Absorption of Metrizamide from Cerebrospinal Fluid to Blood: Pharmacokinetics in Humans

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Abstract □ The rate of transfer of contrast agents from cerebrospinal fluid to blood is of clinical importance in radiological examinations of the subarachnoid space. Metrizamide, a potential contrast medium, was injected intrathecally to humans and serum levels at different times after injection were measured. A one-compartment open model was found to apply to the data. Considerable individual variations were found, but the mean absorption rate constant indicated that more than 50% of the absorbed dose had disappeared from the cerebrospinal fluid 0.75 hr after injection. TLC of the fraction excreted in the urine showed that metrizamide was not metabolized in the body.

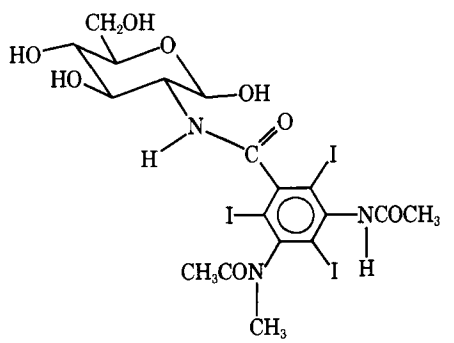
Keyphrases □ Metrizamide—pharmacokinetics after intrathecal administration, concentration in cerebrospinal fluid, humans □ Pharmacokinetics—metrizamide absorption from subarachnoid space after intrathecal administration, humans □ Radiology—pharmacokinetics of metrizamide absorption from subarachnoid space after intrathecal administration, humans □ Absorption kinetics—metrizamide from cerebrospinal fluid, humans

Metrizamide (I) is a contrast agent (1) developed for use in the subarachnoid space. The absorption of metrizamide and other water-soluble contrast agents from cerebrospinal fluid to blood was previously followed by evaluation of X-ray films taken at different times after intrathecal injection of the contrast agents (2–6). However, it is difficult from subjective evaluation of X-ray films to estimate the biological half-life of the contrast agent in the subarachnoid space. Therefore, the absorption process was examined further by determining pharmacokinetic parameters describing the absorption, distribution, and elimination of metrizamide after intrathecal injection in humans.

EXPERIMENTAL

Subjects—The subjects were patients who volunteered to participate after the test was discussed with them. The patients were part of a previously reported study (2), and each patient was examined and had a medical evaluation as described in that study.

Methods—For the present study the following sampling was relevant. Venous blood samples were taken at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 23 hr after intrathecal injection of 1700 mg of I (170 mg I/ml) in the lumbar region (L1–L4). The weight of the patients was in the 59–94-kg range. Cerebrospinal fluid samples were obtained by a second spinal puncture taken at 6 or 24 hr after the injection.



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Quantitative urine collection was performed during the first 24 hr after injection. Serum and cerebrospinal fluid samples were analyzed for their iodine content by a modification of the alkaline ashing method[1] (7) and urine samples were analyzed by the oxygen flask combustion method[2] (8).

Pharmacokinetic Analysis—To determine the kinetic constants related to the absorption of metrizamide into the blood, a one-compartment open model was used. In this model the serum concentration follows the equation of Teorell (9):

$$C = \frac{FDk}{V(k - K_E)}[e^{-K_E(T-T_0)} - e^{-k(T-T_0)}] \qquad \text{(Eq. 1)}$$

where:

C = serum concentration
T = time after injection
T_0 = lag time
F = fraction of dose absorbed
D = dose
k = first-order rate constant for absorption
K_E = first-order rate constant for excretion
V = apparent volume of distribution

Initial estimates for the parameters k, K_E, and V/F were obtained from observed serum levels using the feathering technique described by Wagner (10). Final estimates were found by fitting the theoretical curve (Eq. 1) to the observed values. The curve fitting was done by computer[3]. From the final estimates for the absorption rate constant, the percentage absorbed from the subarachnoid space was calculated as a function of time by the equation:

$$\left(\frac{A_T}{FD}\right)100 = (1 - e^{-kT})100 \qquad \text{(Eq. 2)}$$

where A_T = amount of substance that has entered the volume of distribution at time T. The derivation of this equation was described previously (11). All calculations using Eq. 2 have been done

Table I—Serum Values and Percent Absorbed from the Subarachnoid Space after Intrathecal Injection

Time after Injection, hr	Observed I Serum Concentration, μg/ml		Percent of Dose Absorbed[a]
	Mean ± SD	Range	
0.5	6.0 ± 5.1	1.2–7.8	30.2
0.75	8.6 ± 6.9	1.6–22.4	51.7
1	11.4 ± 8.3	3.2–28.4	66.6
1.5	15.4 ± 8.6	5.2–28.0	84.0
2	15.6 ± 8.2	5.2–29.2	92.4
3	14.9 ± 5.8	5.6–24.0	98.2
4	13.9 ± 4.6	7.2–21.2	99.6
6	11.7 ± 3.9	7.2–18.4	99.9
23	3.0 ± 1.7	1.0–4.4	100.0

[a] Calculated from Eq. 2.

