JOURNAL OF NUCLEAR MEDICINE 6:183-191, 1965

The Renal Clearance of ^{131}I Labeled Meglumine Diatrizoate (Renografin) in Man[1]

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The renal clearance of inulin is the universally accepted measure of glomerular filtration in man. The chemical quantitation of this substance, however, is tedious and time consuming. Even in the best of hands, the standard deviation for repeated chemical determinations on the same sample of insulin is 4.3 per cent (1). In order to simplify the measurement of glomerular filtration rate, a group of substances believed to be excreted in the same manner as inulin and labeled with gamma-emitting isotopes have been employed in clearance studies. These include ^{131}I (2) and ^{125}I (3) allyl inulin, vitamin $B_{12}{}^{57}CO$ (4), and ^{131}I labeled sodium diprotiozoate (Miokon) (5), sodium diatrizoate (Hypaque) (5,6), meglumine diatrizoate (Renografin) (5,7), and sodium iothalamate (Angio-Conray) (8). The radioactivity of these labeled compounds in plasma and urine, necessary for the calculation of clearances, can easily and accurately be measured in a well type scintillation counter.

Renografin ^{131}I, when first used for radiorenography (9), was thought to be handled by both glomerular filtration and tubular secretion. Woodruff and Malvin, however, showed in dogs that the changes in Renografin ^{131}I concentration paralleled those of creatinine in urine obtained from different levels of the renal tubule during stop-flow studies (5). This inference that Renografin is handled exactly like exogenous creatinine in the dog, that is, solely by glomerular filtration, was supported by further data which indicated that the clearance of a tracer dose of Renografin ^{131}I after a single intravenous injection was equal to that of continuously infused creatinine, once a small correction had been made for that fraction of Renografin bound to plasma proteins. Meschan *et al* (7), in eleven studies on five dogs, noted that although the average ratio between the clearance of Renografin ^{131}I, given in a single intravenous tracer dose, and that of inulin, administered by continuous infusion, was 1.01, the ratios obtained in each separate study ranged from 0.92 to 1.15 when all studies were considered. This paper reports the results of simultaneous clearances of Renografin ^{131}I and inulin, both determined by constant infusion techniques, in 15 human subjects.

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[1]Supported by U.S.P.H.S. General Research Support Grant No. 1-301-SR-05400-01, the Junior Board of Buffalo General Hospital, United Health Foundation of Western New York, Grant No. G-64-BGH-1, Buswell Fellowship, and United Health Foundation of Western New York Grant No. S-64-UB-5.

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MATERIALS AND METHODS

All clearance studies were performed according to the method of H. Smith (10). Subjects included patients with and without renal disease, selected to represent all levels of glomerular filtration rate. Diuresis was induced by oral water loading and maintained by means of a constant intravenous infusion of lactated Ringer's solution. The total amount of inulin required for each study was mixed with 150 μc of Renografin ^{131}I, having a specific activity which ranged from 150 μc/mg to 300 μc/mg. The ^{131}I labeled Renografin used in the study contained 2 per cent of unbound iodine three weeks after labeling, as determined by paper chromatography.[1] In 69 clearances, only tracer amounts of Renografin were utilized. Eight clearances were performed at high plasma concentrations of stable Renografin by combining the labeled compound with 60 cc of 60 per cent meglumine diatrizoate solution. This was then divided into a priming and a sustaining dose. Immediately after the administration of the priming dose, the sustaining infusion was begun and maintained at a rate of 0.494 ml/min. After a 30-minute equilibration period and the establishment of satisfactory diuresis, 15-minute sequential urine collections were begun. Peripheral venous blood samples were drawn six minutes prior to the midpoint of each collection period. Urine was collected by means of an indwelling Foley catheter when total clearances were performed, and by the use of indwelling ureteral catheters during split renal function studies. The resorcinol method (11) was utilized for the chemical determination of inulin. The activity of ^{131}I in plasma and urine was measured in a well type scintillation counter. All samples were counted to a statistical accuracy of 1 per cent or better.

