Measurement of the fall in the level of plasma radioactivity after intravenous administration of radiohippuran as a test of renal function

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SYNOPSIS The level of plasma radioactivity following a single intravenous injection of ^{131}I -labelled sodium orthoiodohippurate (radiohippuran) falls with time in a tri-exponential fashion. The rate of fall of plasma radioactivity after an intravenous injection of radiohippuran was measured over the period 25 to 40 minutes from the time of injection and was expressed as the half-life of radiohippuran. The results suggest that this procedure may provide a valid measure of renal function which is more sensitive than the blood urea estimation but less sensitive than the creatinine clearance.

Since the introduction of ^{131}I -labelled sodium orthoiodohippurate (radiohippuran) by Nordyke, Tubis, and Blahd (1960) there have been many reports of its value as an agent in isotope renography, particularly in the detection of unilateral renal disease (Burbank, Hunt, Tauxe, and Maher, 1963; Doig, Lawrence, Philp, Tothill, and Donald, 1963). Approximately 83% of radiohippuran is removed from the plasma in a single passage through the kidney and its clearance value can thus be used as a measure of effective renal plasma flow (Lawrence, Doig, Knight, MacLaren, and Donald, 1964), and Gott, Pritchard, Young and MacIntyre (1961) and Blaufox, Frohmuller, Campbell, Utz, Orvis, and Owen (1963) have shown that the clearance value obtained following a single intravenous injection of radiohippuran correlates well with effective renal plasma flow measured by P.A.H. clearance. Magnusson (1962), studying the biokinetics of radiohippuran in rats, showed that following a single intravenous injection the level of plasma radioactivity fell with time in a tri-exponential fashion. He postulated that the form of the curve was due to the diffusion of radiohippuran between the plasma and extracellular fluid, phase 1 representing renal excretion plus diffusion of radiohippuran from plasma into the extracellular fluid, phase 2 representing mainly renal excretion with diffusion between the plasma and extracellular fluid now in equilibrium, and phase 3 representing renal excretion plus diffusion of radiohippuran back into plasma. Yoshitoshi, Araki, Kashima, Nakano, Miyazaki, and

Mizukoshi (1963) have described a similar tri-exponential fall of plasma radioactivity in man.

The present study was undertaken to determine whether the measurement of the fall of plasma radioactivity following a single intravenous injection of radiohippuran might afford a useful index of overall renal function.

MATERIALS AND METHODS

An initial experiment was conducted, in which 25 μC of radiohippuran was administered intravenously to two normal subjects. Serial venous blood samples were collected at frequent intervals for five hours thereafter and the plasma radioactivity was measured in a low background, automatic, well scintillation counter. The fall of plasma radioactivity was plotted semilogarithmically with time and was shown to be tri-exponential by the method of Veall and Vetter (1958). It was decided to study the fall of plasma radioactivity over the period of 25 to 40 minutes following the intravenous injection of radiohippuran, as this chiefly represented phase 2 of the tri-exponential curve.

Radiohippuran, 10 μC , was given intravenously irrespective of body weight to 16 control subjects and to 57 patients with varying degrees of renal impairment. Four venous blood samples were taken through an indwelling needle into heparinized bottles, the red cells were separated, and the plasma radioactivity was measured. In most subjects, the blood samples were obtained at 25, 30, 35, and 40 minutes following the radiohippuran injection, but in patients with marked impairment of renal function blood samples were collected over a longer period of time because of the slower decline in plasma radioactivity. The values for plasma radioactivity, in counts per 100 seconds, were plotted for each subject

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against time on semi-logarithmic graph paper, and a straight line was drawn through the points. The gradient of this line was arbitrarily expressed as the biological half-life of the isotope and the results were then corrected to a standard surface area of 1.73 square metres. Table I shows representative values of the plasma radioactivity at 25, 30, 35, and 40 minutes following the intravenous injection of radiohippuran.

TABLE I

REPRESENTATIVE VALUES OF PLASMA RADIOACTIVITY FROM 25 TO 40 MIN. AFTER INTRAVENOUS INJECTION OF RADIOHIPPURAN¹

$T_{\frac{1}{2}}$	Plasma Radioactivity in Counts per 100 sec. per 5 ml. Plasma			
	25 min.	30 min.	35 min.	40 min.
22	1,200	1,020	860	740
22.5	1,280	1,030	840	780
24	1,900	1,580	1,370	1,230
30	1,880	1,700	1,500	1,400
41	1,200	1,100	1,000	960
51	2,220	2,050	1,900	1,730
96	2,700	2,590	2,450	2,330

¹ Background count is 50 counts per 100 sec.

Blood urea estimations were carried out using the Technicon AutoAnalyzer. Glomerular filtration rates were measured by means of the endogenous creatinine clearance (Hare, 1950). Renal tubular concentrating ability was assessed by measurement of the maximum specific gravity of the urine obtained during the 24 hours following the intramuscular administration of 5 units of pitressin tannate in oil, except in patients with hypertension or severe renal impairment, in whom the test was not carried out.

