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The Measurement of Glomerular Filtration Rate in Man With Sodium Iothalamate ^{131}I (Conray)[1]

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INTRODUCTION

The newest addition to a group of contrast media utilized in excretory urography is iothalamate (Conray) (1,2). Its basic chemical structure, 2,4,6-triiodobenzoic acid, is shared with acetrizoate (Urokon), diatrizoate (Hypaque and Renografin), and diprotrizoate (Miokon). The structural differences between these organic iodides (Fig. 1) are determined by the nature of the radicals at positions three and five. Iothalamate differs from diatrizoate by the substitution of $-CONHCH_3$ for $-NHCOCH_3$ in position three. Conray-60—60%, is the methylglucamine salt. Whereas, Conray-400—66.8% and Angio-Conray—80% are the Na salts of iothalamate. The Na salts, although more likely to produce tissue irritability, are less viscous than the methylglucamine preparations in solutions of the same concentration. In a previous study, the renal clearance of ^{131}I labeled Na iothalamate was found to approximate that of inulin (3). However, no inferences could be made as to clearances at both high and low plasma concentrations, because the carrier utilized in this study was the methylglucamine instead of the Na salt of iothalamate. The purpose of this study is to investigate the use of a radioactive form of this contrast medium for the measurement of glomerular filtration rate (GFR) in man.

MATERIALS AND METHODS

Subjects with and without renal impairment were included in order to study the clearance of iothalamate over a wide range of filtration rates. The simultaneous clearances of inulin and labeled Na iothalamate were performed by the constant infusion technique. Diuresis was initiated by an oral water load of 1500 cc and maintained by means of an intravenous infusion of lactated Ringer's solution. Urines were collected by means of a previously inserted indwelling Foley catheter.

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The total amount of inulin required for each study was combined with 100μC of Na iothalamate ^{131}I. The Na iothalamate ^{131}I utilized for this study was prepared and supplied by Dr. Howard J. Glenn of Abbott Laboratories. The specific activity of this labeled compound ranged from 80 μC/mg to 600 μC/mg and was found to contain less than two percent unbound iodide[2] up to 60 days after shipment. The unbound I^- was measured by means of paper chromatography performed bi-weekly. The mixture was then divided into priming and sustaining solutions. Following the administration of the priming dose, which contained 50 mg of inulin per kg of body weight, the sustaining dose was infused at a rate of .494 ml/min by means of an automatic pump. The sustaining dose was calculated to maintain a plasma concentration of 0.25 mg/ml. After a 45-minute equilibration period, sequential 15-minute urine collections were obtained. Venous blood samples were drawn six minutes prior to the midpoint of each collection period.

Clearances were calculated by the formula $C = \frac{UV}{P}$, where C is the clearance in ml/min, V the urine flow in ml/min, U the urine, and P the plasma concentration. The concentrations of Na iothalamate ^{131}I were expressed in net counts/min/ml and those of inulin in mg/ml. A well-type scintillation counter was used to measure ^{131}I activity in plasma and urine to a statistical accuracy of one per cent or less. Inulin concentrations were determined by the resorcinol method (4). The plasma binding of Na iothalamate ^{131}I was found to be less than three per cent. No attempt was made to chemically determine the ^{131}I labeled na iothalamate either in the blood or in the urine.

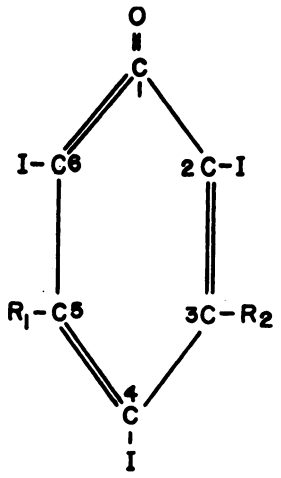
RESULTS

A total of 100 simultaneous clearances of inulin and na iothalamate ^{131}I were performed in 24 studies on 16 subjects. The data are presented in Table I and shown graphically in Figure 2. Individual glomerular filtration rates ranged from 2 to 167 ml/min. The clearance ratios of iothalamate-to-inulin ranged from .937 to 1.138 with a mean of 1.005.