All clearances were calculated by the formula $C = \frac{UV}{P}$, where C is the plasma clearance in ml/min, V is the minute urine volume in ml/min, U the urine concentration, and P the plasma concentration. The concentrations of inulin were expressed in mg/ml, and those of Renografin ^{131}I in net counts per minute per milliliter. Although the binding of Renografin to plasma proteins were not determined in this study, a report by Lasser *et al* (12) indicates that the binding of diatrizoate by human plasma does not exceed 5 per cent.

RESULTS

The results of 69 clearances of inulin and tracer amounts of Renografin ^{131}I determined simultaneously on 13 subjects are presented in Table I. The same data are shown graphically in Figs. 1 and 2. The individual clearance ratios of Renografin ^{131}I/inulin ranged from 0.76 to 1.86, with a mean of 1.04.

Because the use of clearance ratios can be misleading at low glomerular filtration rates, the data were analyzed by the "t" test of paired differences. The level of significance was set at 0.05. Since the probability of the observed "t" of 1.41 was approximately 1.7, the mean difference of minus 1.96 ml/min cannot be considered to be significantly different from zero. Statistically, therefore,

[1]Paper chromatography was performed by Squibb Laboratories.

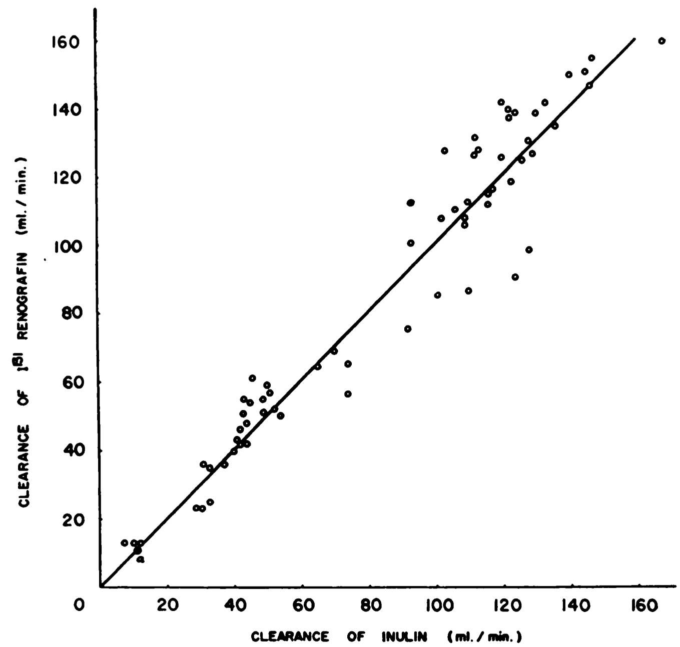

Fig. 1. The relationship between 69 simultaneously determined inulin and ^{131}I labeled Renografin clearances as performed on 13 subjects.

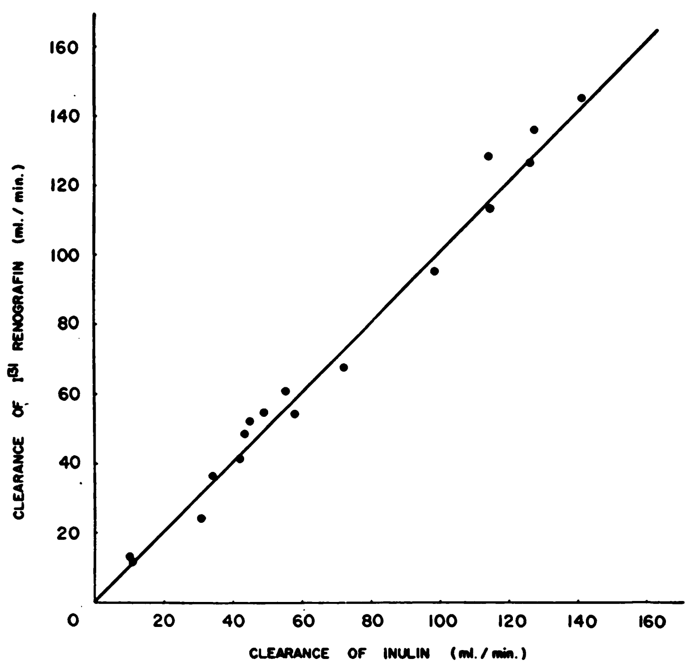

Fig. 2. The average simultaneous clearances of inulin and ^{131}I labeled Renografin, as determined in 13 subjects.

there is no difference between the two methods in either the level or the magnitude of clearance.

