PHARMACOKINETICS OF GdDTPA/DIMEGLUMINE AFTER INTRAVENOUS INJECTION INTO HEALTHY VOLUNTEERS

WEINMANN, H. J.,[1] LANIADO, M.,[2] and MÜTZEL, W.[1]

[1]From the Research Laboratories of Schering Berlin (West) and Bergkamen, Müllerstrasse 170-178, 1000 Berlin 65, Federal Republic of Germany, and [2]the Department of Radiology, Klinikum Charlottenburg of the Free University of Berlin.

● *Pharmacokinetic studies of GdDTPA/dimeglumine in man show a rapid renal clearance and no evidence for dissociation or retention of the complex in the body. These features, in conjunction with its strong proton relaxation enhancement and its low toxicity suggest that this complex may be an excellent contrast medium for magnetic resonance imaging.*

INTRODUCTION

The MRI contrast medium GdDTPA/dimeglumine was extensively investigated in preclinical studies.[1-3] The good tolerance observed in animal studies and the potential to enhance contrast in MRI were confirmed in a Phase I study in 20 healthy male volunteers the results of which are reported in the preceding paper of this volume. Data obtained from pharmacokinetic studies in rats, rabbits and dogs suggested that the fate of the substance in the organism after intravenous administration is comparable to that of iodinated urographic contrast agents.[1,4-6] This paper describes the plasma level, distribution and excretion of GdDTPA/dimeglumine when administered intravenously in man in dosages ranging from 0.005 mmol/kg to 0.25 mmol/kg.

MATERIALS AND METHODS

Following the protocol described in the preceding report, the paramagnetic contrast medium GdDTPA/dimeglumine was administered as an aqueous solution containing 0.5 mol/L. The volunteers were divided into four groups of five healthy volunteers each: Group I (0.005 mmol/kg), Group II (0.05 mmol/kg), Group III (0.1 mmol/kg) and Group IV (0.25 mmol/kg).

In Groups I and II, only the urinary excretion was monitored, for up to three days post-injection. In Groups III and IV plasma, urine and feces were collected at time intervals up to five days post-injection. Plasma kinetics, excretion and biotransformation studies were performed in Groups III and IV.

In order to avoid contamination of plasma samples by the contrast medium itself, the GdDTPA/dimeglumine was injected into the left antecubital vein, whereas blood samples were taken from the right cubital vein via a catheter or a cannula, respectively. Blood was collected in tubes containing NH^4-heparinate, and then the tube was centrifuged at 1000g for 10 minutes.

The daily feces samples were mixed with distilled water, incubated at room temperature for 24 hours and then centrifuged at 15,000 g/min for 30 minutes. Plasma and aliquots of urine and feces specimen were frozen at −18°C for later analysis.

Gadolinium analysis was performed by means of inductively coupled plasma atom emission spectrometry (ICP) using the ICP spectrometer 3520 OES (APL, Switzerland). The detection limit for Gadolinium was 0.1-0.2 μg/mL (about 1 μmol/L). An external Gadolinium Standard (SPEX Industries, Inc., Metuchen, NJ 08840, No. AQGd) was also measured. The overall method variation was estimated to be less than 10%. Calcula-

tion of the various pharmacokinetic parameters was based on the assumption that the distribution and elimination of GdDTPA/dimeglumine are subject to first-order kinetics (open two-compartment model). A Honeywell Bell CHB 66/40 computer system with special pharmacokinetic software was used to evaluate the data.

Data were adjusted to body surface or total plasma-volume if necessary. Body surface was calculated using the nomogram of DuBois and DuBois,[7] while plasma volume was determined using the nomogram of Dagher et al.[8]

High-performance liquid chromatography (HPLC) was used in biotransformation studies of the urine of Group III and IV, which was collected three to six hours after dosing. A reversed-phase HPLC column (precolumn: LiChrosorb RP2, analytical column: LiChrosorb RP8, length 25 cm, internal diameter 4.7 mm, Bischoff Analysentechnik) was used. Methanol and water (20 + 100 v/v) containing 7.5 mmol/L of tetrabutylammonium perchlorate (flow rate 2.0 mL/min.) was used as eluent.

Ultraviolet (UV) absorptions at a wave length of 238 nm was recorded by means of a Knauer UV recorder. Changes in refractive index were measured simultaneously by a Knauer Differential-Refractometer. The eluent was sampled automatically in one minute fractions using a model LKB 2111 Superrac sampling instrument.

