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Use of Mannitol During Neurosurgery: Interpatient Variability in the Plasma and CSF Levels

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Summary. An i.v. infusion of mannitol was given over 15 min to 12 patients before they underwent intracranial surgery under general anesthesia. Samples of blood, CSF and urine were taken over 4 h.

Mannitol disappeared from plasma in a bi-exponential manner. The mean maximal plasma concentration was 4.08 mg/ml at 15 min, and at 4 h it had declined to 0.53 mg/ml. The mean distribution rate constant was 11.2 h^{-1}, corresponding to a plasma distribution half-life of 0.11 h. The mean elimination rate constant was 0.41 h^{-1}, the plasma half-life was 2.2 h, the central distribution volume was 16.3 l, and total plasma clearance was 100.4 ml/min. The mean concentration of mannitol in CSF during the 4 h period increased up to 0.10 mg/ml. There were marked interindividual differences in the concentration ratio blood/CSF, and the CSF concentration varied 7.5 fold between patients.

Optimal use of mannitol during neurosurgery requires further prolonged study of its pharmacokinetics.

Key words: mannitol, neurosurgery; pharmacokinetics, interpatient variability, CSF kinetics

Mannitol, a 6-carbon hexahydric alcohol, has long been used clinically to measure the rate of glomerular filtration [1] and the volume of the extracellular fluid [2]. At the beginning of the 60 s interest was focused on hypertonic mannitol solution as an agent which temporarily could lower intracranial pressure (ICP) and thereby facilitate cerebral surgery [3]. Since then, mannitol has become the most frequently used agent for this purpose throughout the world.

In spite of this widespread use, however, the recommended doses of mannitol have been chosen empirically. Some experimental and clinical studies have been done on the effect of different doses of mannitol on renal haemodynamics and electrolyte balance disturbances [4-8], on blood and plasma volumes [9], and many on its influence on cerebral haemodynamics and intracranial pressure [10-15]. The results of these studies, in which mannitol has been given either by a single bolus injection or by continued infusion over several hours, have shown that the physiological response in the individual patient is unpredictable, at least as far as cerebral haemodynamics and ICP are concerned.

One explanation for the variable effect of mannitol could be differences in its pharmacokinetics. This possibility appears not to have been examined previously. The present study is an account of the pharmacokinetics of mannitol given intravenously over 15 min to 12 patients undergoing intracranial surgery. A gas chromatographic/mass spectrometric technique for the assay of mannitol in plasma, CSF and urine is also presented.

Patients and Methods

Twelve patients, 5 males and 7 females (mean age 40 years, range 20-65 years) were included in the study after giving their informed consent and gaining the prior approval of the Ethics Committee of the Karolinska Hospital. Patient data are summarized in Table 1. Anaesthesia was induced with thiopentone followed by phenoperidine and droperidol [16]. After the start of the operation, and when the patient had reached a circulatory steady state, mannitol 500 (-1000) mg/kg body weight was infused i.v. over 15 min as a 200 mg/ml solution.

Tabelle 1. Details of the patients

Patient	Sex	Age (years)	B.wt. (kg)	Dose mann. (mg/kg)	Diagn.	Preop Grade H-H	SAH blood on CT	Postop course
1	M	44	80	1100	Lt MCA	I	Moderate	Moderate dysphasia
2	F	34	55	473	LT Pcom	II	None	Uneventful
3	F	31	52	923	Lt Pcom	I	None	Uneventful
4	M	63	105	500	Rt Pcom	II	Extensive diffuse deposit	Gait disturbance
5	F	32	50	660	Acom	I	None	Uneventful
6	F	38	82	500	Rt MCA	II	Small amount	Uneventful
7	F	40	67	506	TC	I	-	Uneventful
8	F	29	53	470	Acom	II	Extensive diffuse deposit	Transient ischaemic symptoms
9	F	35	55	455	Rt Pcom	I	None	Uneventful
10	M	20	90	556	Lt MCA	I	Moderate	Uneventful
11	M	65	82	379	Acom	II	Small haematoma min blood	Uneventful
12	M	52	70	529	Lt MCA	III	Extensive diffuse deposit	Desorient and moderate dysphasia
Mean ± SD		40/14	70/18	588/212				

