^{99m}TPAC, A NEW RENAL SCANNING AGENT. II. EVALUATION IN HUMANS

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We have recently reported our experience on ^{99m}Tc-penicillamine acetazolamide complex (TPAC) (*1*) as a potential kidney scanning agent and found it to show promise in this regard. This paper is an evaluation of TPAC in man.

MATERIALS AND METHODS

^{99m}TPAC was made for intravenous injection by the method previously described by the authors (*1*). To confirm our observation in animals that TPAC is excreted only slightly in the urine, simultaneous clearances of creatinine and TPAC were performed in 15 patients using a single injection technique. The subjects were first administered an oral load of 500–1,000 cc of water to insure a good urine flow. The patients were taken 45 min later to the isotope laboratory, and an intravenous infusion of normal saline was started. An indwelling needle with an attached three-way stopcock was placed in a large vein in the opposite arm and flushed with saline after a baseline blood sample was obtained. The patient was then seated in a cloth-back chair and stationed in such a manner that the face of the collimator of the scintillation camera was opposite the patient's back. Three to 15 mCi of TPAC was then administered by a bolus technique into the arm opposite the indwelling needle, and images were made at 5, 15, 25, 45, 60, and 90 min postinjection. Heparinized blood was drawn at 10, 40, 60, and 180 min postinjection. The patients emptied their bladders 30 min postinjection, and the urine was collected at as close to 50 and 70 min postinjection as possible. Variation in this was never more than 1 min. The urine and plasma counting rates were used to compute the TPAC clearance by the standard UV/P formula. Just before or just after the TPAC clearances, 24-hr creatinine clearances were performed by the Jaffe chromagen method.

The plasma proteins in 1 ml of blood were precipitated with 1 ml of 10% $ZN(OH)_2$ and the precipitate washed with zinc hydroxide. The precipitate and supernatant were counted in a well counter. The percent plasma protein binding was computed from these data. Some of the plasma samples were dialyzed against normal saline for 24 hr to confirm the findings of the zinc hydroxide method.

Plasma TPAC half-times were determined by plotting the plasma counts against the time that the sample was obtained. The clearance of free TPAC was computed by data derived from nonprotein bound plasma counts.

All DTPA compounds used were those made from a Squibb Renotec kit. While it is well known that a major component of this preparation is ^{99m}Tc-Fe-ascorbic acid complex, it was chosen over the ^{99m}Tc-DTPA preparation as described by Atkins, et al (*2*) because of its commercial availability. The ^{99m}Tc-DTPA data hereafter presented should not be construed as a comparison with "true" ^{99m}Tc-DTPA. When comparisons of scintiphotos were made, all camera settings remained the same for all technetium-labeled agents. This, of course, was impossible for the iodine- and mercury-labeled agents. All patients in whom clearance data are available have either normal renal function or bilateral renal disease. Tissue diagnosis was not known for all of those studied.

RESULTS

Table 1 shows the data on the 15 patients in whom renal clearances were performed. Five patients had normal renal function, four had diminished renal function, and six had markedly reduced renal function. As can be seen, very little TPAC is cleared from the plasma by the kidney from any of these

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TABLE 1. CLEARANCE OF TPAC AND FREE TPAC (CfTPAC) COMPARED WITH CLEARANCE OF CREATININE