[1] At the Central Laboratory, Ullevål Hospital, Oslo, Norway.
[2] By the Analytical Department of Nyegaard & Co, Oslo, Norway.
[3] A nonlinear iterative program written in BASIC for the Honeywell-Bull time-sharing system.

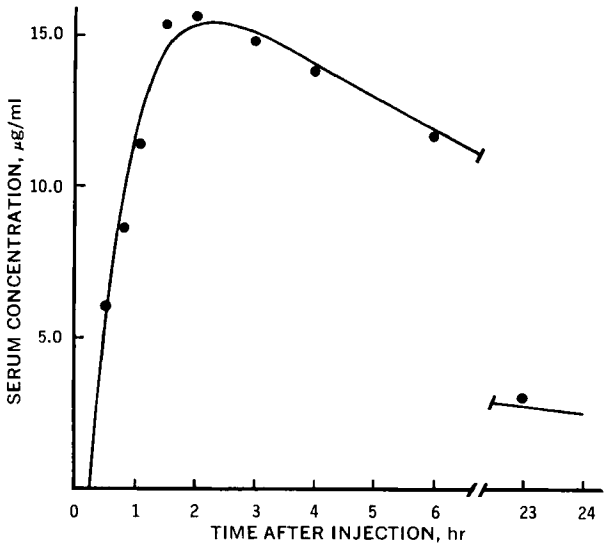

Figure 1—*Serum iodine concentrations. Mean values of observed concentrations after intrathecal injection of metrizamide in eight patients* (●). *Theoretical curve of best fit was calculated from Eq. 1* (—).

with the value of $F = 1$, assuming all metrizamide to be absorbed from the subarachnoid space.

The concentrations of metrizamide in the cerebrospinal fluid at different times after injection were also used for calculation of the biological half-life of metrizamide in the subarachnoid space. When assuming first-order kinetics, the biological half-life ($T_{1/2}$) was calculated by the equation:

$$T_{1/2} = \frac{\ln 2(T_2 - T_1)}{\ln C_1 - \ln C_2} \qquad \text{(Eq. 3)}$$

where C_1 = concentration at time T_1 (hours) after injection, and C_2 = concentration at time T_2 (hours) after injection.

Metabolism—All urine samples were examined for metabolites by TLC. The urine was applied to silica gel plates, which were developed in two systems as described by Frey (12). After development the plates were examined under UV light.

RESULTS

Serum Concentration—Eight patients were injected with metrizamide intrathecally. Metrizamide could be detected in the blood after about 15 min, and the maximum serum concentration appeared about 2 hr after injection (Table I). Relatively large individual variations were found. Estimates for the pharmacokinetic parameters were determined for each subject from the observed serum concentrations and are presented in Table II, where the parameters calculated from the mean serum values are shown also. The fit of the theoretical curve to the observed data is shown in Fig. 1.

Biological Half-Life—From the estimated mean rate constant for absorption, the percentage absorbed from the subarachnoid space to blood at different times after injection was calculated using Eq. 2. The values (Table I) show that about half of the dose disappeared from the cerebrospinal fluid in 0.75 hr.

In three patients the concentration of metrizamide in the cerebrospinal fluid was measured 6 hr after injection, and in three other patients the concentration was measured 24 hr after injection (Table II). When the mean values of these measurements were used for calculation, the biological half-life of metrizamide in the subarachnoid space was found to be 11 hr.

Excretion in Urine—In the six patients from which urine was sampled, 55–86% of the administered I was recovered within 23 hr.

Metabolism—The metabolic studies showed that no metabolites of metrizamide were found in the part of the dose excreted in the urine (Table II). The detection limit was estimated to be less than 5% of the recovered dose.

DISCUSSION

The results support the preliminary assumption that the one-compartment open model is valid for describing the absorption of metrizamide from the subarachnoid space to blood, as was found in a previous study (11) where metrizamide was injected intracisternally to cats. In this study, the first-order constant for absorption was also 1.5 hr^{-1}. However, in neither of the two studies was an attempt made to incorporate the amount of metrizamide that penetrates into the extracellular space of the nervous tissues into the pharmacokinetic model because of the acceptable fit to the blood data obtained by the one-compartment open model.

From the structure of the ependyma (13), it is probable that some injected metrizamide enters the extracellular space of the nervous tissue relatively fast. This migration implies a longer biological half-life of metrizamide in the subarachnoid space than is found by the one-compartment open model and may partly explain the discrepancy found between the two different methods of measuring the biological half-lives used in the present study.

