Table II—Precision of the Assay for Valproic Acid and Valpromide in Human Plasma

Conc., μg/mL	Valproic Acid: Conc. Found[a], μg/mL	Valproic Acid: SD	Valproic Acid: CV, %	Valpromide: Conc. Found[a], μg/mL	Valpromide: SD	Valpromide: CV, %
20	20.30	1.86	9.18	19.53	0.91	4.66
30	30.52	1.71	4.21	31.76	3.00	9.45
40	41.88	3.24	7.74	41.50	2.80	6.75
50	49.84	3.97	7.96	49.08	3.95	8.00
60	57.84	4.75	8.21	62.5	5.12	8.19

[a] Mean of 10 determinations.

assayed separately by two different systems (2, 4). The proposed method is very useful and advantageous in any pharmacokinetic or metabolic study of valpromide.

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Pharmacokinetics of Iohexol, a New Nonionic Radiocontrast Agent, in Humans

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Abstract □ Sixteen healthy men received iohexol intravenously at a concentration of 346 mg of iodine/mL. Doses of 500, 750, 1000, and 1500 mg of iodine/kg of body weight were administered to four volunteers each. Neither clearance nor percent of dose excreted in the urine showed any significant correlation with size of the dose. The overall mean (±*SD*) renal and total body clearances were 120 ± 18.6 and 131 ± 18.6 mL/min, respectively. The overall mean apparent volume of distribution was 165 (±30.7) mL/kg. Urine contained 92.3 ± 4.4% of the dose. Most of the drug (89.9%) was excreted within the first 12 h. An open three-compartment body model gave the best fit to the experimental data. The mean apparent first-order terminal elimination (γ-phase) half-life was 12.6 h.

Keyphrases □ Iohexol—pharmacokinetics, intravenous administration, humans □ Pharmacokinetics—iohexol intravenous administration, humans □ Radiocontrast agents—iohexol, plasma and urine levels, intravenous administration, pharmacokinetics, humans

Ionic contrast media that are approved for human use are hyperosmolar to plasma. Administration of the large volumes necessary for visualization can result in large detrimental fluid shifts within the body. Prior to conducting intensive clinical trials with a new contrast medium, the route and rate of excretion must be adequately assessed. Previous studies with ionic contrast media have suggested that excretion occurs almost exclusively *via* the kidney at a rate that is consistent with passive handling by glomerular filtration (1).

Iohexol[1], 5-[acetyl(2,3-dihydroxypropyl)-amino]-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide, is a new nonionic radiographic contrast agent which is intended for vascular and intrathecal use in humans. The biological properties of iohexol (2) are similar to those of metrizamide, the first nonionic contrast medium approved for clinical use (3). A significant advantage of iohexol is its stability in solution to terminal heat sterilization, and its preparation as a ready-to-use solution.

This report describes the results of our investigations into the excretion of iohexol, and includes a nonlinear least-squares estimate of the pharmacokinetic parameters of iohexol following intravenous administration.

EXPERIMENTAL SECTION

Study in Human Volunteers—Four groups of four healthy male volunteers, between the ages of 18 and 50 years, received iohexol intravenously at doses

[1] Omnipaque; Sterling Drug, New York, N.Y.