Patient	Ccr (cc/min)	CTPAC (cc/min)	CfTPAC (cc/min)	CTPAC/ Ccr × 100	CfTPAC/ Ccr × 100	Plasma $T_{1/2}$ TPAC	Diagnosis
1	154	0.81	14.0	0.53	9.1	64	Normal
2	125	0.66	3.47	0.53	2.77	113	Normal
3	104	1.98	29.0	1.90	27.9	60	Normal
4	100	1.26	14.1	2.88	14.1	44	Normal
5	95	0.94	17.9	0.99	18.9	58	Normal
6	68	0.83	15.5	1.22	22.8	85	Bilateral renal disease, etiology unknown
7	66	0.29	4.08	0.42	6.2	46	Diabetes, presumed Kimmelstiel Wilson disease
8	55	2.38	44.0	0.43	80.0	76	Bilateral renal disease
9	24	0.02	0.94	0.21	3.9	111	"End-stage" kidney disease, bilateral (Bx obtained)
10	14.6	0.245	4.34	0.168	29.8	93	Chronic glomerulonephritis (Bx obtained)
11	11.6	0.36	4.96	3.0	42.8	145	Atherosclerosis
12	5.7	0.109	3.44	0.21	60.4	123	Phenacetin nephritis (Bx obtained)
13	4.4	0.535	11.0	1.2	250.0	110	Phenacetin nephritis (Bx obtained)
14	3.7	0.52	6.83	14.0	185.0	92	Chronic glomerulonephritis (Bx obtained)
15	3.0	0.33		11.0		76	"End-stage" renal disease

As glomerular filtration rate decreases, TPAC/Ccr and CfTPAC/Ccr ratios increase. Plasma TPAC half-times increase only slowly with diminishing renal function.

patients, regardless of their renal function. As renal function diminished, the clearances of TPAC did not drop to the same extent. Thus the TPAC-to-creatinine ratio tended to rise significantly in those patients who were nearly anephric. The "free" TPAC clearances [(CfTPAC/Ccr) × 100], which are much lower than creatinine clearances in those patients with normal renal function, approach and even exceed in some cases the clearances of creatinine, as the glomerular filtration rate decreases. Plasma protein binding in all cases remains between 95 and 98%, averaging approximately 97%. The constancy of this latter figure was remarkable. Patients with normal renal function had plasma half-times varying from 44 to 115 min with a median of 60 min. As renal clearance diminished, there was an increase in plasma half-time.

Figure 1 shows a study in a patient with normal renal function. The first study was performed with

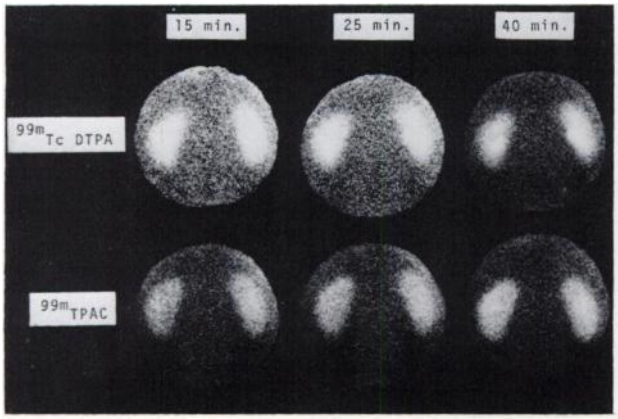

FIG. 1. Normal kidneys scanned with ^{99m}Tc-DTPA and ^{99m}TPAC.

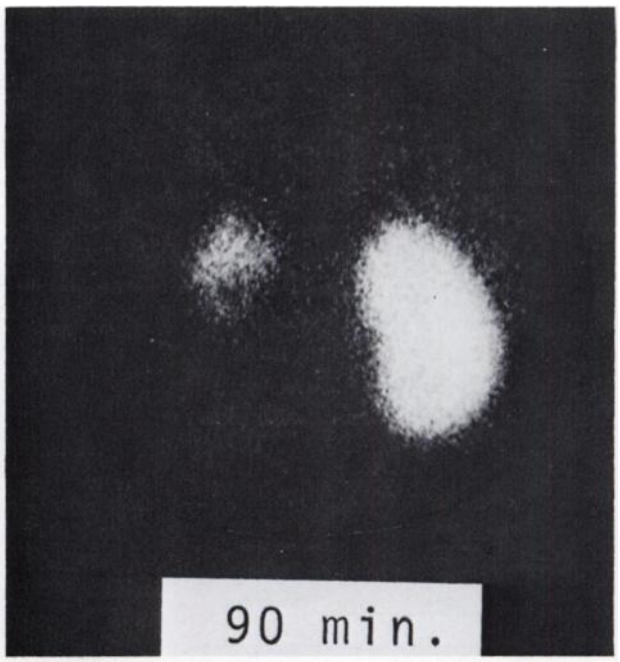

FIG. 2. TPAC. Left hydronephrosis.

