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Assessment of split renal function with ^{99m}Tc-aprotinin*

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Abstract. The aim of this work is to correlate the net kidney uptake of ^{99m}Tc-aprotinin (TcA) in 103 subjects with separate effective renal plasma flow (ERPF) and some blood chemistry parameters at 90, 180, and 360 min postinjection both in the normal and diseased kidney. Correlations found with separate ERPFs are highly significant at any time ($P < 0.001$). However, although the slope of the regression line is steeper at 180 min, r tends to deteriorate slightly with time postinjection and a higher intercept on the y axis; this pattern is more pronounced if diseased kidneys are considered separately. The following are probably related to the renal handling of TcA: (1) Early scans better reflect blood flow to the kidney, while later scans are more related to the metabolism/excretion tubular mechanisms; (2) correlations found with urea, creatinine, urea clearance, and creatinine clearance are highly significant at any time; (3) in 20 additional patients with diseased kidneys, renal uptake measurements done 360 min postinjection first with TcA and then with DMSA showed better correlations with ERPF employing TcA. Our results indicate that TcA is a feasible indicator of split renal function even at 90 min postinjection when a scan is easily carried out on an outpatient basis.

Key words: ^{99m}Tc-Aprotinin – ^{99m}Tc-DMSA – ERPF – Kidney scan

^{99m}Tc labeling of the polypeptide aprotinin (6500 dalton) provides a radiopharmaceutical with high affinity for renal tissue (Pedroso de Lima and Segura Moreira 1976; Janoki et al. 1978; Bianchi et al. 1981, 1982; Cox 1982). We previously reported higher fixation in the target, faster blood clearance, and lower urine excretion of ^{99m}Tc-aprotinin (TcA) in comparison with ^{99m}Tc-DMSA both in normal and diseased kidneys (Aprile et al. 1983, 1984).

In this paper we report results concerning the correlation between separate net kidney uptake and separate renal plasma flow values (ERPFs), as well as between total net kidney uptake and some blood chemistry parameters.

Materials and methods

Of the 103 patients studied (18–72 years of age), 86 had apparently normal renal function and were without electrolyte imbalance (normal kidney, NK) and 17 had chronic renal failure (CRF) and serum creatinine levels greater than 1.5 mg/dl. In addition, 20 CRF patients were also studied both with TcA and DMSA 6 h postinjection only. A commercially available single-step kit was employed (Renocis, Sorin Biomedica, I-Saluggia VC) containing 0.402 mg (3300 kalikrein inhibiting units, KIU) of aprotinin, glycine buffer, and tin (II) q.s. (final pH 10.1–10.5). ^{99m}Tc labelling was performed according to the manufacturer's instructions. The DMSA kit used for comparison was supplied by CIS. After IV injection of 110–185 MBq (3–5 mCi), measured in a dose calibrator, serial scans were taken in the posterior view with the patient in a prone position at 90, 180, and 360 min by means of a large field of view camera linked to a data processor ($128 \times 128 \times 16$ acquisition matrix). Patients were also imaged the right and left lateral views with a radioactive marker placed on the skin of their backs to evaluate kidney depth.

After data collection, calculation of the net kidney uptake was performed according to the method of Massin (1979) as previously described (Aprile et al. 1984). Briefly, net counts in the kidney region of interest (ROI) (outlined on a 50% background cutoff image) were obtained after subtraction of the counts recorded in a perirenal ROI (about 6 pixels width) and with reference to the net counts recorded in a 250 ml plastic flask containing a known amount of the injected dose, after correction for the organ depth and radioactive decay.

Separate ERPFs (Hippuran Clearance Rates) were calculated after injection of 1.2 MBq (30 μCi) of 131I-OIH (Hippuran) employing a three-probe device linked to a minicomputer according to the method of Meldolesi (1973, 1977). Results were expressed as percent injected dose (i.d.) and ml/min, respectively: all data were normalized to 1.73 m^2 body surface area (BSA).

An interval of 24–48 h was allowed between studies. Urea and creatinine clearance values were assayed on a 24-h urine specimen. ERPF determination and TcA uptake was repeated in five and six patients, respectively, within 10 days to assess test reproducibility.