Table I—Pharmacokinetic Parameters in Volunteers Receiving Intravenous Iohexol

Subject	Regression-Dependent Parameters						Model-Independent Parameters		
	α, h^{-1}	β, h^{-1}	γ, h^{-1}	A, $\mu g/mL$	B, $\mu g/mL$	C, $\mu g/mL$	Volume of Distribution, mL/kg	AUC_0^{96}, $\mu g \cdot h/mL$	Renal Clearance, mL/min	Total Body Clearance, mL/min
					500 mg of Iodine/kg					
1	1.60	0.271	0.060	5190	2130	25.1	146	12,000	97.1	111
2	1.64	0.291	0.093	4800	2410	41.6	147	12,200	86.0	110
3	2.79	0.431	0.139	3570	2590	80.8	171	8,150	112	128
4	2.99	0.412	0.145	5810	3220	166	116	11,500	113	134
Mean ± *SD*	2.26 ± 0.738	0.351 ± 0.08	0.109 ± 0.048	4840 ± 945	2590 ± 462	78.4 ± 62.9	145 ± 22.5	11,000 ± 1900	102 ± 12.9	121 ± 12.1
					750 mg of Iodine/kg					
5	0.946	0.258	0.006	8400	1440	1.74	162	14,800	125	142
6	4.60	0.437	0.048	9690	5010	18.3	108	14,900	162	163
7	1.35	0.309	0.026	5680	2490	6.18	196	13,100	116	141
8	2.69	0.363	0.035	7300	4430	13.6	136	16,400	98.6	97.7
Mean ± *SD*	2.40 ± 1.65	0.342 ± 0.08	0.029 ± 0.018	7770 ± 1700	3340 ± 1660	9.96 ± 7.41	151 ± 37.5	14,800 ± 1350	125 ± 26.7	136 ± 27.4
					1000 mg of Iodine/kg					
9	1.49	0.340	0.051	9390	2990	18.1	172	16,100	127	133
10	1.75	0.345	0.061	7980	4440	21.1	172	18,800	145	165
11	1.22	0.297	0.030	5980	3770	11.3	219	18,900	129	141
12	1.55	0.339	0.030	10200	3790	8.68	152	18,900	108	111
Mean ± *SD*	1.50 ± 0.219	0.330 ± 0.02	0.043 ± 0.016	8390 ± 1850	3750 ± 593	14.8 ± 5.78	179 ± 28.4	18,200 ± 1380	127 ± 15.2	138 ± 22.3
					1500 mg of Iodine/kg					
13	1.56	0.303	0.039	11600	6200	20.4	179	29,900	116	115
14	1.32	0.324	0.031	12100	5770	8.45	179	28,400	130	130
15	2.64	0.351	0.081	9910	8950	62.0	169	31,800	131	130
16	0.632	0.224	0.006	13600	1330	1.36	214	25,600	119	138
Mean ± *SD*	1.54 ± 0.833	0.301 ± 0.06	0.039 ± 0.031	11,800 ± 1520	5560 ± 3150	23.1 ± 27.1	185 ± 19.7	28,900 ± 2620	124 ± 7.62	128 ± 9.60
Overall Mean ± *SD*	1.92 ± 0.988	0.331 ± 0.06	0.055 ± 0.041				165 ± 30.7		120 ± 18.6	131 ± 18.6

of 500, 750, 1000, and 1500 mg of iodine/kg. Iohexol was administered at a concentration of 346 mg of iodine/mL of solution at a temperature of 37°C. The injection was made into an antecubital vein at a rate that delivered the total dose in 3 min. Time zero ($t = 0$) is defined as the time at which the injection was completed. Blood samples were drawn from the contralateral antecubital vein. Plasma and urine samples were collected at appropriate intervals and stored frozen until analyzed.

Table II—Urinary Recovery of Intact Iohexol in Humans

Subject	Administered Dose, mg[a]	Iohexol Excreted in Urine (0–96 h), mg	Dose Excreted (0–96 h), %
	500 mg of Iodine/kg		
1	79,800	70,000	87.6
2	80,600	63,900	79.3
3	62,700	54,700	87.2
4	92,500	83,700	90.6
Mean ± *SD*			86.2 ± 4.83
	750 mg of Iodine/kg		
5	126,000	111,000	87.7
6	146,000	145,000	99.4
7	111,000	95,400	85.8
8	96,300	97,400	101.0
Mean ± *SD*			93.5 ± 7.83
	1000 mg of Iodine/kg		
9	129,000	123,000	94.8
10	186,000	163,000	87.9
11	160,000	146,000	91.3
12	126,000	122,000	96.9
Mean ± *SD*			92.7 ± 3.96
	1,500 mg of Iodine/kg		
13	206,000	207,000	101
14	221,000	221,000	100
15	248,000	250,000	100
16	212,000	183,000	86.1
Mean ± *SD*			96.8 ± 7.13
Overall Dose Excreted, %			92.3 ± 4.44

[a] Expressed as iohexol.

Appropriate institutional review and approval were obtained. No subject had a clinical history or laboratory findings that were suggestive of renal or hepatic dysfunction.

Assay Procedure—The analysis of plasma and urine for iohexol concentration was dependent on separation by HPLC. The mobile phase was a mixture of 0.01 M phosphate buffer, pH 7.4, and methanol; the column was a 5-μm Spherisorb ODS[2] column, 25 cm × 4.6 mm i.d. The UV detector was set at 254 nm. Details of the HPLC procedure will be reported elsewhere (4). Plasma and urine standards, which were prepared in normal human biological fluids, were processed and anlayzed with each set of samples from the subjects in the study. The concentrations of iohexol were determined by inverse prediction (5), using the linear regression of the peak height ratios of the standards. The minimum quantifiable level of iohexol was estimated as the concentration whose lower 80% confidence limit just encompassed zero (6).

Pharmacokinetic Calculations—The data obtained from the analysis of the plasma samples was described by an open three-compartment body model by means of a weighted nonlinear regression (NLIN) procedure using the Marquardt algorithm (7); the weighting factor was the reciprocal of the square of the concentration. The model was defined with the following equation:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where C_p is the plasma concentration; A, B, and C are constants; and α, β, and γ are the hybrid rate constants for the three-compartment model.