Gadolinium concentration in the eluent was monitored by analysis of T2 relaxation times. The measurements were performed with an automated pulse spectrometer operating at 0.47 T using the Carr-Purcell-Meiboom-Gill pulse sequence (Minispec pc 20, Bruker). In order to increase sensitivity and to decrease interactions of Gadolinium ions within the lattice, the specimens were acidified using HCl to pH 1 before measurement. The Gadolinium concentration (C) was calculated using the formula $1/T2 \sim C$. The detection limit for Gd was on the order of 20 μmol/L.

Differences between values obtained from the two dose levels (0.1 and 0.25 mmol/kg) were verified after confirming normal distribution by the Bartlett method using analysis

TABLE I: Plasma level of GdDTPA/dimeglumine after intravenous injection of 0.1 and 0.25 mmol/kg in healthy volunteers. Values are given in mmol/L and percent of dose given in the total plasma volume.

Time After Dose	0.1 mmol/kg		0.25 mmol/kg	
	mmol/L	%	mmol/l	%
1 min	0.63 ± 0.17	29.9 ± 7.7	2.06 ± 0.29	40.1 ± 4.3
3 min	0.66 ± 0.10	31.0 ± 4.6	1.78 ± 0.19	34.7 ± 3.30
8 min	0.53 ± 0.08	25.1 ± 3.8	1.41 ± 0.15	27.5 ± 2.80
18 min	0.42 ± 0.06	19.9 ± 2.9	1.08 ± 0.12	21.1 ± 1.60
28 min	0.35 ± 0.04	16.3 ± 1.9	0.88 ± 0.09	17.2 ± 1.11
58 min	0.24 ± 0.02	11.3 ± 1.1	0.61 ± 0.06	11.9 ± 0.69
2 hr	0.12 ± 0.02	5.7 ± 0.75	0.33 ± 0.04	6.49 ± 0.60
3 hr	0.08 ± 0.02	3.75 ± 0.71	0.20 ± 0.03	4.00 ± 0.43
6 hr	0.02 ± 0.01	1.04 ± 0.39	0.07 ± 0.01	1.26 ± 0.24
24 hr	< 0.01	< 0.05	0.01 ± 0.00	0.11 ± 0.07

of variance. The difference between two groups was analyzed using the Scheffe method, whereas for inhomogeneity the method of Kruskal-Wallis was used. The p-value was defined as $p \leq 0.05$.

RESULTS

Plasma level. Three minutes after intravenous injection of 0.1 mmol/kg GdDTPA/dimeglumine a mean plasma concentration of 0.66 ± 0.1 mmol/L was observed. Using 0.25 mmol/kg, a plasma concentration of 1.78 ± 0.19 was detected (Table I).

The gadolinium concentrations in plasma declined according to a bi-exponential function, which can be explained by a distribution phase with a mean half-life of 0.20 ± 0.13 hours and a disposition and elimination phase with a half-life of 1.58 ± 0.13 hours. Twenty-four hours after injection, the gadolinium concentration in plasma was near the detection limit. The apparent distribution volume of the central compartment was calculated to be 137 ± 28 mL/kg, while the apparent distribution volume was calculated to be 256 ± 27 mL/kg (Table II).

A total clearance of 1.94 ± 0.28 mL/min/kg was calculated corresponding to 122 mL/min for a standard body surface of 1.73 m^2.

No statistical differences were found between the parameters calculated from the two different dose studies.

Excretion. Six hours after dosing 83 (±14)% of the dose given had been eliminated by the renal route (Figure 2), with 91 (±13)% leaving the body within the first twenty-four hours. Following dosages of 0.005, 0.05, 0.1 and 0.25 mmol/kg, 87 (±4)%, 96 (±21)%, 93 ± 5% and 87 (±14)%, respectively, of the dose was eliminated renally. These differences are statistically insignificant.

The amount of Gadolinium measured in the feces of Groups III and IV excreted within five days of injection was lower than 0.1% of the given dose. The ratio of the amount excreted renally to the amount excreted extrarenally was greater than 100:1.

The mean half-lives of renal excretion calculated from Group III and IV were 1.6 (±0.3) h. The mean renal clearance of 1.76 (±0.39) mL/min·kg or 111 (±19) mL/min·kg was calculated for a male volunteer having a body surface of 1.73 m^2.

Biotransformation. HPLC analysis of GdDTPA/dimeglumine, combined with refractive index and relaxation time measure-

TABLE II. Pharmacokinetic parameters of GdDTPA/dimeglumine after intravenous injection of 0.1 and 0.25 mmol/kg in volunteers. V_c = apparent volume of distribution of the central compartment; V_d = total distribution volume; α = half-life of distribution; β = half-life of elimination calculated from plasma values; $t_{1/2}$ = half-life of elimination calculated from urine values; Cl = total clearance of plasma; Cl_R = mean renal clearance.