The radiohippuran used was supplied by the Radiochemical Centre at Amersham, Bucks., and was assessed for contamination by chromatography. In no sample did the concentration of free I^{131} exceed 3%.

The 16 control subjects studied fell into two groups according to age, 11 being in the range 21 to 28 years, and five in the range 46 to 50 years. The 57 patients with impaired renal function were suffering from a variety of renal conditions, including chronic pyelonephritis, chronic glomerulonephritis, focal glomerulonephritis, nephrotic syndrome, hypertensive nephrosclerosis, and polycystic kidneys.

RESULTS

The range of radiohippuran half-life for the 16 control subjects was 16 to 26 minutes with a mean of 20 minutes. An upper limit of normal of 25 minutes was obtained by adding two standard deviations to the mean. There was no significant difference in results when subdivided according to age, the mean value for the age range 21 to 28 years being 20 minutes and that for the age range 46 to 50 years also 20 minutes (Table II). Neither was there a significant

TABLE II

RADIOHIPPURAN HALF-LIFE VALUES IN CONTROL SUBJECTS SUBDIVIDED ACCORDING TO AGE

Age Range (Years)	No.	Mean Age	$T_{\frac{1}{2}}$ Range	Mean $T_{\frac{1}{2}}$
21-28	11	22.5	16-22	20
46-50	5	48.6	17-26	20

TABLE III

RADIOHIPPURAN HALF-LIFE VALUES IN CONTROL SUBJECTS SUBDIVIDED ACCORDING TO SEX

	No.	$T_{\frac{1}{2}}$ Range	Mean $T_{\frac{1}{2}}$
Male	9	18-26	20
Female	7	16-22	19

difference in results when subdivided according to sex (Table III).

In the 57 patients with impairment of renal function the half-life ranged from 25 to 189 minutes. Figure 1 shows the radiohippuran half-life plotted against the blood urea in all the patients studied. A good correlation was obtained, the correlation coefficient being +0.82. The radiohippuran half-life was also plotted against the logarithm of the endogenous creatinine clearance. The correlation coefficient of this was -0.78 (Fig. 2). A poor correlation was obtained on plotting the radiohippuran half-life against the maximum specific gravity of the urine following pitressin administration.

In order to test the reproducibility of the radiohippuran half-life technique, repeat studies were carried out on 11 patients on two consecutive days (Table IV). The difference between the two values ranged from 0 to 3 minutes, the mean difference being 1 minute.

FIG. 1. Radiohippuran half-life values plotted against blood urea.

FIG. 2. Radiohippuran half-life values plotted against the logarithm of the endogenous creatinine clearance.

TABLE IV

REPEAT ESTIMATIONS OF RADIOHIPPURAN HALF-LIFE IN THE SAME SUBJECTS

Subject	Diagnosis	First Reading	Second Reading
1	Cystinuria	27	25
2	Cerebrovascular accident	31	31
3	? Cholecystitis	22	21
4	Diabetes mellitus	28	29
5	Proteinuria (no cause found)	20	19
6	Healthy medical student	20	20
7	Healthy medical student	20	23
8	Focal nephritis	14	14
9	Nephrotic syndrome	19	18
10	Chronic glomerulonephritis	32	32
11	Hypertension	31	30

DISCUSSION

The above results suggest that the biological half-life of radiohippuran following a single intravenous injection may be used as a test of renal function. Half-life values of over 25 minutes appear to be indicative of renal impairment. Comparison of the radiohippuran half-life with blood urea shows that if one accepts the upper limit of normal of blood urea to be 40 mg. per 100 ml, impairment of renal function can be detected with the radiohippuran half-life technique while the blood urea is still within normal limits. There were in the present study 10 patients (14%) who had renal disease with impaired creatinine clearances but normal blood urea values. In all of these patients the radiohippuran half-life exceeded 25 minutes.

Comparison of the radiohippuran half-life, however, with creatinine clearance shows that the creatinine clearance is often less than 70 ml. per minute before the former becomes raised, indicating that the half-life technique is less sensitive than the creatinine clearance.

The poor correlation between the radiohippuran half-life and the pitressin test is probably due to two facts: firstly, the pitressin test measures only one aspect of renal function, namely, tubular function, and secondly, that the estimation of the concentrating power of the kidney by measurement of the specific gravity is a relatively inaccurate technique. The radiohippuran half-life technique involves the use of radioactivity and is of intermediate sensitivity between the blood urea estimation and the creatinine clearance. These facts would seem to preclude its use as a routine diagnostic test of renal function. It has the advantage, however, that it can be repeated at intervals of two or three hours unless renal function is seriously impaired, nor does it require timed urine collections with their known source of error. We suggest that its value may be proved to lie in measuring acute changes in overall renal function, such as may be produced by acute haemodynamic change.

The dose of radiation to which the patient is subjected during the radiohippuran half-life test is very small: in a patient with severe renal impairment in whom the biological half-life of the isotope is five hours, the amount of radiation to which the body is exposed is 0.1 m.rem.

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