In addition to the regression-dependent parameters, the plasma concentration data were used to calculate the area under the plasma concentration *versus* time curve during the 96-h study period (AUC_0^{96}). Both total body clearance and renal clearance were estimated by dividing the dose administered and the amount of drug excreted into the urine during 96 h, respectively, by the AUC_0^{96}.

RESULTS AND DISCUSSION

The concentrations of iohexol in the plasma samples from each of the volunteers were determined. After intravenous administration, the plasma concentrations declined triexponentially with time, suggesting that a three-compartment body model would be appropriate. Pharamacokinetic parameters were estimated for each subject after computer-fitting of the plasma data by

[2] Excalibar, Applied Science, State College, Pa.

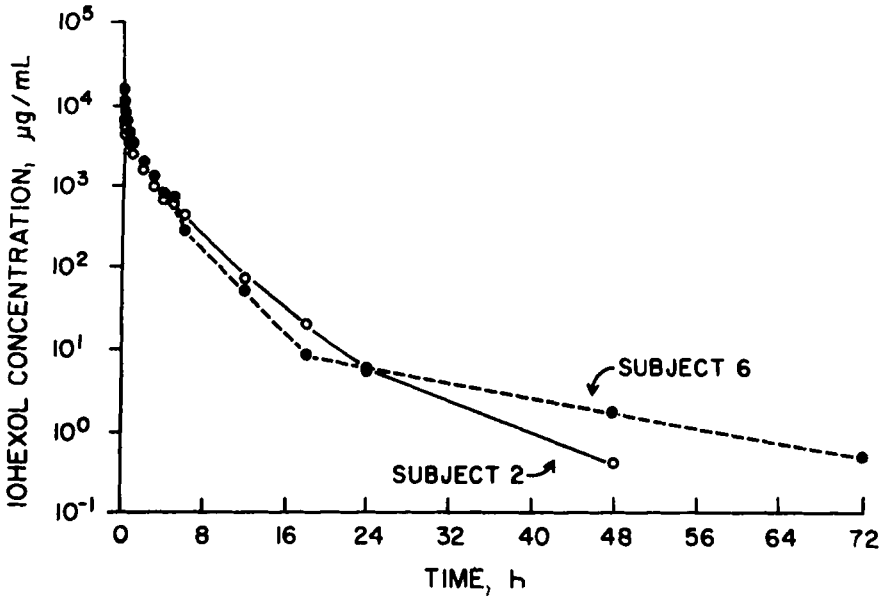

Figure 1—*Plasma concentration of iohexol in human volunteers after intravenous administration. Plasma concentrations were observed in subject 2 (○), and in subject 6 (●), with widely divergent renal clearance rates and concentrations predicted by the open three-compartment body model (lines).*

an iterative nonlinear least-squares regression technique (7). Despite the threefold range in both the total dose administered and the infusion rate, the same model was fitted to the plasma concentration data of each subject, with satisfactory results (Table I).

The mean apparent first-order terminal (γ-phase) elimination half-life for iohexol was ~12.6 h. The mean value for α, 1.92 h^{-1}, corresponds to a half-life of 22 min; the mean value for β, 0.331 h^{-1}, corresponds to a half-life of 2.1 h. The mean ($\pm SD$) apparent volume of distribution was 165 (±30.7) mL/kg of body weight. This value suggests that iohexol distributes into extracellular water.

The AUC during the 96-h study period was estimated by the trapezoidal method (Table I); linear regression analysis indicated a good correlation between the amount of drug injected and the AUC_0^{96} ($r = 0.94$; $p < 0.001$).

From the amount of drug excreted into the urine and the regression-independent AUC, the renal clearances were calculated (Table I). Although there is almost a twofold difference between the highest (subject 6) and lowest (subject 2) renal clearances, the observed concentration data were adequately described by the open three-compartment body model for both of these subjects. A comparison of the observed and predicted concentrations is shown in Fig. 1; the agreement between the observed values and those predicted by the pharmacokinetic model is apparent.

The urinary excretion of intact iohexol is summarized in Table II. The overall mean ($\pm SD$) percent of dose excreted into urine was 92.3 ± 4.4%; the recovery was not significantly different across doses ($p < 0.158$). Most of the drug was excreted into the urine within the first 12 h[3] with a mean of 89.9 ± 7.0%. As can be determined from the clearances presented in Table I, renal clearance accounts for 95% of the total body clearance; obviously, iohexol is not metabolized appreciably.

Iohexol was well tolerated in these subjects, in doses up to 1500 mg of iodine/kg of body weight. No drug-related adverse reactions were reported, although, in a few cases, a sensation of heat was recorded following injection of iohexol.

[3] Unpublished results.

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