B.wt. body weight; Lt left; Rt right; MCA middle cerebral artery; Comm communicating; A anterior; P posterior; SAH subarachnoid bleeding; CT computerized tomography; TC tumour; H-H Hunt-Hess grading where: I Asymptomatic, or minimal headache and slight nuchal rigidity; II moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy; III drowsiness, confusion, or mild focal deficit

The mean dose given was 588 ± 212 mg/kg. Before the infusion and 0.25, 0.33, 0.5, 0.75, 1, 2, 3 and 4 h after starting it venous blood samples (5 ml) were collected in heparinized Venoject glass tubes for the analysis of mannitol in plasma. Cerebrospinal fluid (CSF) samples were taken from a catheter placed in the lumbar region at 0.25, 0.5, 1, 2, 3 and 4 h. Urine was collected until the end of the operation. If the operation lasted for less than 4 h, blood, CSF and urine samples were collected up to the end of the operation. The samples were frozen until analysed.

Drug Assay

CSF Internal standard 100 µl (xylitol 25 µg/ml) was added to 100 µl CSF and the mixture was evaporated to complete dryness under a stream of air.

Plasma Internal standard 50 µl (xylitol 0.5 mg/ml) was added to 50 µl plasma and the mixture was evaporated to complete dryness under a stream of air.

Urine 100 µl internal standard (xylitol 4 mg/ml) was added to 100 µl urine and 900 µl water. 50 µl $ZnSO_4$ 0.17 M and 50 µl Ba $(OH)_2$ 0.34 M were also added. The mixture was centrifuged and 50 µl supernatant was evaporated to complete dryness under a stream of air.

All samples were then prepared in the same way. The residue was dissolved in 300 µl dry ethanol by sonication and centrifuged. After evaporation of the supernatant, the residue was dissolved in acetone 100 µl, and after addition of 25 µl HMDS (hexamethyldisilazane) and 25 µl TMSI (N-(trimethylsilyl)-imidazol) the mixture was allowed to react for 30 min at 60 °C. After appropriate dilution with acetone the samples were analysed by GC-MS.

The analysis employed selected ion monitoring (SIM). The glass column (1.5 m × 2 mm i.d.) was packed with 1% SE-30 on Gas Chrom Q 10–120 mesh and was conditioned at 280 °C for 24 h, and operated at 190 °C, using a helium flow of 20 ml/min. The temperatures of the injector and the ion source were 230 °C and 270 °C, respectively. The mass spectrometer (LKB 2091), was set at:

ionizing energy 70 eV, ionizing current 50 μA, accelerating voltage 3.5 kV. The multiple ion detector was focused on the ion at m/z 319, for registration both of mannitol and the internal standard.

Materials

Mannitol, xylitol and other chemicals were obtained from commercial sources. HMDS (hexamethyldisilazane) and TMSI (N- (trimethylsilyl)-imidazol) were derivatization agents for silylether formation.

Pharmacokinetic calculation

The area under the plasma concentration-time curve (AUC) was estimated by the log-trapezoidal method, and the area to infinite time beyond the last sampling point was added by integration (C_{tn}/β). C_{tn} is the last concentration point on the regression line of the terminal slope of the plasma concentration-time curve.

The best fit of the plasma concentration data from each patient was obtained by nonlinear regression analysis of the data according to a two-compartment equation describing the time course in the plasma of a drug during and after infusion [17]:

$$C = \frac{k_o(k_{21}-\alpha)\,(1-e^{\alpha T})e^{-\alpha t}}{V_c\alpha\,(\alpha-\beta)} + \frac{k_o(\beta-k_{21})\,(1-e^{-\beta T})e^{-\beta t}}{V_c\beta\,(\alpha-\beta)}$$

Initial estimates of the distribution rate constant (α), the elimination rate constant (β), and the volume of distribution of the central compartment (V_c), as well as of the rate constant between the peripheral and central compartments (k_{21}), were used in the computer calculations. k_{12} is the rate constant between the central and peripheral compartments. k_0 and T denote the infusion rate and infusion time for mannitol. The latter corresponds to the elapsed time since the start of the infusion.