Another source of error is that when the biological half-life of metrizamide in the subarachnoid space was determined from measurements of the cerebrospinal fluid concentration, the same group of patients was not examined 6 and 24 hr after injection. Furthermore, the calculation used in Eq. 3 is based on the assumption that metrizamide has the same distribution at 6 and at 24 hr after injection. This may not be the case, but the results of Prockop and Fishman (14) indicate that the assumption is valid. They found that the concentration of inulin followed a straight line in a semilogarithmic plot of cerebrospinal fluid concentration *versus* time. The biological half-life of inulin was 68.8 min^{-1} during the observation period of 30–150 min after percutaneous injection in cisterna magna of dogs.

In the three patients examined 6 hr after the injection, a mean concentration of 3600 μg of I/ml was found. This value is only one-fourth of that which would have been found (Table II) if the volume of the subarachnoid space in humans is 118 ml (13), if no disappearance had taken place, and if the contrast agent had distributed uniformly in the cerebrospinal fluid. A uniform distribution in the cerebrospinal fluid within the first few hours after the injection is not likely, and the value of 3600 μg of I/ml thus shows that the biological half-life of metrizamide in the cerebrospinal fluid is far less than 11 hr during the first 6 hr after injection.

In the previous study (11) as well as in this study, considerable variation in the serum levels was found between subjects. This finding should be related to the observations by Skalpe *et al.* (2) who, by examining the radiographs, found that no contrast could be seen in some patients 3–5 hr after injection while traces could still be seen in other patients after 8 hr. The disappearance of other contrast agents from the subarachnoid space after intrathecal injection in humans also seems to show similar individual variations. Thus, Schmerwitz and Rösch (5) found meglumine iocarmate to be completely "radiologically" absorbed within 2–8 hr after injection. For meglumine iothalamate, the corresponding time was 4–8 hr (6).

One reason for the individual variation in the data in the present study is the variation in dose per unit body weight. Another, and perhaps the main, reason may be that the patients made different movements after the injection, thus provoking differences in the circulation of the cerebrospinal fluid. It has been shown that movements of the body are very important for the circulation in spinal cerebrospinal fluid of cats. Grundy (15) found virtually no movement of dye from 7 to 85 min after sacral injection when the cats were kept immobile. Since the importance of the movements for the circulation was not recognized in the previous study in cats (11) and in this study, special attention was not paid to this factor so the rate constants for absorption found cannot be correlated with the movements of the patients and the handling of the cats.

Inflammatory involvements of the meninges may also change the absorption rate from cerebrospinal fluid (14, 16, 17). If, however, inflammatory involvements of the meninges are present and have any effect on absorption, they must mainly be located in the lumbar area of the subarachnoid space, because radiographs showed that no visible contrast passed above the 12th thoracic vertebra. Although the mean value of T_0 shows that 0.25 hr passes after the injection before metrizamide enters the blood, the fact that the blood level reaches its peak within 2 hr after injection correlated with the assumed slow circulation in the cerebrospinal

Table II—Pharmacokinetic Constants, Cerebrospinal Fluid Concentrations, and Urinary Recovery after Intrathecal Injection of 1700 mg of I

Patient	k, Rate Constant for Absorption, hr^{-1}	K_E Rate Constant for Excretion, hr^{-1}	T_0, Lag Time, hr	$\frac{V}{F}$, ml/kg	Cerebrospinal Fluid Concentration[a,b]		Percent Recovered in Urine 23 hr after Injection
					6 hr after Injection, μg I/ml	24 hr after Injection, μg I/ml	
1	2.1	0.08	0.54	96	2200	—	86
2	1.4	0.07	0.16	130	—	1510	63
3	1.3	0.20	0.41	141	—	—	60
4	0.4	0.04	0.13	210	—	1540	55
5	0.7	0.14	0.29	117	—	460	79
6	1.0	0.23	0.16	53	200	—	82
7	0.3	0.13	0.25	80	8500	—	—
8	5.7	0.12	0.38	80	—	—	—
Mean ± SD[c]	1.5 ± 0.2	0.09 ± 0.01	0.25 ± 0.05	121 ± 5			

[a] The cerebrospinal fluid was obtained by a second spinal puncture. [b] When assuming uniform distribution in the subarachnoid space and no disappearance from the cerebrospinal fluid, the concentration would have been 14,400 μg of I/ml. [c] Calculated from the observed mean serum values in Table I.

fluid (15) and makes it probable that, with the doses used in this study, most of the absorption takes place in the lower part of the spinal canal.

CONCLUSION

Absorption and excretion of metrizamide after intrathecal injection in the lumbar area of humans seem to follow first-order kinetics. The one-compartment open model is valid for calculations of the blood level data obtained after intrathecal injection of metrizamide. After intrathecal injection of 10 ml of metrizamide (170 mg of I/ml) in the lumbar area, most absorption probably takes place from the lower part of the spinal canal. About 70% of the injected dose is excreted in the urine within 24 hr after the injection.

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