The *t* test of paired differences was used to analyze the data. The level of significance was set at 0.05. Since the probability of the observed *t* of minus *0.92* was approximately *0.40*, the mean difference of minus *0.46* ml/min was not significantly different from zero. Therefore, statistically, no difference has been detectable between the iothalamate and inulin clearances.

DISCUSSION

The difficulties associated with the chemical determination of inulin have encouraged the investigation of gamma-emitting inulin substitutes. The use of radioactive compounds whose clearances approximate those of inulin greatly facilitates the measurements of GFR. The quantification of radioactivity in blood and urine, necessary for clearance calculations, is simple and not hampered by the presence of interfering substances as is the determination of inulin by, for example, glucose.



2,4,6 - TRIIODOBENZOIC ACID

COMPOUND	R_1 (position 5)	R_2 (position 3)
Iothalamate	$NHCOCH_3$	$CONHCH_3$
Diatrizoate	$NHCOCH_3$	$NHCOCH_3$
Diprotrizoate	$NHCOCH_2CH_3$	$NHCOCH_2CH_3$
Acetrizoate	H	$NHCOCH_3$

Fig. 1. Organic contrast media derived from 2,4,6-triiodobenzoic acid.

The gamma-emitting compounds which have been used for the measurement of glomerular filtration rate include vitamin B_{12} ^{57}Co (5), allyl inulin ^{131}I (6) and ^{125}I (7), and diatrizoate ^{131}I (8,9). When freed of unbound radioiodine prior to use, our mean clearance ratios of ^{131}I labelled allyl inulin-to-inulin in 16 clearances involving five subjects was .984. The use of vitamin B_{12} ^{57}Co requires presaturating all potential binding sites with stable vitamin B_{12} as well as a correction factor (total plasma clearance of vitamin B_{12} ^{57}Co = .89 x inulin clearance) to compensate for the proteinbound fraction. Both allyl inulin ^{131}I and ^{125}I have the same clearance as simultaneously measured inulin, but their preparation requires the meticulous removal of unbound radioiodine immediately prior to use. Labelled Renografin and Hypaque, the meglumine and Na salts of diatrizoate,