The nonlinear regression analysis was done with Statistical Analysis System NLIN-program (SAS Institute Inc., Cary, NC). The program was run on an IBM 470 computer at the Stockholm Computer Center via a printer terminal. The best fit of V_c, α, β and k_{21} was obtained for each patient and these values were then used to calculate the other pharmacokinetic parameters:

$$k_{el} = \frac{\alpha \cdot \beta}{k_{21}} \quad \text{and} \quad k_{12} = \alpha + \beta - k_{21} - k_{el}$$

Plasma clearance (CL), the apparent volume of distribution (Vz), plasma half-life of the distribution ($t^1/2\,\alpha$) and the elimination phases ($t^1/2\,\beta$) were calculated according to [17]. Renal clearance (CL_R) was calculated according to the equation:

$$CL_R = \frac{(X_u)t_1 \rightarrow t_2}{(AUC)\ t_1 \rightarrow t_2}$$

where X_u is the amount of mannitol excreted in urine between time t_1 and t_2, and AUC represents the area under the plasma concentration-time curve during the same period.

Results

The trimethylsilyl derivatives of mannitol and the internal standard showed excellent chromatographic properties, giving symmetrical peaks. A chromatogram obtained from CSF is given in Fig. 1. Selective ion monitoring (SIM) solved problems with interfering peaks, especially in CSF. However, urine analysis required an additional precipitation step.

The standard curves were linear. They covered concentrations up to 8 mg/ml, 0.5 mg/ml, and 100 mg/ml for plasma, CSF and urine, respectively. Least-squares analysis of a standard curve obtained from CSF gave a correlation coefficient of 0.9996, a slope of 30.45 ± 0.62, and an intercept of 2.00 ± 1.36.

In all analytical procedures it was shown that the relative standard deviation, as a measurement of precision, was less than 4%, as calculated from 20 duplicate analyses spread over the relevant concentration range.

The lowest level of sensitivity of the technique was expected to be a few nanograms/ml. Since the

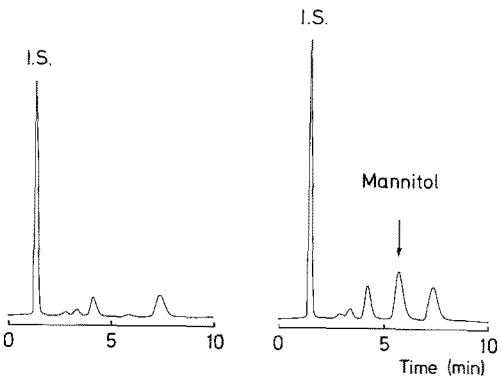

Fig. 1. Chromatogram obtained from CSF containing mannitol 31 μg/ml using ion monitoring with a 1.5 m column packed with 1% SE-30 at 190 °C