FIG. 3. TPAC. Hypoplastic right kidney.

Renotec. The study was repeated 2 days later using TPAC (lower three scintiphotos). Identical camera settings were used in both. Exposure times were the same in both. Both studies showed excellent renal morphology. It is the opinion of the authors that the scan performed with the TPAC is slightly better than that with the ^{99m}Tc-DTPA because the renal pelvic radioactivity tended to degrade the image of the latter.

Figure 2 is a TPAC scintiphoto performed in a 10-year-old white male who had suffered recurrent urinary tract infections since the age of 7. Despite continuous antibiotic coverage, frequent hospitalizations had become necessary for treatment of his condition. Cystoscopy revealed a dilated bladder with postvoiding residual urine and Grade III left ureteral reflux. An intravenous pyelogram (IVP) showed prompt excretion of the contrast media by the right kidney and a nonfunctioning left kidney. Laboratory values showed a hemoglobin of 12.4 gm% and serum creatinine of 0.7 mg%. The TPAC scintiphotos show a normal right kidney and a small but functioning remnant of the left kidney.

Figure 3 shows a TPAC study in a 15-year-old white female with a history of recurrent urinary tract infections for approximately 2 years. An IVP revealed a barely visible right kidney with normal function of the left kidney. It was difficult to ascertain the exact size of the right kidney by this method. A retrograde pyelogram revealed a shrunken atrophic right kidney that accounted for only 1% of the total urinary excretion of PSP. A right nephrectomy was performed. Gross findings revealed a small yet well developed kidney from which the capsule was easily stripped. The cortex of the kidney, although very thin, was for the most part normal, and the final pathological diagnosis was hypoplastic kidney. The scan shows a normal-to-slightly enlarged left kidney and a very small right kidney. The anatomical detail of this shrunken right kidney is quite good in view of the clinical and laboratory impression that it contributed only 1% to the total renal PSP excretion.

Figure 4 shows a TPAC and ^{131}I-Hippuran study in a 50-year-old white male who first presented to the hospital in pulmonary edema, and was found to be markedly hypertensive with a blood pressure of 210/120 mm Hg. The hypertension was thought by the patient to have begun within the last 2 years since he had been seen by a physician just prior to that time. An IVP revealed the left kidney to be smaller than the right by approx 2 cm. A Stamey-Howard test showed a decreased urine volume and sodium concentration and an increased creatinine concentration. The specific gravity of the urine from the left kidney was increased. A translumbar aortagram showed a high degree of stenosis of the left main renal artery at its origin from the aorta. The urinary creatinine clearance was normal. Bilateral renal vein catheterization revealed a left renal vein renin of 500 μg% which rose to 1,666 μg% following the injection of 20 mg apresoline. The right renal vein renin was 628 μg% with a rise to 684 μg% following the apresoline. Following surgical anastomosis of

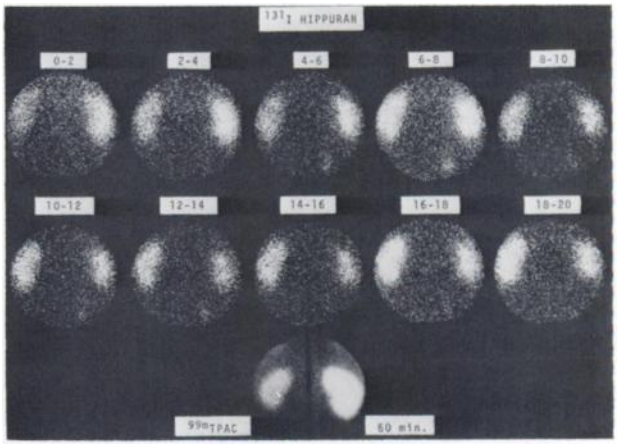

FIG. 4. TPAC and ^{131}I-Hippuran study of patient with renal artery stenosis. Note typical excretion pattern of vascular stenosis in left kidney on Hippuran study, and difference in size and counting rate of two kidneys on TPAC study.

