Single-Dose Subcutaneous Iodine-131-Iodohippurate for Determination of Renal Plasma Flow

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Subcutaneous administration of a single dose of ^{131}I-iodohippurate was used for determination of renal plasma flow (RPF) in 20 subjects during water diuresis. Slow release of tracer (200 μCi) permitted serial clearance measurements over 5 hr that were compared to standard, constant infusion, PAH clearance (mean 379.5 ± 34.9 ml/min/1.73 m^2, range 50.9 to 696.3 ml/min/1.73 m^2). $RPF_{Isotope}$ was 424.9 ± 30.3 ml/min/1.73 m^2 (range 144.4 to 746.5 ml/min/1.73 m^2) and highly correlated with RPF_{PAH} ($r = 0.883$, $p < 0.0001$). This technique permits prolonged studies of renal plasma flow under steady-state conditions without constant infusion.

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Renal plasma flow has traditionally been measured by constant infusion and clearance of para-aminohippurate (PAH). Single-injection techniques with isotopes have also been used to measure plasma disappearance of an isotope after intravenous injection of a tracer dose (*1*). Renal function studies often require water loading to assure constant and adequate diuresis and a steady state is not achieved for several hours after the beginning of the study (*2*). Clearance techniques with constant isotope infusion have been used for prolonged studies when the utility of single intravenous injection methods is diminished due to short effective tracer half life.

This paper describes a method for determination of renal plasma flow over prolonged time periods using subcutaneous ^{131}I-iodohippurate as a tracer. Renal plasma flow determined from the clearance of the isotope was compared with simultaneous PAH clearance. Subcutaneous injection of ^{125}I-iothalamate for the determination of GFR has been shown to produce sustained plasma levels, but no such technique has been described for RPF determination (*1*).

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MATERIALS AND METHODS

Participants in this study, 5 healthy employees and 15 patients with Type I diabetes mellitus, were free of overt systemic complications of diabetes (heart disease, edema, neuropathy, blindness, amputations). Informed consent was obtained.

The study was begun after the participants had consumed a light breakfast and after the patients had taken half their customary doses of insulin. Blood glucose concentration was maintained between 120 and 240 mg/dl. Diuresis was initiated by the administration of an oral water load (1% of body weight) over 30 min followed by 150 ml of water every 30 min until the end of the study. Urine and plasma samples were obtained 60 min after initiation of the water load; the precise timing was determined by the occurrence of spontaneous diuresis (collection 0). Complete voiding was encouraged by manual pressure over the bladder.

Iodine-131-hippuran was given subcutaneously in the upper arm (200 μCi) in a volume of 0.5–1.0 ml 0.9% NaCl together with 1 ml of norepinephrine in a 1:1000 dilution. Care was taken to administer the dose with a single stick in two adjacent subcutaneous sites and massaging of the injection site was avoided. A constant infusion of PAH in a total of 250 ml of 5% Dextrose was administered simultaneously through an intravenous catheter, sufficient to achieve plasma concentrations between 0.4 and 1.5 mg/dl during steady-state. Another catheter (heparin lock) was placed in the contralateral arm for repetitive blood sampling. Urine and plasma samples were collected every 30 min for the duration of the study.

Radioactivity in plasma and urine was determined in a gamma counter, while PAH was determined by an autoanalyzer technique (Technicon). Renal plasma flow was determined from 30-min PAH clearance periods using the standard formula, $U \times V / P \times T$ and the average of clearance periods 5–9 was taken as mean plasma flow rate (RPF_{PAH}). I^{131} clearances for each 30 min interval (RPF_{Std}) was calculated similarly. The mean of adjacent plasma samples were used in these calculations. Cumulative urine isotope excretion and plasma activity was evaluated, using a linear open model of a single compartment with renal elimination only and continued absorption from the subcutaneous site. The slope of cumulative urine activity plotted against the area under the plasma curve (AUC) for ^{125}I-iodohippurate represent renal plasma flow (RPF_{AUC}). AUC was calculated by the trapezoidal rule. There was no correction by constant factor for incomplete extraction of hippurate compounds.

Comparisons between results are given as a mean ± s.e. using analysis of variance and t-test for comparisons. A p-value of <0.05 was accepted as significant.

RESULTS

The subjects in this study had a mean age of 30.5 ± 2.9 yr, weight of 78.7 ± 3.2 kg, and a body surface area of 1.98 ± 0.48 m^2. All subjects completed the study without adverse effects.

The mean clearance of PAH during collection periods 5–9 was used to obtain a steady-state estimate of renal plasma flow (3.5–5.5 hr after initiation of water loading). RPF_{PAH} ranged from 50.9 to 696.3 ml/min/1.73 m^2 with a mean of 379.5 ± 34.9 ml/min/1.73 m^2. Plasma ^{131}I concentrations varied widely between subjects, reaching a peak within 60 min after injection and declining steadily during the study (Fig. 1). Renal plasma flow determination by isotope was highly correlated with RPF_{PAH} (Fig. 2). RPF_{AUC} ranged from 144.4 to 746.5 ml/min/1.73 m^2 with a mean of 424.9 ± 30.3 ml/min/1.73 m^2. Similar results were obtained for RPF_{Std} (413.8 ± 29.9 ml/min/1.73 m^2, range 117.3 to 765.8 ml/min/1.73 m^2). The intercept of isotope on PAH clearance was at 36.4 which is similar to the difference in means.