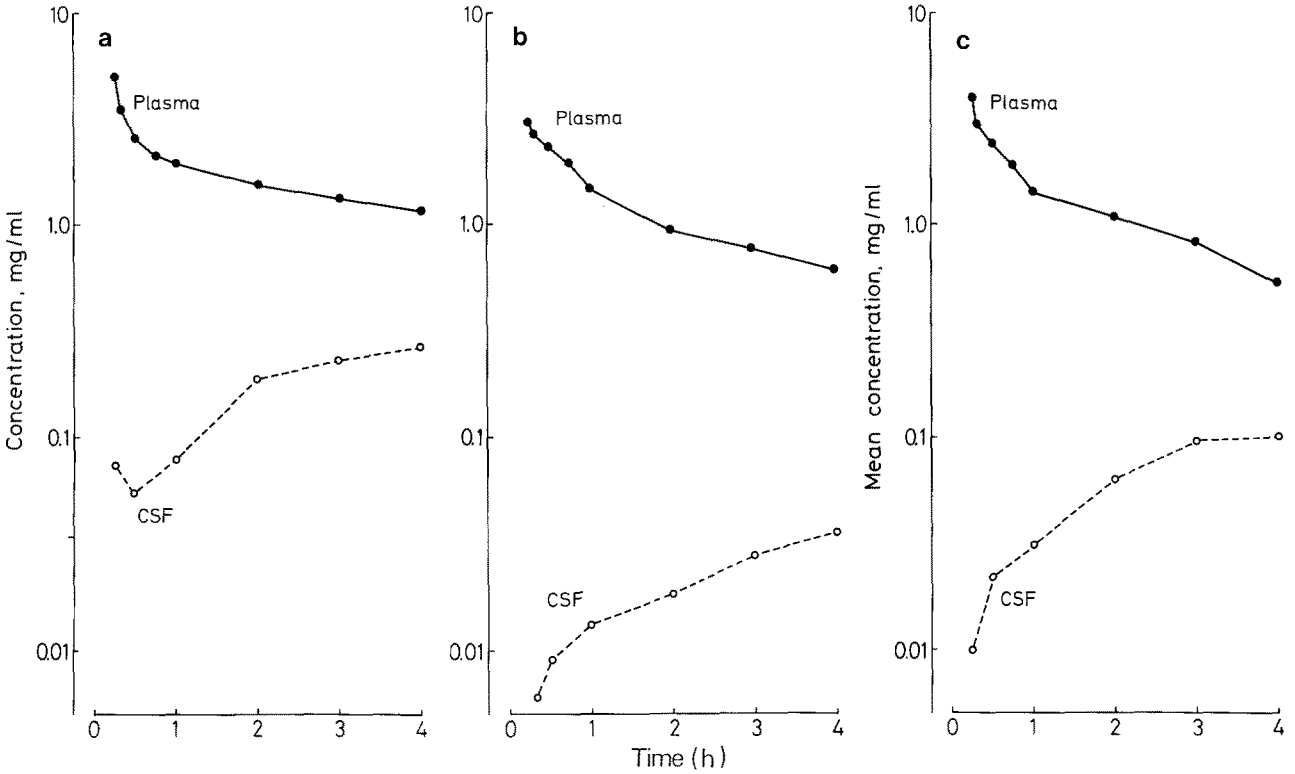

Fig. 2a–c. Plasma and CSF concentration - time curves for mannitol in patient SL **(a)** BME **(b)** in the 12 patients studied mean values **(c)**

Tabelle 2. Pharmacokinetics of mannitol after i.v. infusion of mannitol 200 mg/ml (mean 588 ± 212 mg/kg b.wt.) during 15 min

		Mean	(SD)
AUC	(h·mg/ml)	7.267	3.560
α	(h^{-1})	11.19	5.67
$t^1/_{2\alpha}$	(h)	0.11	0.12
β	(h^{-1})	0.41	0.19
$t^1/_{2\beta}$	(h)	2.17	1.26
V_C	(l)	5.2	2.2
V_Z	(l)	16.3	4.8
k_{12}	(h^{-1})	6.95	4.00
k_{21}	(h^{-1})	3.24	1.34
k_{el}	(h^{-1})	1.41	0.79
CL	(ml/min)	100.4	30.0
CL_R	(ml/min)	72.0	20.5
CL_{NR}	(ml/min)	25.7	19.2

AUC: area under plasma versus time curve to infinity; α: rate constant for the distribution phase; β: rate constant for the elimination phase; $t^1/_{2\alpha}$: plasma half-life for the distribution phase; $t^1/_{2\beta}$: plasma half-life for the elimination phase; V_c: apparent volume of central compartment; V_Z: apparent volume of distribution; k_{12}, k_{21}, k_{el}: rate constants in a two-compartment model CL: clearance; CL_R: renal clearance; CL_{NR}: non-renal clearance

samples, even CSF, never fell below 5 µg/ml, the lowest limit was never determined.

