

Renal Clearance and Extraction Parameters of ortho-iodohippurate (I-123) Compared with OIH(I-131) and PAH

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***o*-[¹³¹I] iodohippurate [OIH(I-131)] has been used for many years in the estimation of effective renal plasma flow. This compound suffers from low photon yield and poor images when the quantity used is limited to stay within a reasonable radiation dose. To test the validity of substituting I-123 for I-131, a series of experiments was performed in a surgically prepared dog model. The extraction ratios and clearance values OIH(I-123) prepared from radionuclidically pure I-123 were compared with those of commercial OIH(I-131) and PAH. The extraction ratios for OIH(I-123) and OIH(I-131) were 0.65 and 0.67, representing 0.86 and 0.88 that of PAH, respectively. The clearance values (cc/min/kg) for the I-123 and I-131 compounds were almost identical ($P = 0.77$). Therefore OIH(I-123) can be used to estimate effective renal plasma flow; moreover, because of the high yield within an acceptable radiation dose range, images of good quality can be produced.**

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Iodine-123 has almost ideal radionuclidic properties for in vivo diagnostic procedures. It decays solely by electron capture with a 13.3-hr half-life, giving an 83% abundant 159-keV gamma photon, which is suitable for imaging with scintillation camera systems. When used in patients with normal renal function, *o*-[I-123] iodohippurate [OIH(I-123)] results in only one-fifth of the radiation dose delivered by OIH(I-131) (1,2). This dose reduction is particularly important in sequential studies and in tests on patients with abnormal renal function.

An important index of renal function is the effective renal plasma flow (ERPF), routinely measured by the clearance of para-aminohippurate (PAH) (3). New agents for the measurement of ERPF should compare favorably with standard values for PAH clearance and extraction ratio. OIH(I-131) can substitute for PAH, but its radiations restrict the permissible dose, and poor counting statistics result. Because of improved decay characteristics, OIH(I-123) should be better. The potential clinical usefulness of (I-123) has been described (1,2,4-9), but no data have been presented that rigorously compare this compound with (I-131) and PAH. The present paper provides such a physiologic comparison.

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MATERIALS AND METHODS

Production of I-123. Iodine-123 is prepared in the Crocker Nuclear Laboratory. At the end of bombardment, the initial contamination by I-125 is less than 0.1 %T. The concentration of the high-purity carrier-free I-123, as sodium iodide in 0.1 *N* NaOH solution, is about 300 mCi/ml (10).

The OIH(I-123) was prepared by the exchange method of Zielinski (1). The I-123 used was dissolved in 0.003 *N* sodium thiosulfate at pH 3, along with 4 μ g of iodide carrier. A total of 20-50 mCi I-123 (as iodide) in 0.9 ml was oxidized with 0.1 ml of 0.06 *N* iodate, then 0.5 ml of sodium OIH solution (300 mg/ml, pH 5.6) was added, and the mixture was flame-sealed in a glass ampoule and autoclaved at 121°C for 90 min. The product was transferred through a sterile, 0.22- μ membrane filter into a sterile, apyrogenic vial for use.

Radiochemical purity. The radiochemical purity of the final OIH(I-123) preparation was measured by ascending paper chromatography (Whatman No. 1) using *n*-butanol:glacial acetic acid:water (4:1:1 v/v) as a solvent [OIH_{Rf} = 0.9; iodide _{Rf} = 0.1]. To test stability of the OIH, solutions were stored and samples withdrawn at intervals up to 80 hr. Better than 98.2% of the activity was identified chromatographically as OIH(I-123).

Animal preparation and experimental design. In nine anesthetized, female mongrel dogs, catheters were placed in the veins of both forelegs, constantly replacing fluid loss, and for the admin-

TABLE 1.

	Hippuran(I-123) Hippuran(I-131)	Hippuran(I-123) PAH	Hippuran(I-131) PAH
Extraction ratio*	0.98 ± 0.13	0.86 ± 0.13	0.88 ± 0.07
Clearance ratios*	0.99 ± 0.05	1.09 ± 0.09	1.11 ± 0.07

* Nine animals.

istration of necessary drugs. The abdomen was surgically opened and the ovarian vein ligated. Catheters were placed in the left femoral artery, left renal vein (via the femoral vein), and both ureters. The abdomen was then closed and the dog allowed to stabilize for 30–45 min. Replacement fluids (including 10% mannitol) were infused at a rate to ensure 2 cc/min urine flow from each kidney. After this was achieved and the vital signs were stable, a priming dose was given, consisting of OIH (I-123) (8.0 μ Ci/kg), commercial OIH(I-131) (4.8 μ Ci/kg), and PAH (8 mg/kg) (11). The level of activity was chosen to provide 10,000 cpm/cc plasma at the time of assay. A sustaining infusion containing 0.18 μ Ci/kg/min of OIH(I-131), 0.3 μ Ci/kg/min of OIH(I-123), and 0.27 mg/kg/min of PAH was then begun.

Sustaining infusion concentrations were based on a mean 13.5 cc/min/kg effective renal plasma flow (12), and the priming dose was calculated assuming a distribution volume of 40% body weight for hippurate derivatives. After initiation of infusion and a 30-min period for equilibrium, three successive 20-min urine collections were obtained. Arterial and renal-vein blood samples were withdrawn at the midpoint of each collection period.