The results of eight clearances utilizing high plasma concentrations of Renografin are presented in Table II. These data were not subjected to statistical analysis because of the limited number of cases included in this study. The clearance ratios of Renografin to inulin ranged from 0.87 to 1.04, with a mean of 0.94.

The data suggest that the clearance of meglumine diatrizoate parallels the simultaneous clearance of inulin both in tracer amounts and in pyelographic amounts. This is characteristic of a compound that is handled by glomerular filtration only.

DISCUSSION

Because of the problems involved in the chemical determination of inulin, the clearance of this substance has been used only infrequently for the measurement of glomerular filtration in man. This function of the kidney is usually grossly estimated by the level of blood urea nitrogen or serum creatinine. The endogenous clearance of creatinine, which can be determined readily by simple chemical means, may be used as an estimation of glomerular filtration rate in man, but does not always equal that of simultaneously determined inulin.

The availability of substances which are handled primarily by glomerular filtration and which can be labeled with gamma-emitting isotopes should make for more widespread use of clearance methods in the study of renal and hypertensive disease. Radioactivity in plasma and urine can be measured accurately in a well type scintillation counter. Moreover, substances which interfere with chemical determinations, such as high plasma levels of glucose in the case of inulin, cause no difficulty when radioactive techniques are employed.

Allyl inulin labeled with gamma-emitting isotopes has proven to be a satisfactory inulin substitute, but at present is not available commercially. Except for vitamin $B_{12}{}^{57}CO$, all other compounds currently used as insulin substitutes are contrast media which share a basic chemical structure, that of triiodinated benzoic acid derivatives. Thus, sodium diatrizoate (Hypaque) and methylglucamine diatrizoate (Renografin) differ only in respect to a side-chain substitution, as do sodium iothalamate (Angio-Conray), and methylglucamine iothalamate (Conray). Since iothalamate is an isomer of diatrizoate, it is not surprising that all four compounds are excreted similarly by the human kidney.

The special usefulness of Renografin in the performance of split renal function studies is shown by data obtained from four patients who were investigated for the possibility of renovascular hypertension. According to Stamey (13), the functional disturbance in surgically correctable renal hypertension is excessive water reabsorption by the ischemic or, in the case of bilateral disease, the more ischemic kidney. This is reflected by a higher concentration in the urine from the ischemic side of substances excreted but not reabsorbed by the kidney, such as creatine, inulin, para-amino-hippurate or Renografin. In patients No. 4 and No. 8, there was little difference in either the inulin or Renografin concentrations of the urines from the right and left kidneys. No renovascular lesions were demonstrated by selective renal angiography. Patient No. 2 had labile hypertension with a minimal lesion of the right renal artery. There was a slight

TABLE I

THE SIMULTANEOUS CLEARANCES OF INULIN AND ^{131}I LABELED RENOGRAFIN IN MAN

Patient, No.	15-min period	V ml/min	Inulin			^{131}I Renografin			C Renografin / C Inulin
			U mg/ml	P mg/ml	C ml/min	U CPM/ml	P CPM/ml	C ml/min	
1	1	5.47	2.73	0.201	74	21618	1809	65	0.88
	2	5.67	2.25	0.183	70	21417	1769	69	0.99
					Average 72			Average 67	Average 0.93
2	Left Kidney 1	8.10	2.03	0.253	65	32067	4086	64	0.98
	Left Kidney 2	7.80	1.70	0.266	50	30622	4062	59	1.18
	Left Kidney 3	5.50	2.60	0.279	51	42097	4040	57	1.12
					Average 55			Average 60	Average 1.09
	Right Kidney 1	6.50	2.01	0.253	52	32412	4086	52	1.00
	Right Kidney 2	6.40	2.03	0.266	49	34945	4062	55	1.12
	Right Kidney 3	4.60	2.74	0.279	45	47086	4040	54	1.20
					Average 49			Average 54	Average 1.11
3	1	8.00	1.23	0.327	30	5668	1957	23	0.77
	2	8.00	1.07	0.292	29	5179	1772	23	0.79
	3	7.67	1.15	0.270	33	5643	1773	25	0.76
					Average 31			Average 24	Average 0.77
4	Left Kidney 1	4.07	2.68	0.263	42	27034	2622	42	1.00
	Left Kidney 2	4.60	2.17	0.225	44	23381	2546	42	0.95
	Left Kidney 3	4.33	2.33	0.253	40	22739	2452	40	1.00
					Average 42			Average 41	Average 0.98
	Right Kidney 1	3.07	2.82	0.263	33	30041	2622	35	1.06
	Right Kidney 2	3.60	2.34	0.255	37	25562	2546	36	0.97
	Right Kidney 3	3.67	2.15	0.253	31	24025	2452	36	1.16
					Average 34			Average 36	Average 1.06

