinal fluid followed a single-exponential decay and was considerably slower than that in serum (half-life, 1.3–7.7 hours).

Conclusions: The maximal cerebrospinal fluid concentration/maximal serum concentration ratio was low for sorbitol, thus suggesting a small potential risk of inducing an increase of intracranial pressure after osmotherapy (rebound effect).

(Stroke 1992;23:1276–1279)

KEY WORDS • cerebrospinal fluid • pharmacokinetics • sorbitol

Glycerol, mannitol, and sorbitol have been used since the early 1960s to reduce intracranial pressure (ICP). While in the United States mannitol is most frequently used, in Europe the preferences differ from hospital to hospital. When considering the pharmacokinetic properties, each drug has characteristic advantages and disadvantages. Sorbitol can be infused intravenously at a concentration of 40% (wt:vol), so that large increases in serum osmolality can be achieved with small volumes of infusion. Because of its limited solubility in water, mannitol solutions are 20% at most, and glycerol infusions of more than 10% are contraindicated because they provoke hemolysis. In contrast to mannitol, which is eliminated only by the kidneys, sorbitol and glycerol are also subject to metabolism in various tissues, mainly the liver. For this reason the latter two drugs may be applied in renal insufficiency; however, they may affect blood levels of other carbohydrates.

The passage of osmotically active drugs into the central nervous compartment is probably related to the so-called rebound effect, i.e., the increase of ICP after cessation of infusion of osmotic agents. Some authors assert that the hazard of inducing a rebound effect is smaller with sorbitol than with mannitol. The present study was performed to investigate the pharmacokinetics of intravenous sorbitol in blood and cerebrospinal fluid (CSF) at a dose applied in osmotherapy. The findings are discussed in view of data available for mannitol and glycerol.

Subjects and Methods

Six patients (five women and one man; age range, 46–70 years) suffering from cerebral edema due to cerebrovascular accidents received 125 ml of a 40% solution of sorbitol (Tutufisin S40, Pfrimmer, Erlangen, FRG, or Sorbit 40, Braun, Melsungen, FRG) over 20 minutes as part of their therapy. The patients had undergone external ventriculostomy for obstructive hydrocephalus. In cases 1 and 2 hydrocephalus developed after compression of the fourth ventricle; in cases 4–6 blood coagula obstructed the aqueductus cerebri. For further details on the patients studied see Table 1.

Arterial blood and ventricular CSF samples were drawn from indwelling catheters before beginning the sorbitol infusion to determine basal endogenous concentrations and at the end and 0.17, 0.5, 1, 2, 3, 5, 8, and 11 hours after termination of the infusion. Blood and CSF were centrifuged for 10 minutes at 3,000g immediately after sampling. The supernatant was stored at −20°C until assaying, which was performed within 2 weeks. The study protocol was approved by the Ethics Committee of the University Hospital. Informed con-
sent to participation was obtained from either the patient or nearest relative.

Sorbitol concentrations in serum and CSF were determined by means of an enzymatic assay based on the conversion of sorbitol to fructose by sorbitol dehydrogenase. This process was coupled to auxiliary enzymatic reactions leading to the formation of formazan with maximal absorption at 492 nm.10 The test kit was purchased from Boehringer Mannheim, Mannheim, FRG. Assays using the sorbitol dehydrogenase reaction have been previously validated in biological fluids6,11 (manufacturer's information). CSF and 1:3 diluted serum were deproteinized by heat (95°C for 5 minutes) and measured in appropriate dilutions (0.002–0.4 ml). At sample concentrations of 100 mg/l the recovery of sorbitol as determined by an external standard was 100.1% and the interday coefficient of variation was 4.7% (n=10). At 10 mg/l recovery was 103.8% and the interday coefficient of variation was 5.7% (n=13). The detection limit was 0.2 mg/l. At −70°C sorbitol was stable in serum for at least 2 months; at room temperature no decline in sorbitol concentrations was seen during the first 20 hours. Xylitol, which is present in concentrations of <0.9 mg/l (mean±2 SDs)12 in human plasma, is also a substrate of sorbitol dehydrogenase and interferes with the assay.10

Pharmacokinetic parameters were determined using standard noncompartmental and compartmental methods.13 Maximal sorbitol concentrations in serum and CSF ($C_{max}$ and $C_{maxCSF}$, respectively) were taken directly from the concentration–time curves, and the time from end of the infusion to $C_{max}$(tmax) was recorded. Basal sorbitol concentrations were subtracted from the concentrations measured during and after the infusion for the following calculations. Terminal serum and CSF elimination rate constants ($k_e$ and $k_{eCSF}$, respectively) were determined by log-linear regression analysis and half-lives as $\ln(2)/k$. Area under the concentration–time curve (AUC) was estimated by using the trapezoidal rule, and area to infinity beyond the last measurable sorbitol concentration ($C_t$) was estimated by $C_t/k$. Total body clearance of sorbitol (CL) was calculated as dose/AUCs. The apparent volume of distribution was estimated as dose/AUCs × $k_e$ and volume of distribution in the steady state as area under the moment versus time curve (AUMC) in serum:CL/AUCs. A two-compartment model was applied to the serum sorbitol concentration–time curves. Calculations were performed by means of the program TOPFIT 1.1 (Godecke-Schering-Thomae, FRG).