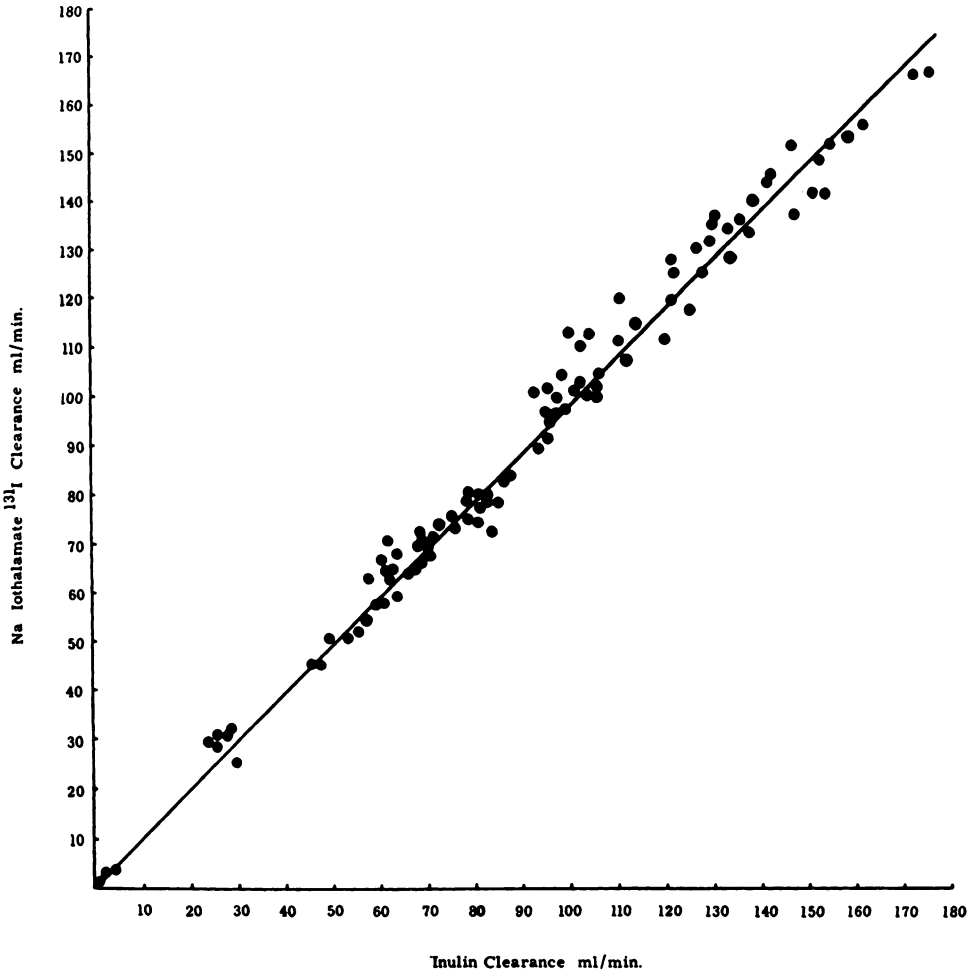


Fig. 2. 100 clearances of simultaneously determined inulin and na iothalamate ^{131}I in man.

appear to be adequate inulin substitutes. But as currently prepared, they vary too widely in the content of free I^- to be employed for clearance studies, without prior assay for free I^- content and removal of this contaminant if it be greater than two per cent.

The initial observation that na iothalamate ^{131}I was cleared by the kidney in a manner similar to inulin prompted this study of iothalamate as a compound for the measurement of GFR. In the original series of 34 clearances, the average iothalamate-to-inulin clearance ratio was 1.06 with a range from .65 to 1.31 (3).

Accumulated experience in the performance of clearance studies and inulin determinations, along with the use of a labeled iothalamate preparation virtually free of unbound I^- has allowed the authors to obtain, in this second series of 100 clearances, an iothalamate-to-inulin ratio of 1.005. Preliminary studies utilizing pyelographic amounts of Conray-400, 66.8% Na iothalamate ^{113}I, as a carrier, indicate that labelled iothalamate approximates the clearances of inulin at both

high and low plasma concentrations. Since the reproducibility of inulin determinations in our laboratory is only five per cent, we assume that the clearances of inulin and iothalamate are identical. The use of iothalamate ^{131}I makes the determination of GFR readily available for clinical and investigative studies in man.

TABLE I

SIMULTANEOUS CLEARANCES OF INULIN AND SODIUM IOTHALAMATE ^{131}I IN MAN

Study Number	*Clearance Number*	*Inulin Clearance*		*Na Iothalamate ^{131}I Clearance*	
		C ml/min	*Aver. C ml/min*	*C ml/min*	*Aver. C ml/min*
1.	1	81	80	78	77
	2	81		79	
	3	77		74	
2.	1	74	73	73	72
	2	79		73	
	3	65		64	
	4	81		77	
	5	74		75	
	6	62		67	
3.	1	67	66	71	68
	2	61		64	
	3	69		68	
4.	1	80	67	79	67
	2	65		63	
	3	67		65	
	4	60		64	
	5	61		63	
5.	1	142	155	146	153
	2	176		167	
	3	153		152	
	4	151		148	
6.	1	152	155	140	146
	2	171		167	
	3	146		137	
	4	150		141	

TABLE I (continued)

Simultaneous Clearances of Inulin and Sodium Iothalamate ^{131}I In Man

Study Number	*Clearance Number*	*Inulin Clearance*		*Na Iothalamate ^{131}I Clearance*	
		C ml/min	*Aver. C ml/min*	*C ml/min*	*Aver. C ml/min*
7.	1	104	102	103	104
	2	109		111	
	3	92		97	
8.	1	120	120	128	128
9.	1	145	134	151	141
	2	129		135	
	3	129		136	
10.	1	135	128	136	129
	2	128		132	
	3	125		130	
	4	131		135	
	5	124		117	
	6	126		125	
11.	1	98	101	113	109
	2	103		113	
	3	101		110	
	4	103		100	
12.	1	63	63	62	59
	2	52		49	
	3	69		62	
	4	67		62	
13.	1	97	95	106	100
	2	77		79	
	3	91		101	
	4	109		120	
	5	105		105	
	6	94		102	
	7	92		90	
	8	96		100	