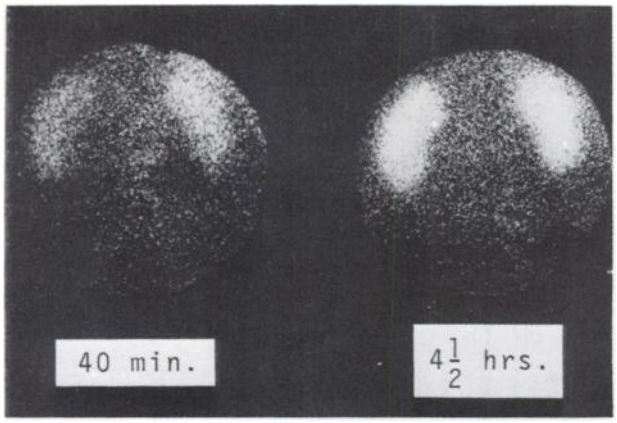

FIG. 5. TPAC effect of delayed scanning in patient with bilateral renal disease and azotemia.

the left splenic artery to the left renal artery, the blood pressure decreased to 130/80 and has remained at this level for over 1 year.

Figure 4 shows a Hippuran excretion pattern which is often seen in patients with renal artery stenosis. There is a prolonged time to peak height of the radioactivity on the left and slow drainage following the peak height. The TPAC scintiphotos performed 60 min after injection revealed marked accumulation of radioactivity on the right compared with the left. There also appears to be some difference in renal size on this study.

Figure 5 shows the effect of delayed scanning in a patient with markedly diminished renal function. The patient is a 41-year-old white male with a clinical history of chronic glomerulonephritis and clinical renal failure with a serum creatinine of 8 mg%. The kidneys were seen on an IVP, but the nephrogram effect was poor.

Scans were performed 40 min and 4½ hr postinjection of TPAC. The image performed at 40 min, while showing bilateral renal tissue, does not show outstanding anatomical detail. When the scan was performed at 4½ hr postinjection, excellent detail could be obtained.

The studies in Fig. 6 were performed on a 63-year-old Guammanian male, who had been a known diabetic since 1959, and was controlled on 40 U of NPH insulin daily. In 1968, he developed swelling of his feet and 3+ proteinuria and in 1970 developed severe lower extremity edema and ascites. Efforts at diuresis failed to alter the situation significantly. At the time of admission, the patient had clinical uremia with nausea and vomiting, loss of appetite, severe ascites, and generalized edema. At the time the renal scans were performed, the patient's serum creatinine was 12 mg% and creatinine clearance 2.26 cc/min. The final clinical diagnosis was Kimmelstiel-Wilson's disease with clinical renal failure.

In the figures shown, one fails to see visualization of the kidneys using the Renotec while these organs are easily discernible at 60 min postinjection on the TPAC study.

A similar study was performed using three radiopharmaceuticals in a patient with a bilateral renal disease. The results of this are shown in Fig. 7. The patient is a 57-year-old white female diabetic who entered the hospital complaining of increasing fatigue and vomiting over a period of 1 month. She had been diabetic for 20 years and controlled on oral hypoglycemics. On physical exam no pertinent abnormalities were noted with the exception of the fact that the patient was pale. Laboratory data showed the patient to have a hemoglobin of 8.5 gm%, glucose of 171 mg%, a BUN of 102 mg%, and a creatinine clearance of 4.6 cc/min. An IVP revealed small kidneys bilaterally, and renal biopsy showed inflammation with periglomerular fibrosis. There was loss of tubules and hyaline casts within tubules. The pathologists favored the diagnosis of chronic pyelonephritis; however, the disease was so far advanced that a definitive diagnosis could not be made with