Endogenous concentrations of sorbitol measured before starting the infusion ranged from 0.2 to 2.2 mg/l in serum and from 2.2 to 7.3 mg/l in CSF. Sorbitol serum concentrations were maximal at the end of the infusion (range, 2.705–5.821 mg/l; median, 3.227 mg/l). CSF maxima ranging from 6.7 to 130.7 mg/l (median, 19.5 mg/l) were observed 0.17–3 hours after the end of the infusion (Figure 1, Table 2). Sorbitol infusion decreased ICP for 1–2 hours.

Elimination of sorbitol from CSF approximated a single-exponential decay. The decline of the sorbitol serum concentration–time curves was not log linear (Figure 1). The elimination half-lives of sorbitol in CSF were 1.3–7.7 hours compared with terminal elimination half-lives in serum of 0.41–0.65 hours as estimated by noncompartmental analysis (t1/2, Table 2) and of 0.23–0.61 hours by two-compartment analysis (t1/2a, Table 2). Compartmental analysis demonstrated that the rapid decline immediately after terminating the sorbitol infusion had a short half-life of 0.05–0.14 hours (t1/2a, Table 2). The sorbitol serum data were adequately described

### Table 1. Characterization of Patients in Order of Increasing Maximal Sorbitol Concentration in CSF After Intravenous Infusion of 50 g Over 20 Minutes

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Body wt (kg)</th>
<th>Disease</th>
<th>Stroke to infusion (days)</th>
<th>CSF protein (mg/l)</th>
<th>CSF-serum albumin ratio (×10^-2)</th>
<th>CSF WBC/mm³</th>
<th>CSF RBC/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/70/F</td>
<td>65</td>
<td>Pontine hemorrhage</td>
<td>5</td>
<td>99</td>
<td>1.9</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>2/46/F</td>
<td>65</td>
<td>Cerebellar infarction</td>
<td>5</td>
<td>339</td>
<td>5.7</td>
<td>13</td>
<td>5,888</td>
</tr>
<tr>
<td>3/46/F</td>
<td>60</td>
<td>Subarachnoid hemorrhage</td>
<td>3</td>
<td>182</td>
<td>2.8</td>
<td>1</td>
<td>1,669</td>
</tr>
<tr>
<td>4/48/F</td>
<td>70</td>
<td>Intracerebral hemorrhage</td>
<td>23</td>
<td>764</td>
<td>20.1</td>
<td>14</td>
<td>7,381</td>
</tr>
<tr>
<td>5/61/M</td>
<td>60</td>
<td>Intracerebral hemorrhage, hepatitis B</td>
<td>10</td>
<td>788</td>
<td>7.3</td>
<td>1</td>
<td>853</td>
</tr>
<tr>
<td>6/64/F</td>
<td>60</td>
<td>Intracerebral hemorrhage</td>
<td>4</td>
<td>1,734</td>
<td>27.4</td>
<td>5</td>
<td>1,195</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; WBC, white blood cell count; RBC, red blood cell count; F, female; M, male.
by a two-compartment model \((r \geq 0.99)\). The use of triexponential equations did not improve data curve fitting.

Owing to the slower elimination of sorbitol in CSF than in serum, the concentration–time curve in CSF lagged behind that in serum. The corresponding ratios between sorbitol concentrations in CSF and serum \((C_{\text{CSF}}/C_s)\) were not constant. Dependent on time, \((C_{\text{CSF}}/C_s)\) ranged from 0.019 to 0.461 (median, 0.037).

\(C_{\text{maxCSF}}, C_{\text{maxCSF}}/C_{\text{maxS}},\) and \(AUC_{\text{CSF}}/AUC_s\) correlated positively with the CSF protein content and the CSF/serum albumin ratio \((Q_{\text{Ab}})\) (Table 1). The correlations between \(C_{\text{maxCSF}}\) and \(Q_{\text{Ab}}\) \((r_s=0.94)\), between \(C_{\text{maxCSF}}/AUC_s\) and \(Q_{\text{Ab}}\) \((r_s=0.89)\), between \(AUC_{\text{CSF}}/AUC_s\) and \(Q_{\text{Ab}}\) \((r_s=0.83)\) and between \(C_{\text{maxCSF}}/C_{\text{maxS}}\) and \(Q_{\text{Ab}}\) \((r_s=0.90)\) were all significant \((p < 0.05)\).