TABLE I (continued)

Simultaneous Clearances of Inulin and Sodium Iothalamate ^{131}I In Man

Study Number	*Clearance Number*	*Inulin Clearance*		*Na Iothalamate ^{131}I Clearance*	
		C ml/min	*Aver. C ml/min*	*C ml/min*	*Aver. C ml/min*
14.	1	129	102	121	101
	2	100		101	
	3	94		91	
	4	93		93	
	5	101		103	
	6	98		98	
	7	104		100	
	8	96		97	
15.	1	70	77	70	77
	2	86		85	
	3	85		82	
	4	67		70	
16.	1	82	77	71	74
	2	83		78	
	3	77		78	
	4	67		70	
17.	1	28	27	31	30
	2	28		31	
	3	25		30	
18.	1	4	3	4	3
	2	3		4	
	3	2		2	
19.	1	25	26	28	27
	2	24		29	
	3	29		24	
20.	1	59	58	66	66
	2	60		70	
	3	56		62	

TABLE I (continued)

Simultaneous Clearances of Inulin and Sodium Iothalamate ^{131}I In Man

Study Number	*Clearance Number*	*Inulin Clearance*		*Na Iothalamate ^{131}I Clearance*	
		C ml/min	*Aver. C ml/min*	*C ml/min*	*Aver. C ml/min*
21.	1	48	51	47	49
	2	54		50	
	3	52		50	
	4	48		50	
22.	1	45	48	45	46
	2	49		46	
	3	51		46	
	4	48		47	
23.	1	66	70	67	69
	2	65		65	
	3	70		71	
	4	81		78	
	5	68		66	
24.	1	63	70	65	70
	2	66		68	
	3	65		69	
	4	85		83	
	5	70		67	

SUMMARY

The average inulin-to-iothalamate ^{131}I clearance ratio obtained from 100 renal clearance studies in 16 subjects was 1.005. Iothalamate ^{131}I provides an accurate measurement of glomerular filtration rate in man.

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REFERENCES

1. MARSHALL, T. R., AND LING, J. T.: Clinical Evaluation of a New Contrast Medium for Excretory Urography, *Southern Med. J.*, **56**:1424, 1963.

2. MUDD, J. G., AND WILLMAN, V. L.: Sodium Iothalamate, Angio-Conray, in Selective Angiography, *Amer. J. Roentgen., Rad. Ther., and Nucl. Med.*, **90**:1287, 1963.

3. SIGMAN, E. M., ELWOOD, C., REAGAN, M. E., MORRIS, A. M., AND CATANZARO, A.: The Renal Clearance of ^{131}I Labeled Sodium Iothalamate in Man, *Invest. Urol.*, **2**:432-438, March, 1965.

4. SCHREINER, G. E.: Determination of Inulin by Means of Resorcinol, *Proc. Soc. Exp. Biol. Med.*, **74**:117, 1950.

5. NELP, W. N., WAGNER, H. N., JR., AND REBA, R. C.: Renal Excretion of Vitamin B_{12} and Its Use in Measurement of Glomerular Filtration Rate in Man, *J. Lab. Clin. Med.*, **63**:480-491, March, 1964.

6. BROOKS, S. A., DAVIES, J. W. L., GRABER, I. G., AND RICKETS, C. E.: Labelling of Inulin with Radioactive Iodine, *Nature*, **188**:675-676, 1960.

7. CONCANNON, J. P., SUMMERS, R. F., BREWER, R., COLE, C., WEIL, C., AND FOSTER, W. D.: ^{125}I Allyl Inulin for the Determination of Glomerular Filtration Rates, *Amer. J. Roentgen.*, **92**:302-308, 1964.

8. BURBANK, M. K., TAUXE, W. N., MAHER, F. T., AND HUNT, J. C.: Utilization des Substances Marquees dans les Epreuves Classiques de Clearance Renale, *J. Physiol.* Paris, **55**:433-444, 1963.

9. MORRIS, A. M., ELWOOD, C., SIGMAN, E. M., AND CATANZARO, A.: The Renal Clearance of ^{131}I Labeled Meglumine Diatrizoate (Renografin) in Man, *J. Nucl. Med.*, **6**:183-191, March, 1965.