	Group III (0.1 mmol/kg)	Group IV (0.25 mmol/kg)	
V_c (mL/kg)	54 ± 28	120 ± 15	137 ± 28
V_d (ml/kg)	276 ± 57	256 ± 27	266 ± 43
α (h)	0.24 ± 0.17	0.16 ± 0.05	0.20 ± 0.13
β (h)	1.56 ± 0.19	1.61 ± 0.06	1.58 ± 0.13
$t_{1/2}$ (h)	1.51 ± 0.28	1.69 ± 0.31	1.60 ± 0.30
Cl (ml/min · kg)	2.03 ± 0.32	1.85 ± 0.23	1.94 ± 0.28
Cl_R (ml/min · kg)	1.89 ± 0.34	1.63 ± 0.42	1.76 ± 0.39
Cl (ml/min · 1.73m^2)	128 ± 16	117 ± 11	122 ± 14
Cl_R (ml/min · 1.73m^2)	118 ± 16	104 ± 22	111 ± 19

ment, showed one main peak with a retention time of about 6-8 minutes. The compound is invisible in UV recordings. A similar peak was found in all urine fractions collected 3-6 h after injection. The main peak corresponded to 92 (±20) percent of the amount injected into the HPLC column. No differences in Gd-recovery were found between urine samples and references.

GdDTPA/dimeglumine was hardly visible in the refractive index recordings because of poor sensitivity and specificity, and because of interference by other biological substances which were eluted with the same retention time. However, there was no hint that any fraction of the eluate sampled at other retention times contain any amount of a relaxation-time-shortening compound.

DISCUSSION

The fate of GdDTPA/dimeglumine after intravenous administration in the organism is influenced by its extremely hydrophilic properties. The partition coefficient between n-butanol and water of about 0.0001 shows its extraordinary hydrophilicity.[4] After dosing, GdDTPA/dimeglumine is distributed in the vascular system rapidly and diffuses into the extracellular compartment of the body. The reported total distribution volume of about 25% of the body size correlates quite well with the extracellular water space of the human body. However, some infiltration into some cellular compartments cannot be excluded. The compound is excreted unmetabolized predominately by the renal route.

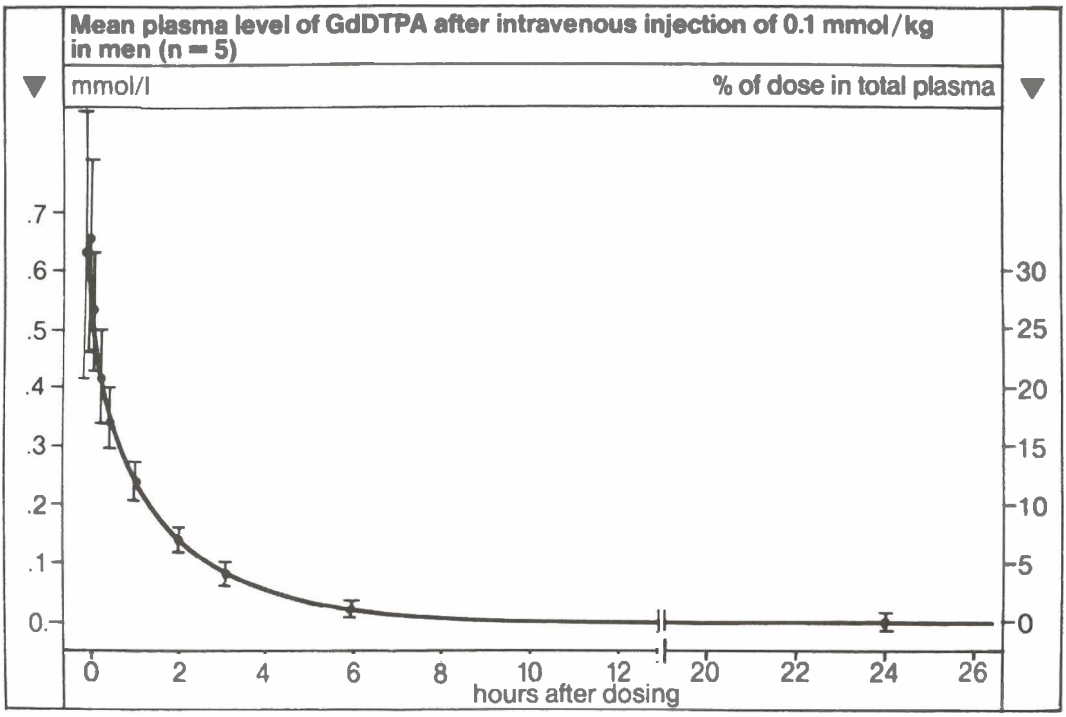

FIGURE 1. Plasma level of GdDTPA/dimeglumine after intravenous injection of 0.1 mmol/kg in five healthy male volunteers. Values are given in mmol/L plasma and percent of dose given in total plasma volume (mean and standard deviation).