### Discussion

The sorbitol concentrations observed by us before infusion were close to those determined enzymatically in serum \((0.5–0.8\ mg/\text{l})^{11}\) and chromatographically in CSF \((4.8±3.0\ mg/\text{l}, \text{mean}±\text{SD})^{14}\) of healthy subjects, suggesting an endogenous CSF-to-serum concentration gradient.

Infused intravenously over 20 minutes, 125 ml of a 40\% solution of sorbitol is highly effective in producing osmotically active serum concentrations; the levels measured in the present study were equivalent to increases in serum osmolality of 15–32 mosm/kg. As has been reported with the osmotherapeutic agents glycerol and mannitol,\(^8,\)\(^9\) serum concentrations exhibited an individual variability not solely related to body weight. In the case of sorbitol, this is mainly due to differences in liver perfusion and function because the liver in healthy subjects accounts for approximately 85\% of CI.\(^6\) Thus, it is not surprising that our patient with the lowest CI (case 5) had a history of hepatitis B.

The duration of osmotically active sorbitol serum levels after the infusion was short; after 30 minutes the serum concentration did not exceed 900 mg/l, equivalent to 5 mosm/kg, in any patient. This can be explained by kinetics of sorbitol that were not compatible with a single-exponential decay but were adequately described by a two-compartment pharmacokinetic model with a rapid initial decline \((t_{1/2o};\) median, 0.1 hour) and a slower terminal decline; the rapid component limited the duration of effective serum sorbitol concentrations. As in previously published reports,\(^5,\)\(^16\) the ICP reduction lasted approximately 1–2 hours.

\(C_{\text{maxCSF}}\) amounted to 0.2–3.8\% (median, 0.5\%) of \(C_{\text{maxS}}\), \(C_{\text{maxCSF}}\) and \(AUC_{\text{CSF}}\) correlated with increases in CSF protein content and with \(Q_{\text{Ab}}\) as parameters of a disturbed blood–CSF barrier.\(^17\) This indicated that sorbitol passed more readily into CSF in the presence of a disturbed blood–CSF barrier. As outlined in Table 1, four patients had >1,000 red blood cells/ml in their CSF. Blood in CSF acts as a foreign body and, therefore, may have been involved in the development of an impaired blood–CSF barrier. However, because the interval from the hemorrhage to sorbitol infusion was at least 3 days, blood contamination should not have affected the results. Consequently, the \(AUC_{\text{CSF}}/AUC_s\) ratios did not correlate with the number of red blood cells in CSF \((r_s=−0.03)\).

Elimination of sorbitol from CSF was several times slower than that in serum, leading to CSF concentrations that increased the CSF-to-serum concentration gradient in all patients during the elimination phase (Table 2). Because no additional barrier exists between CSF and the brain, the persistence of sorbitol in CSF probably reflected similar conditions in the interstitial fluid of the brain. The same phenomenon has been described in patients after intravenous glycerol treatment\(^7\) and probably occurs with mannitol as well, as can be deduced from results reported by Anderson and [Table 2. Pharmacokinetics of Sorbitol in Serum and CSF After Single Infusion of 50 g Over 20 Minutes](#)