After a single intravenous infusion of mannitol 500 mg (-1000 mg) per kg body weight during 15 min, mannitol disappeared from plasma in a biexponential manner. The plasma concentration-time curves from two of the patients are shown in Fig. 2a, b. Both patients received the same amount of mannitol, resulting in similar plasma profiles. However, there was a great difference in the mannitol concentrations in CSF in these patients. The mean plasma and CSF concentration curves for mannitol from all the patients are presented in Fig. 2c. The plasma concentration of mannitol decreased biexponentially, with a distribution phase up to 1 h after the start of the infusion and an elimination phase thereafter. The mean maximal plasma concentration obtained was 4.08 mg/ml at 15 min, and by 4 h it had declined to 0.53 mg/ml.

The CSF concentration of mannitol varied greatly between the patients. Even those receiving the same dose of mannitol per kg body weight showed comparable variability. The mean concentration of mannitol in CSF increased up to 0.10 mg/ml throughout the 4 hour period studied.

In each of the 12 patients the best fit of the observed plasma concentrations was obtained using non-linear regression analysis. The mean pharmacokinetic parameters obtained after the intravenous infusion of mannitol are presented in Table 2. The distribution phase was rapid with much variation between patients. The mean (± SD) distribution

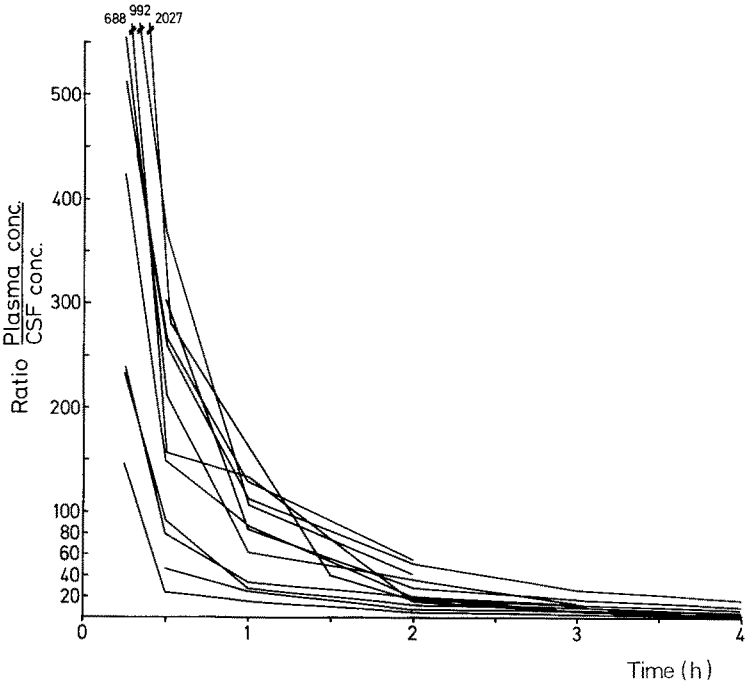

Fig. 3. Ratios between plasma and CSF concentrations of mannitol versus time in the 12 patients studied

rate constant (α) was 11.19 h^{-1} (5.67 h^{-1}), which corresponds to a plasma distribution half-life ($t^1/2\alpha$) of 0.11 ± 0.12 h. The mean elimination rate constant (β) was 0.41 h^{-1} (0.20 h^{-1}), the plasma half-life was 2.17 h (1.26 h), the central distribution volume was 5.3 l (2.2 l) and the total volume of distribution (V_Z) was 16.3 l (4.8 l). The total plasma clearance (CL) was 100.4 ml/min (30.0 ml/min). The micro constants are also shown in Table 2.

In 9 of the patients it was also possible to measure the renal excretion of mannitol. The mean plasma clearance in them was 97.7 ml/min and the mean renal clearance of mannitol (CL_R) was 72.0 ± 20.5 ml/min. Thus, the mean non-renal elimination of mannitol (CL_{NR}) was calculated to be 25.7 ± 19.2 ml/min.

Discussion

As the therapeutic dose of mannitol to lower intracranial pressure is extremely high compared to doses of drugs in general analysis of mannitol in biological samples does not require a technique of high sensitivity. However, there are reasons to believe that endogenous molecules similar to mannitol can interfere with techniques of quantitation, so an assay with high accuracy must be employed. Unlike previous reports, mannitol here in plasma, CSF and urine was measured by gas chromatography - mass spectrometry (selected ion monitoring), one of the most accurate techniques known.