Results

Figure 1 shows the correlation between separate percent net kidney uptakes and separate ERPFs 180 min postinjection, and Table 1 shows the regression lines and significances at various times postinjection. The correlations found are highly significant at any time ($P < 0.001$), though the regression coefficient tends to deteriorate slightly from

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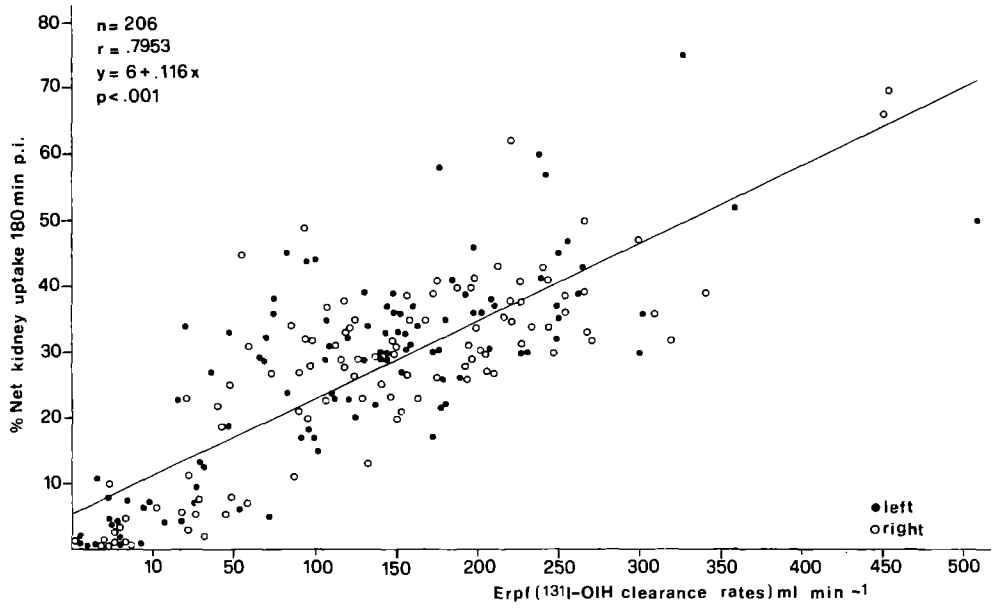

Fig. 1. Correlation between ^{99m}Tc-aprotinin percent net kidney uptake (y) and separate ERPFs (x) in 206 normal renal units studied 180 min postinjection (p.i.)

Table 1. Regression line and significances of the correlation between separate ERPFs (X) and percent net kidney uptake (Y) at various times postinjection in the normal kidney (NK) group

Time post-injection (min)	Renal units	X	Y	$a+bx$	r	$P<$
90	202	TcA	ERPF	$4.04+0.097x$	0.8145	0.001
180	206	TcA	ERPF	$6.01+0.116x$	0.7953	0.001
360	206	TcA	ERPF	$8.47+0.12x$	0.7797	0.001

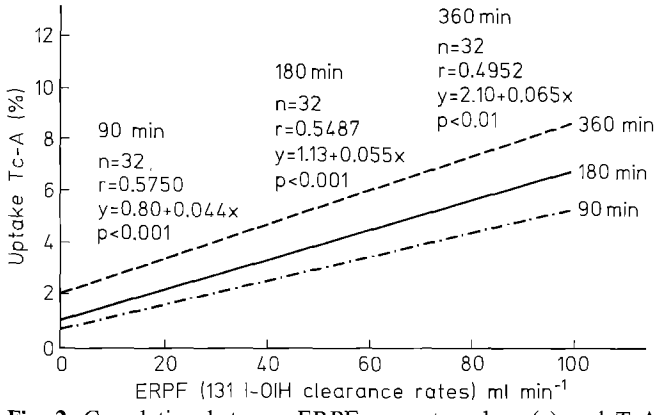

Fig. 2. Correlation between ERPF separate values (x) and TcA net kidney uptake in 16 CRF patients (32 renal units) at various times postinjection