DISCUSSION

Effective renal plasma flow has traditionally been measured with PAH clearance techniques. These methods, however, require constant infusions and analytical equipment not commonly available in the clinical laboratory. Radioisotopes, on the other hand, are readily measured. Radiolabeled iodohippurate, available for over 30 yr (*3*), is handled by the kidney in a similar fashion to PAH, and can be used clinically to estimate renal plasma flow (*1,4*).

Both ^{125}I- and ^{131}I-iodohippurate have been used to estimate renal plasma flow in human and animal models. These techniques measured isotope clearance during constant infusion (*5*), or monitored plasma disappearance of isotope after single injection (*6*). Such methods proved accurate when compared to direct measurements of renal blood flow in dogs (*7*) and in comparison to standard PAH clearance techniques in humans (*8*). Single-injection techniques were attractive because constant infusions were no longer necessary.

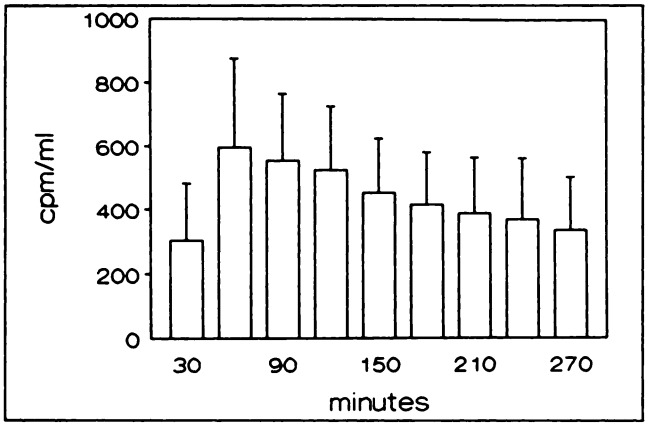

FIGURE 1. Plasma concentration of ^{131}I-iodophippurate after subcutaneous injection in 20 subjects (mean ± s.e.).

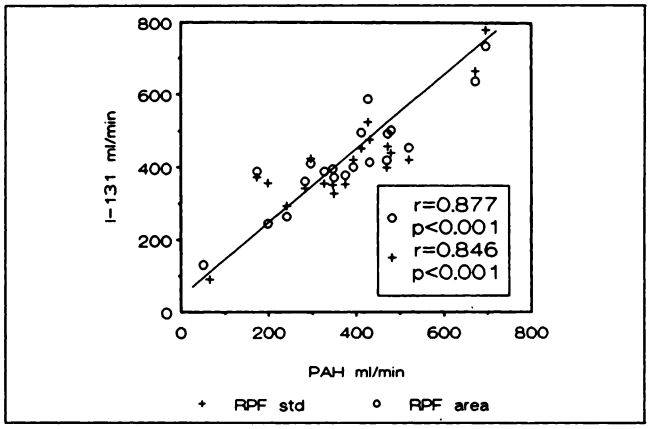

FIGURE 2. Relationship between PAH clearance (PAH) and ^{131}I-iodohippurate clearance (RPF) in 20 subjects.

Plasma disappearance of iodohippurate is dependent upon plasma flow rate; the effective half-life is short (about 20 min) under normal conditions. Timing of plasma samples is critical with single-injection studies because of the short half-life of the tracer in the circulation. Two or more samples are taken, generally within 1 hr after injection (*6*). Tauxe et al. suggested that a single plasma measurement at 44 min after injection was equally valid (*9*). Other investigators found that with renal plasma flow values <200 ml/min, accuracy of estimation was improved with more samples taken at longer intervals (*8,10*). Such sampling problems appear to be inherent in single-injection models with variable iodohippurate disappearance curves dependent upon underlying renal plasma flow.

In an effort to attain prolonged steady-state conditions and to maintain the clinical convenience of a single injection, we injected ^{131}I-iodohippurate subcutaneously. The type of injection is important. Imaging of a single 0.5-ml subcutaneous tracer sample injection showed prompt dispersal of dose into adjacent tissues and disappearance with an apparent half-time of about 35 min. Given 200 μCi in 0.5 ml presents a dose of about 67 rad at the center of the injected volume with an estimated surface radiation of 10 rad. Increasing the injection volume to 2 ml and injecting into two separate sites leads to significant (>10-fold) reduction of surface radiation as the effective diameter is more than doubled. Further reduction in surface radiation is due to the rapid dispersal of the dose into adjacent tissues. We are not aware of any short- or long-term complications resulting from the subcutaneous deposition of ^{131}I aggregates.

Other investigators have utilized subcutaneous injections of ^{125}I-iothalamate to estimate glomerular filtration rate (*11*), but the use of subcutaneous ^{131}I-iodohippurate

to estimate renal plasma flow has not been previously attempted. Because of the continuous release of ^{131}I-iodohippurate from its subcutaneous depot, we were able to make plasma measurements over more than 6 hr. The results compared favorably with those derived from simultaneous PAH clearances during steady-state. This subcutaneous injection method does not mandate varying sampling periods based upon previous knowledge of renal plasma flow. Indeed, renal plasma flow ranged from 117 ml/min to 765 ml/min in the present study. The convenience and applicability of this technique to a wide range of underlying renal function makes it an attractive alternative to other available methods of estimating renal plasma flow.

NOTE

Further reduction of radiation may be obtained with a reduced tracer dose. Since completion of this work, we have been able to reduce the dose by 50% with the use of newer counting equipment.

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