<table>
<thead>
<tr>
<th>Pt</th>
<th>(C_{\text{max}}) (mg/l)</th>
<th>(t_{\text{max}}) (hr)</th>
<th>(C_{\text{max}}) (mg/l)</th>
<th>AUC (mg·hr/l)</th>
<th>CI (l/hr)</th>
<th>(V_{\text{d1}}) (l)</th>
<th>(V_{\text{d2}}) (l)</th>
<th>(t_{1/2o}) (hr)</th>
<th>(t_{1/2q}) (hr)</th>
<th>(C_{\text{maxCSF}}/C_{\text{maxS}})</th>
<th>(AUC_{\text{CSF}}/AUC_s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3,116</td>
<td>...</td>
<td>0.5</td>
<td>1,480</td>
<td>33.8</td>
<td>31.7</td>
<td>15.4</td>
<td>0.65</td>
<td>0.11</td>
<td>0.52</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>3,049</td>
<td>...</td>
<td>0.0</td>
<td>1,470</td>
<td>33.9</td>
<td>20.2</td>
<td>13.0</td>
<td>0.41</td>
<td>0.14</td>
<td>0.37</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>3,970</td>
<td>...</td>
<td>0.1</td>
<td>2,020</td>
<td>24.7</td>
<td>18.6</td>
<td>9.9</td>
<td>0.52</td>
<td>0.05</td>
<td>0.23</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>2,705</td>
<td>...</td>
<td>0.2</td>
<td>1,310</td>
<td>38.2</td>
<td>35.3</td>
<td>16.8</td>
<td>0.64</td>
<td>0.12</td>
<td>0.40</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>5,821</td>
<td>...</td>
<td>2.4</td>
<td>2,950</td>
<td>16.9</td>
<td>15.1</td>
<td>9.2</td>
<td>0.62</td>
<td>0.07</td>
<td>0.61</td>
<td>...</td>
</tr>
<tr>
<td>6</td>
<td>3,417</td>
<td>...</td>
<td>0.6</td>
<td>1,630</td>
<td>30.7</td>
<td>19.2</td>
<td>13.0</td>
<td>0.43</td>
<td>0.08</td>
<td>0.44</td>
<td>...</td>
</tr>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6.7</td>
<td>3</td>
<td>2.3</td>
<td>47.2</td>
<td>...</td>
<td>...</td>
<td>7.7</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>9.9</td>
<td>2</td>
<td>1.9</td>
<td>34.4</td>
<td>...</td>
<td>...</td>
<td>3.2</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.003</td>
</tr>
<tr>
<td>3</td>
<td>19.0</td>
<td>1</td>
<td>0.3</td>
<td>39.1</td>
<td>...</td>
<td>...</td>
<td>1.3</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.005</td>
</tr>
<tr>
<td>4</td>
<td>20.0</td>
<td>0.5</td>
<td>4.2</td>
<td>137</td>
<td>...</td>
<td>...</td>
<td>3.6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.007</td>
</tr>
<tr>
<td>5</td>
<td>31.8</td>
<td>0.17</td>
<td>3.0</td>
<td>122</td>
<td>...</td>
<td>...</td>
<td>3.0</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.005</td>
</tr>
<tr>
<td>6</td>
<td>130.7</td>
<td>3</td>
<td>17.5</td>
<td>752</td>
<td>...</td>
<td>...</td>
<td>2.5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.038</td>
</tr>
</tbody>
</table>

S, serum; CSF, cerebrospinal fluid; \(C_{\text{max}}\), maximum concentration; \(t_{\text{max}}\), time from end of infusion to \(C_{\text{max}}\); \(Q_{\text{Alb}}\), concentration above endogenous level (measured before sorbitol infusion) 8 hours after end of sorbitol infusion; AUC, area under concentration–time curve; CI, clearance; \(V_{\text{d1}}\), apparent volume of distribution, estimated by \(k_p\); \(V_{\text{d2}}\), volume of distribution in steady state; \(t_{1/2o}\), elimination half-life as determined by noncompartmental pharmacokinetic analysis; \(t_{1/2q}\) and \(t_{1/2p}\), half-lives estimated by compartmental pharmacokinetic analysis.
coworkers. Unfortunately, the latter authors stopped measuring 4 hours after a 15-minute intravenous man- nitol infusion. At that time mean plasma concentrations had fallen from approximately 4 g/l to <1 g/l, but CSF concentrations were still rising.

An osmotherapeutic agent, first, should have CSF levels as low as possible to minimize a concentration gradient between CSF/brain interstitial fluid and blood leading to water influx into the central nervous compart- ment during the elimination phase, and second, should not accumulate in the blood because this may give rise to the production of “idiogenic osmoles” by the brain. Both mechanisms are probably responsible for the rise in ICP after osmotherapy. Consequently, sorbitol may have a low risk of inducing rebound phenomena. Moreover, the brain is capable of metabolizing sorbitol; this may provide additional protection for the central nervous compartment against sorbitol accumulation.

In conclusion, sorbitol in appropriate doses is an effective osmotherapeutic drug with a rapid onset and a short duration of action. Our data present pharmaco- logical evidence that the risk of increased ICP after osmotherapy (rebound effect) may be low with sorbitol.

Acknowledgment
The authors thank Dr. med. Randall Thomas for his help in the preparation of this manuscript.

References
Low blood-to-cerebrospinal fluid passage of sorbitol after intravenous infusion.
R Nau, T Dreyhaupt, H Kolenda and H W Prange

Stroke. 1992;23:1276-1279
doi: 10.1161/01.STR.23.9.1276

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/23/9/1276

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at: http://stroke.ahajournals.org/subscriptions/