According to Laker et al. [18], mannitol is present in low concentrations in normal human urine. Probably there is also an endogenous level of mannitol in plasma, but both those concentrations were regarded as negligible to the high concentrations served after treatment.

Despite the clinical use of mannitol for more than 40 years for estimation of the glomerular filtration rate and the volume of extracellular fluid, and for more than 25 years as a hypertonic solution for lowering intracranial pressure during cerebral surgery, little is known about its pharmacokinetics. There appear to be only two reports about its kinetics [19, 20]. In the first study [19], the authors used a spectrophotometric technique to analyse mannitol. The protocol involved 56 subjects, 39 of whom suffered from some of renal disease. The subjects received a rapid i.v. bolus injection of 25.5% mannitol 20 ml. The present patients received about 8 times as much i.v. (mean $41 \text{ g} \pm 17.5$) over a 15 min infusion period. In spite of this difference, there are some similarities between the two studies. In both a biphasic pattern of disappearance of mannitol from plasma was evident. A distribution half-life of 0.11 h was found here compared to 0.09 h for the subjects with normal renal function described by Dominguez et al. [19]. The corresponding elimination half-lives were 2.17 h and 0.98 h, and the apparent volumes of distribution were 16.3 l and 14.2 l (all subjects reported in [19]). Plasma clearance is a better way of expressing the elimination of a drug, since

it depends both on plasma half-life and the volume of distribution ($CL = 0.7 \cdot Vz$). Mean plasma clearance in the present patients was 100.4 ml/min, which agreed well with the 109 ml/min calculated for the subjects with normal renal function [19]. In 9 of our patients the renal clearance of mannitol was calculated to be 72.0 ml/min, giving a non-renal clearance of 25.7 ml/min. In view of the use of mannitol to estimate glomerular filtration rate, the non-renal clearance was an unexpected finding. It may have several different explanations, including too short a sampling time for urine, and metabolism or redistribution of mannitol in the body. To clarify the possible non-renal elimination of mannitol further investigations are required. It is interesting that Domingues et al. [18] reported that only 79% of the mannitol injected i.v. in subjects with normal renal function could be collected in urine up to 12 h.

The second pharmacokinetic study on mannitol in humans is that by Cloyd et al. [20]. They gave 2 volunteers and 2 patients mannitol 0.5–0.7 g/kg as an i.v. infusion over 15 min. Mannitol was analysed by an enzymatic method using a specific bacterial mannitol dehydrogenase which catalyzed the NAD-linked oxidation of mannitol to fructose and NADH. The serum concentrations of mannitol were only followed for 3 h, which is probably why they found a shorter $t_{1/2\alpha}$ (2.11 ± 2.67 min), a shorter $t_{1/2\beta}$ (71.15 ± 27.02 min) and higher total body clearance (7.15 ± 10.23 ml $\cdot$ min$^{-1} \cdot$ kg^{-1}) than in the present investigation.

Changes in mannitol concentrations in CSF were followed in the 12 patients. Over the interval studied (4 h), the maximum concentration of mannitol in CSF was not reached, but remarkable differences in distribution rates to this compartment were encountered. The CSF concentration varied 7.5 fold between patients (Fig. 2a, b). If mannitol acts through an osmotic mechanism the consequence of this finding is likely to be variation in the osmotic force. In an attempt to illustrate the concentration gradient of mannitol between blood and CSF, the ratios versus time were calculated (Fig. 3). Interindividual differences in the ratios were considerable especially during the two hours after mannitol administration. This might be one explanation for the clinical observation that some patients show a poor response to treatment with mannitol. There is no evidence that the variability in the pharmacokinetics of mannitol in the patients was related to the diagnosis, preoperative grade or the occurrence of subarachnoid bleeding as diagnosed by CT. From the present study it is evident that mannitol concentration in the CSF had not reached its maximum during the 4 h interval studied. Extension of the experimental period would further enlarge knowledge of the pharmacokinetics of mannitol and should not only offer a better explanation for the interindividual differences but might also give us some hints to a more adequate dosage of mannitol in clinical practice. Such studies are under way.

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