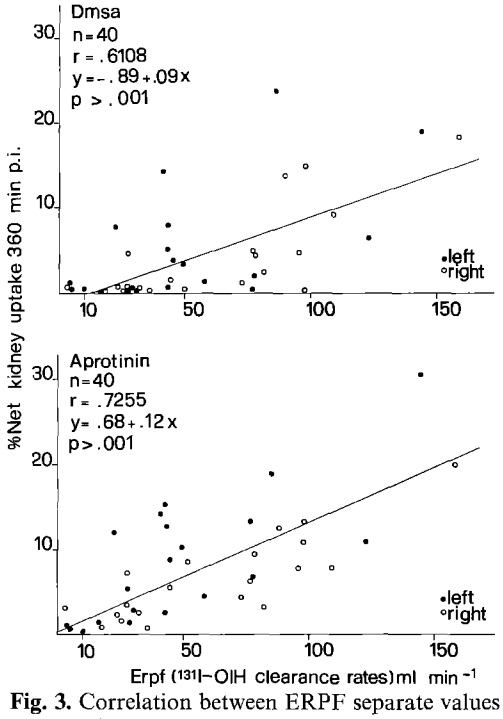

Fig. 3. Correlation between ERPF separate values (x) and net kidney uptake in 20 CRF patients (40 renal units) studied both with DMSA and aprotinin 6 h postinjection (p.i.)

90 to 360 min and the intercept on the y axis is higher. This pattern is more pronounced if we consider separately the CRF patients (Fig. 2), where the r value falls from 0.57 at 90 min to 0.49 at 360 min.

In Fig. 3 the comparison between DMSA and TcA in the 20 additional CRF patients is reported. Although the correlation is significant at the same level ($P<0.001$), the TcA intercept approximates better to the zero value and the slope of the regression line is higher. In addition, if patients with advanced renal failure (i.e., single kidney ERPF of less than 50 ml/min) are considered separately, TcA values correlate at the same level of significance while the DMSA correlation is no longer significant.

In Table 2, correlations between net kidney uptake (right plus left) and urea, creatinine, urea clearance, and creatinine clearance are reported. Correlations found are highly significant at any time considered.

Repetition of TcA tests and ERPF determination gave a correlation coefficient of 0.95 and 0.93, respectively, and Student's t-test for paired data showed no significant differences.

Table 2. Correlation between urea, urea clearance, creatinine, creatinine clearance, and ^{99m}Tc-aprotinin uptake (Y) at various time postinjection. In all cases $P<0.001$

Patients	Time postinjection (min)	r	$a+bx$
Urea (gll)			
100	90	−0.726	$60-32.6x$
102	180	−0.7601	$75-41.3x$
102	360	−0.7800	$87-46.5x$
Urea clearance (ml/min)			
89	90	0.5532	$21+0.54x$
91	180	0.5627	$28+0.66x$
91	360	0.5679	$35+0.72x$
Creatinine (mg/dl)			
101	90	−0.6620	$52-6.31x$
103	180	−0.6846	$66-7.9x$
103	360	−0.7037	$76-8.9x$
Creatinine clearance (ml/min)			
89	90	0.6560	$16+0.28x$
91	180	0.6900	$20+0.37x$
91	360	0.6692	$28+0.38x$

We did not observe adverse reactions in any subject despite a potential for allergic reactions after therapeutic administration of aprotinin (La Ferla and Murray 1984).

Discussion

Rather than being a true percent uptake, the value we employed is more accurately an index of uptake because of the objective difficulties with the correct measurement of radioactive content in a deep organ. However, the values found (68%) are not very different from those found by one of us (Lunghi, unpublished data) for the rat kidney (60%) at 3 h postinjection. The separate TcA net kidney uptake values we estimated show a very good correlation with the separate ERPFs, even when we consider separately the patients with renal failure: in these patients, TcA seems to have some advantages in comparison with DMSA, not only from the point of view of split renal function, but also from the morphological point of view, as previously reported (Aprile et al. 1984).