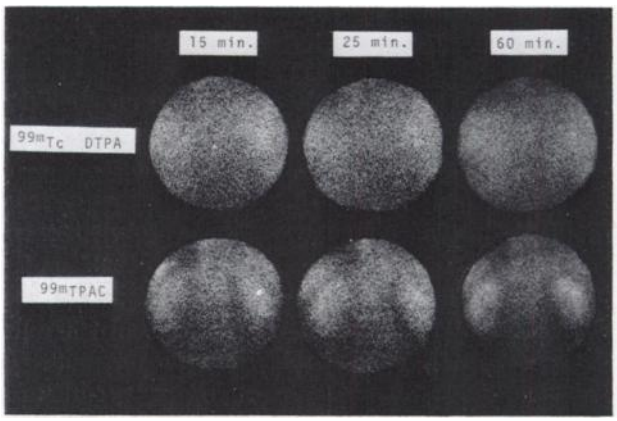

FIG. 6. Comparison of commercial preparation of ^{99m}Tc-DTPA and TPAC in patient with serum creatinine of 12.

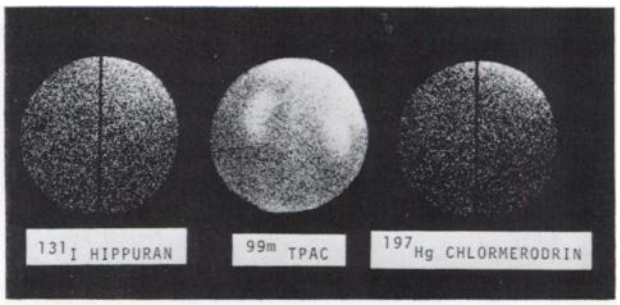

FIG. 7. Comparison of ^{131}I-Hippuran, TPAC, and ^{197}Hg-chloromerodrin as scanning agents in patient with bilateral renal disease and azotemia.

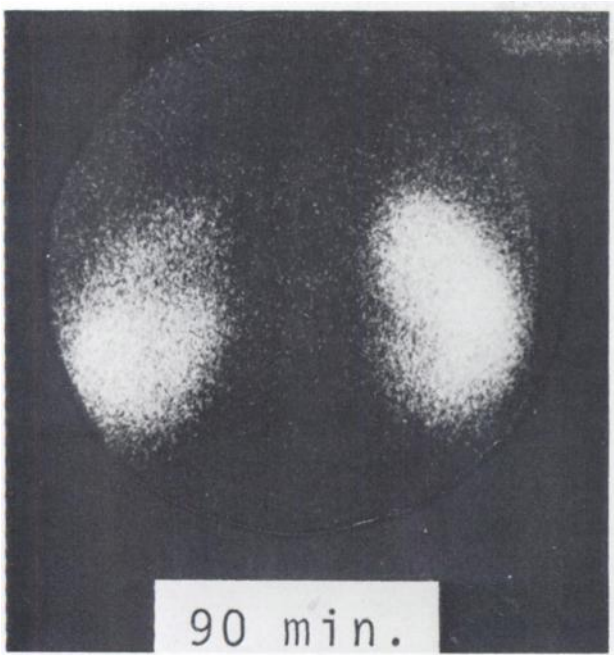

FIG. 8. TPAC study in patient with left upper pole renal cell carcinoma.

certainty. Several of the larger arteries were noted to be quite sclerotic. The scans with the ^{197}Hg-chloromedrin and ^{131}I-Hippuran failed to show a kidney image, but the kidneys were discernible with the TPAC.