The half-life of excretion and total renal clearance are very similar to those of DTPA and other exogenous inert substances.[9,10] The lack of dose dependence of excretion pharmacokinetics leads to the assumption that GdDTPA/dimeglumine has only a very small, if any, interaction within the body.

Assuming that the concentration in plasma and in the interstitial fluid are similar, the efficiency of GdDTPA/dimeglumine to enhance the NMR-signal significantly will last up to about one hour after intravenous injection of 0.1 mmol/kg. A dose of about 0.1 mmol/kg should be sufficient to contrast lesions in magnetic resonance imaging. However, lesions with a relatively small interstitial space may not be enhanced significantly.

In summary, pharmacokinetic results in man verify results of the preclinical animal studies and show that GdDTPA/dimeglumine has rapid renal excretion and no hint of dissociation and retention in the organism. These properties, plus its strong proton relaxation enhancement and its low toxicity, suggest that GdDTPA/dimeglumine may be an excellent MRI-contrast medium.

We thank Mrs. R. Willmanowski, U. Swiderski and U. Todten for their excellent technical assistance, Dr. Phillip Rogers for his editorial assistance, and all other co-workers in the Radiology Department and in the Contrast Media Pharmacology Group who were involved in this investigation.

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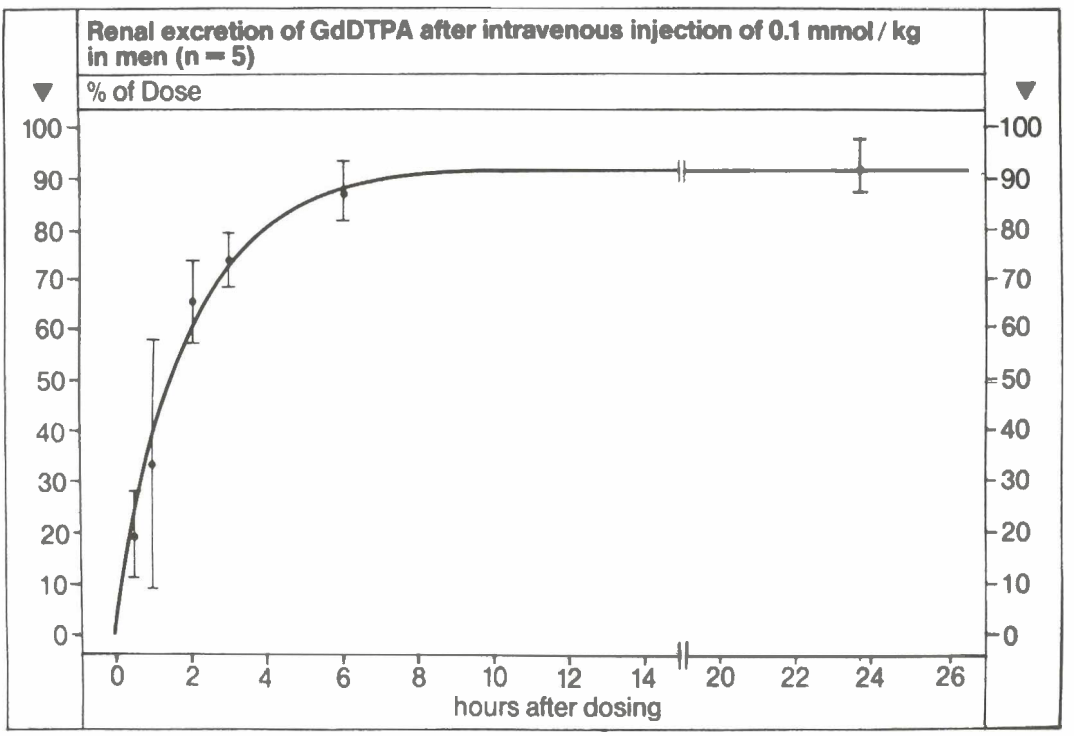

FIGURE 2. Mean renal excretion of GdDTPA/dimeglumine after intravenous injection of 0.1 mmol/kg in five male volunteers. Values are given in percent of dose given (mean and standard deviation).

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(Received June 15, 1984).