In the accurate measurement of renal uptake, statistics play an important role especially in CRF patients. In fact, in this study, the mean TcA:DMSA ratio, at 6 h postinjection is 2.3, even if lower than that previously reported employing a DMSA kit from a different commercial source (Aprile et al. 1983). The large scatter around the regression line (TcA vs. ERPFs) is not immediately explainable, but is probably at least in part, due to lower test accuracy of, instead of a camera, a probe device which does not allow perfect organ localization, background, and depth correction. In addition, the urine collection required for ERPF calculation introduces a further potential source of error. The slight deterioration of the r value from 90 to 360 min postinjection, even if the slope of the regression line is steeper at 180 min, is quite surprising because one would expect better results when blood background is lower and

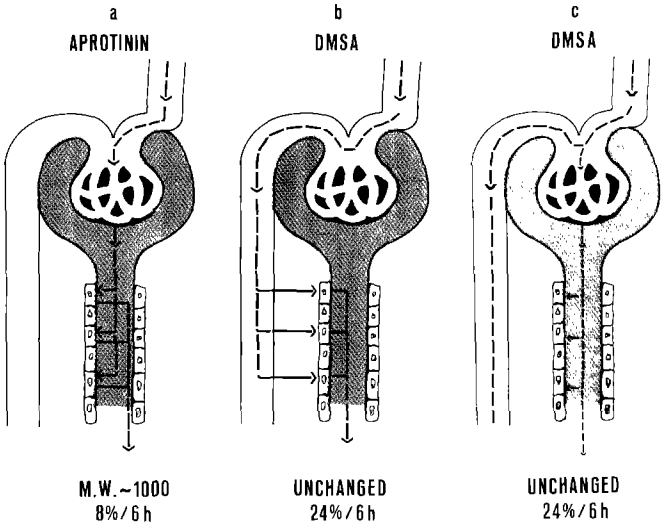

Fig. 4. Renal handling of aprotinin **a** and DMSA according to Chervu and Blaufox (1982) **b** and Piers (1984) **c** respectively

target uptake has reached its maximum. The explanation of this apparently unusual behaviour is probably related to the renal handling of TcA, which is quite different from that postulated for DMSA.

Like other light-chain proteins, TcA is probably filtered through the glomerulus and taken up by the tubular cells (Mogielnicki et al. 1971; Cox 1984), metabolized, and in part excreted as degradation products with molecular weight of approximately 1,000 (Bellitto et al. 1983) (Fig. 4a). On the other hand, DMSA, largely protein-bound, cannot be filtered but is reabsorbed from the peritubular blood and excreted unchanged into the urine (Chervu and Blaufox 1982). More recently, other authors (Piers et al. 1984), have suggested that only the free fraction, approximately 10%, is filtered and reabsorbed like aprotinin (Fig. 4b, c).

In any event, independent of the exact mechanism, DMSA uptake is slower if compared with TcA in the same patients and is still increasing at 24 h postinjection (Aprile et al. 1984). In fact, it is possible to recognize a three-phase pattern in the kidney time activity course after TcA administration: Maximum activity is reached much earlier (at 6 h); between 6 and 9–12 h a plateau is reached; and finally, at 24 h the release of the radiopharmaceutical is observed (Aprile et al. 1984).

Therefore it is possible to postulate that early net kidney measurements better reflect the blood flow, while later measurements reflect not only this parameter, but also the tubular handling of the radiopharmaceutical. This behavior leads us to conclude the following: (1) Taking radioactive decay into account, later scans do not offer real advantages in terms of kidney uptake, at least in the normal subject, even though lower blood background, better counting statistics, faster blood clearance, and reduced urine excretion are observed at any time in comparison with DMSA, as previously reported (Aprile et al. 1984); (2) scans at 6 h, when uptake has reached its maximum, or even at 24 h postinjection, when uptake is decreasing, are less correlated with the tracer transport to the kidney and better reflect the tubular mechanism and excretion, and may be suitable for the study of proximal tubular dysfunction and tubular metabolism of light-chain proteins (Bianchi et al. 1984b).

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