Since the blood leaving the functioning nephron has had most of the plasma hippuric acid derivatives extracted, there is a large differential between red cell and plasma levels. The rate of equilibration between these compartments is variable, and therefore at least 15 min of equilibration was allowed before cells and plasma were separated by centrifugation (13).

Samples of plasma, whole blood, and urine were obtained to determine concentrations of I-131, I-123, and PAH, and the corrected blood microhematocrit. They were counted for both I-123 and I-131 in a NaI well counter with correction for crossover after Belcher and Vetter (14). To obtain an accurate extraction ratio, the basic formula $(A-V)/A$ was modified to correct for OIH and PAH leakage out of the red cells in the venous sample. Extraction ratio (corrected for red cell loss) = $A_{\text{Plasma}} - [V_{\text{Plasma}} - (A_{\text{RBC}} - V_{\text{RBC}})]/A_{\text{Plasma}}$. This calculation assumes that none of the compounds are extracted directly from the red blood cells during their passage through the kidney, and that the arterial and venous RBC activities remained equal. This avoids overestimation of true venous plasma activity. PAH was measured in mg/ml by the autoanalyzer method of Harvey and Brothers (15). The statistical significance of differences was calculated using Student's t-test and probabilities are reported for α - error.

RESULTS

The extraction ratios for OIH(I-123) and OIH(I-131) were 0.65 and 0.67, and represented 0.86 and 0.88 of PAH, respectively (Table 1).

The clearance values for the OIH(I-123) and OIH(I-131) in cc/min/kg were almost identical ($P = 0.90$), but respectively were 9 and 11% higher than those of PAH after correction for the extraction-ratios differences. This is a true representation of the

respective renal clearances.

The arterial RBC contents of OIH(I-123), OIH(I-131), and PAH—expressed as percentages of whole-blood content—were 22.3, 21.4, and 11.8%, respectively (Table 2). The mobility between red cells and plasma appeared to be equal for the two OIH preparations. Although the PAH concentration in the red cell has occasionally been reported as negligible (16), 11.8% of the PAH was in the red cells in our study. One of the pharmacokinetic differences between ortho-iodohippurate and para-aminohippurate is the former's ability to diffuse into the red cell to a significantly greater degree.

DISCUSSION

The evaluation of renal function using OIH(I-131) has had a long and often up-and-down history (17–19). Many studies have been done to show that OIH compares favorably with the classically used compound, PAH, as a means of measuring effective renal plasma flow. Our data demonstrate that the I-123 and I-131-OIH analogs have virtually identical extraction ratios ($p = 0.58$) and clearance ratios ($p = 0.90$).

If enough I-131-labeled compound is used to yield good images with gamma camera, the radiation dose would be unacceptable; hence the conventional dose has been limited to 300 μ Ci OIH(I-131). This results in an absorbed radiation dose of 28.2 mrad to the kidneys, 11.7 mrad to the testes, 18.9 mrad to the ovaries, and 5.4 mrad to the total body (20). With 300 μ Ci, the maximum count output per kidney is about 6,000–10,000 cpm, a level that involves suboptimal images and poor counting statistics. In spite of region-of-interest computer technology and physiologic modeling, these low count rates detract from a potentially useful parameter estimator for renal function.

In contrast, a 1.5 mCi dose of OIH(I-123) administers an equivalent radiation dose in the normal patient (1,2), but because the counting efficiency is 2.4 times that obtained with I-131 (combination of crystal thickness and decay scheme), at least a

TABLE 2. RBC/WHOLE BLOOD RADIOPHARMACEUTICAL RATIO

Ortho-iodo*-hippurate		Para-amino-hippurate
I-123	I-131	
0.223	0.214	0.118
±0.081†	±0.043	±0.064

* Nine animals.

† Standard deviation.

twelfold count rate is available, or about 100,000 cpm per kidney at peak activity. Whereas in the normal patient the kidney dose from I-123 is 20% of the I-131 dose, in the obstructed patient it is 40% with no saving to the bladder.

Note that radiation dose varies with the purity of the I-123 used. Our product had less than 0.1% I-125 and no I-124 or I-126. A product containing 5% I-124 delivers 30–40% more irradiation to the kidneys (21). Since I-124 and I-126 have longer half-lives than I-123, delay in use of such a product would increase the absorbed dose per mCi of I-123 administered. Therefore, only I-123 produced via the Xe-123 intermediary should be used because it is not contaminated by I-124 (6).

In the effort to avoid the drawbacks of I-131, Tc-99m has been attached to many kidney-seeking agents. Of these, essentially only Tc-99m DTPA is well established as a monitor of renal function, but it measures glomerular filtration rate rather than ERPF. Only the hippuric acid derivatives have stood the test of time as valid tools in the estimation of ERPF. Note, also, that Tc-99m DTPA, on a per-millicurie basis, delivers twice as much radiation to the kidney as does OIH(I-123) (21).

Therefore, the data here presented not only demonstrate the identical handling of the I-123 and I-131 OIH analog but also support an adequate physiologic equivalence between them and PAH. The advantages of the increased data density and image excellence of the I-123 compound should serve to return the renogram concept to favor once more. In addition, high-quality blood-flow images to evaluate arterial patency, as well as sequential excretion images, can be obtained with a single radiopharmaceutical.

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