TABLE I—*Continued*

5	1	4.40	3.46	0.308	49	33273	2891	51	1.04
	2	3.33	3.81	0.274	46	39805	2189	61	1.33
	3	2.93	4.43	0.314	41	41719	2812	43	1.05
					Average 45			Average 52	Average 1.14
6	Left Kidney 1	5.33	2.29	0.284	43	16766	1625	55	1.28
	Left Kidney 2	5.53	2.77	0.272	56	13843	1466	52	0.93
	Left Kidney 3	5.27	3.16	0.226	74	14320	1353	56	0.76
					Average 58			Average 54	Average 0.93
	Right Kidney 1	0.37	32.45	0.284	42	203868	1625	46	1.10
	Right Kidney 2	0.31	38.35	0.272	44	227563	1466	48	1.09
	Right Kidney 3	0.31	31.50	0.226	43	221589	1353	51	1.19
					Average 43			Average 48	Average 1.13
7	1	11.67	2.78	0.257	126	11204	1051	124	0.98
	2	9.67	2.90	0.255	110	13139	1136	112	1.02
	3	7.20	4.20	0.251	120	18429	942	141	1.17
	4	5.73	4.60	0.255	103	20737	933	127	1.23
	5	5.67	5.13	0.260	112	23939	1036	131	1.17
					Average 114			Average 127	Average 1.11
8	Left Kidney 1	2.47	1.48	0.357	10	6911	1418	12	1.20
	Left Kidney 2	1.87	1.94	0.327	11	8010	1363	11	1.00
	Left Kidney 3	1.47	2.41	0.315	11	9987	1300	11	1.00
					Average 11			Average 11	Average 1.07
	Right Kidney 1	2.53	1.75	0.357	12	7252	1418	13	1.08
	Right Kidney 2	2.07	1.59	0.327	10	8516	1363	13	1.30
	Right Kidney 3	1.60	1.45	0.315	7	10670	1300	13	1.86
					Average 10			Average 13	Average 1.31
9	1	14.27	1.86	0.285	93	5329	682	112	1.20
	2	14.27	1.92	0.269	102	5205	695	107	1.05
	3	13.07	1.91	0.267	93	5329	695	100	1.08
	4	8.00	3.26	0.249	105	8495	792	86	0.82
	5	4.87	5.31	0.257	101	13302	766	85	0.84
	6	2.27	10.22	0.252	92	26253	793	75	0.82
					Average 98			Average 94	Average 0.97