Figure 8 shows a TPAC renal study in a 49-year-old white male who had a past history of a renal stone with a right pyelolithotomy. A renal infection also occurred at that time which responded to therapy. The patient developed gross hematuria 1 month before his admission in December, 1970, and an IVP showed an abnormal area in the lower pole of the right kidney and evidence for a left renal mass. The mass was compatible with a hypernephroma at arteriography. The pathology of the right kidney could not be completely delineated. The serum creatinine was 0.7 mg% and all other laboratory tests were within normal limits. On December 15, 1970, surgical exploration of both kidneys was performed. A biopsy revealed chronic pyelonephritis of the right kidney. An adenocarcinoma was found involving the upper pole of the left kidney.

The scintiphoto shows an area of diminished uptake in the lower pole of the right kidney and the upper half of the left kidney. Of interest is the fact that some functional tissue remains in the left upper pole. The gross pathology showed the entire upper half of the left kidney to be involved with a yellowish mass; however, light microscopy revealed an area of tissue within the tumor that continued to have near normal architecture.

DISCUSSION

TPAC, from these studies, would appear to be an outstanding renal scanning agent. In people with normal renal function, high-quality scans are obtained by 25 min postinjection or earlier with very little interference from artifacts due to radioactivity in the renal pelvis such as occurs with ^{131}I-Hippuran and Renotec. It shares this property with ^{99m}Tc-Fe ascorbic acid and ^{197}Hg-chloromedrin. Physical properties of the ^{99m}Tc make it possible to do vascular perfusion studies of the kidney with TPAC in the same manner that these can be done with ^{99m}Tc-Fe ascorbic acid and Renotec. Unlike ^{99m}Tc-Fe ascorbic acid complex, the compound does not become degraded upon standing nor does one get the variable results sometimes seen with Renotec (*3*). Furthermore, when the serum creatinine rises above 3 mg%, ^{99m}Tc-Fe ascorbic acid complex scans show an inordinately high liver background and scanning becomes nearly impossible (*4*). Similar problems occur with Renotec.

TPAC appears to be excreted very slowly from the kidneys. The rising CfTPAC/Ccr ratios in the presence of diminishing renal function suggests that it might be a better renal scanning agent than a substance cleared only by GFR, once the renal clearances are severely diminished. The advantages of the TPAC over ^{197}Hg-chloromedrin are obvious in that the latter compound cannot be used for perfusion studies, suffers from poor physical characteristics, and delivers a higher body radiation dose per millicurie than does TPAC. TPAC would also appear to be a better renal scanning agent than ^{131}I-Hippuran for imaging kidneys with markedly diminished renal function unless one chose to perform a constant intravenous infusion of this radiopharmaceutical. As was shown in the patient with reno-vascular hypertension, TPAC data are complementary to the ^{131}I-Hippuran studies. TPAC cannot give data concerning excretion of radiopharmaceutical from the kidneys or evidence of ureteral obstruction while Hippuran is useful in this regard. It would appear, however, from Fig. 4 that hypoperfusion of one kidney will result in a markedly diminished extraction of the TPAC by that kidney and thereby a lower counting rate on that side. Thus some TPAC data may be useful in the workup of patients with suspected renal artery stenosis. It appears from our studies that delayed scanning would improve the image of the TPAC scintiphotos. From previous work in dogs, we have shown that TPAC extraction is greatest within the first 70 min postinjection and decreases markedly after this. We have also shown that even in the anephric animal, this radiopharmaceutical is removed from the plasma at a rate only

twice that of an animal with normal kidneys. This suggests that the complex moves into other pools in the body or is excreted by organs other than the kidneys. One would expect therefore that the reason for the improvement of the scintiphotos is not necessarily the continued uptake of radiopharmaceutical, although this probably does occur to some extent, but by diminution of the vascular background by movement of the radiopharmaceutical into other compartments or excretion by other organs. Recently, continued research has shown that simple ^{99m}Tc-penicillamine can be made and used as an excellent renal scanning agent without the addition of acetazolamide. Chromatographically, the ^{99m}Tc-penicillamine and TPAC appear markedly different. However, the quality of their images are virtually identical. Technetium-99m-penicillamine will be the subject of a separate report.

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