TABLE I—*Continued*

Patient, No.	15-min period	V ml/min	Inulin U mg/ml	Inulin P mg/ml	Inulin C ml/min	^{131}I Renografin U CPM/ml	^{131}I Renografin P CPM/ml	^{131}I Renografin C ml/min	C Renografin / C Inulin
10	1	4.40	7.73	0.303	112	19142	666	126	1.13
	2	5.20	6.70	0.285	122	17337	650	139	1.14
	3	8.40	4.36	0.255	144	12410	613	170	1.18
	4	8.67	3.07	0.207	129	8275	571	126	0.98
	5	8.20	3.28	0.217	124	8921	810	90	0.73
	6	6.93	4.02	0.217	128	10689	758	98	0.77
					Average 126			Average 125	Average 0.99
11	1	9.00	3.44	0.258	120	19265	1386	125	1.04
	2	8.67	3.92	0.243	140	22993	1338	149	1.06
	3	9.00	3.25	0.236	124	19512	1227	138	1.11
	4	14.33	2.10	0.222	136	12042	1283	134	0.99
	5	8.53	2.88	0.218	113	17934	1203	127	1.12
	6	4.47	6.27	0.216	130	38921	1262	138	1.06
					Average 127			Average 135	Average 1.06
12	1	24.80	1.49	0.338	109	7830	1815	107	0.98
	2	21.87	1.53	0.316	106	8793	1748	110	1.04
	3	12.67	2.59	0.300	109	14334	1715	106	0.97
	4	11.80	3.01	0.304	117	16930	1721	116	0.99
	5	12.00	3.02	0.312	116	16027	1736	111	0.96
	6	11.20	2.88	0.278	116	17294	1679	115	0.99
	7	10.00	3.38	0.274	123	19766	1673	118	0.96
					Average 114			Average 112	Average 0.98
13	1	7.00	4.90	0.282	122	27461	1405	137	1.12
	2	8.20	5.03	0.246	168	26987	1394	159	0.95
	3	7.00	4.39	0.231	133	24528	1220	141	1.06
	4	10.67	3.10	0.225	147	17860	1237	154	1.05
	5	8.93	3.05	0.213	128	18345	1256	130	1.02
	6	9.67	2.78	0.184	146	17327	1151	146	1.00
	7	10.00	2.91	0.201	145	17010	1137	150	1.03
					Average 141			Average 145	Average 1.03

decrease in urine volume from the right kidney. Because there were no differences in urine concentrations beteewn the two sides, corrective surgery was not recommended. In the case of patient No. 6, the inulin and Renografin clearances of the right kidney were only slightly less than those of the left, but the concentrations of both compounds in the urine from the right side were over ten times those on the left. This was associated with a proportional difference in urine flows. Bilateral main renal artery lesions were found on angiography, but divided renal clearances directed attention to the greater functional importance of the lesion on the right. Surgical repair of the right renal artery was followed by a prompt fall of the blood pressure to normal levels. The value of Renografin in split function studies in hypertensive patients suggests that it can be employed equally well when the same technique is used to measure the functional status of the presumably normal kidney when removal of a diseased partner is contemplated. It is likely that other clinical uses will be found for Renografin and similar compounds in the future.

TABLE II

THE SIMULTANEOUS CLEARANCES OF INULIN AND ^{131}I LABELED RENOGRAFIN IN MAN, AT HIGH PLASMA CONCENTRATIONS OF MEGLUMINE DIATRIZOATE

Patient	15-min period	V ml/min	Inulin			^{131}I Renografin			C Renografin
			U mg/ml	P mg/ml	C ml/min	U CPM/ml	P CPM/ml	C ml/min	V Inulin
	1	10.27	2.68	.2695	102	43383	3962	101	.99
	2	9.33	2.65	.2590	95	38112	3833	93	.98
A	3	11.93	2.35	.2665	105	32303	4149	94	.90
	4	9.33	2.55	.2740	87	37119	4271	82	.95
					Average 97			Average 93	Average .96
	1	17.33	1.200	.3115	67	19586	5862	58	.87
	2	13.66	1.265	.2890	60	21800	5603	53	.88
B	3	12.53	1.365	.2740	63	24409	5307	58	.92
	4	11.80	1.290	.2920	52	24027	5323	54	1.04
					Average 61			Average 56	Average .92

SUMMARY

The simultaneous renal clearances of tracer amounts of Renografin ^{131}I and inulin were determined for both kidneys in eleven, and for each kidney, in four human subjects. Statistical analysis revealed no significant difference between the clearances of Renografin ^{131}I and inulin performed simultaneously. When the plasma concentration of Renografin was elevated by large doses of stable Renografin in two subjects, the clearances of inulin and Renografin ^{131}I were similar. Renografin ^{131}I can be substituted for inulin as a measure of glomerular filtration rate in man, and is of particular value in the performance of split function studies.

ACKNOWLEDGEMENTS

The authors acknowledged the technical assistance of Mary Louise Kelly, Ann Tirone, and Christine Marcinkiewicz. The statistical analysis of data was performed by Seymour Kantor.

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