

QUALITY CONTROL OF ^{99m}Tc -DTPA BY DOUBLE-TRACER CLEARANCE TECHNIQUE

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Sn-DTPA kits were evaluated by the biological behavior of ^{99m}Tc -DTPA preparations as an index of the quality of the radiopharmaceutical. Plasma clearance and urinary excretion were determined in dogs along with a second tracer such as ^{113m}In -DTPA. Glomerular filtration rates were compared for the two tracers. The results could be divided into two categories corresponding to good and deteriorated ^{99m}Tc -DTPA preparations. A good product behaved kinetically in a manner almost identical to that of the second tracer. Deteriorated products showed (A) reduced urinary excretion, (B) higher plasma activity after 2 hr, (C) appearance of a third component in the plasma clearance curves, and (D) decrease in the calculated values of glomerular filtration rate.

A kit for ^{99m}Tc -DTPA could be assured of sterility, apyrogenicity, and nontoxicity but there remains an uncertainty with respect to radiochemical purity of the product due to analytical pitfalls (1). Sometimes minor differences in the preparation affect a biomedical study significantly even though the preparation is based on the best available method such as that of Eckelman and Richards (2). Indeed, publication of an interesting artifact in radionuclide imaging of kidney (3) reflects the poverty in the quality control both with respect to the use of available methods and the availability of a good method.

MATERIALS AND METHODS

Theoretical consideration. Radioactive indium and ytterbium chelates behave in a manner similar to inulin with respect to their distribution in the extracellular fluid (4) and excretion by the glomerular filtration (5). Renal clearance of ^{51}Cr -EDTA is also similar to inulin (6). Technetium- ^{99m}Tc -DTPA has also been observed to be suitable for measuring glo-

merular filtration rate (7). Therefore, kinetic behavior of all these radiochelates would be the same in an in vivo system. The quality of a ^{99m}Tc -DTPA preparation could be evaluated by monitoring plasma clearance and urinary excretion of a simultaneous tracer dose along with a second radiochelate.

Preparation of the agent. All ^{99m}Tc -DTPA preparations were made with Sn-DTPA kits as proposed by Eckelman and Richards (2). Sterility and pyrogen tests were carried out for each batch of the kits. Earlier, kits were received from Brookhaven National Laboratory. Later, kits were prepared at the Johns Hopkins Laboratory using the basic ingredients. Subsequently, kits were obtained from a commercial source (Diagnostic Isotopes, Upper Saddle River, N.J.). These kits were used in clinical studies primarily in serial imaging of kidneys (8).

Choice of a second tracer. Indium- ^{113m}In -DTPA was chosen as the second tracer which was prepared by simply adding ^{113m}In eluate into half of the material of the Sn-DTPA kit and the pH was adjusted to about 5; the other half was used for the preparation of ^{99m}Tc -DTPA. Preliminary studies (tissue distribution in mice and clearance in dogs) showed the behavior of this type of preparation of ^{113m}In -DTPA (even with a deteriorated Sn-DTPA kit) to be the same as previously reported preparations of ^{113m}In -DTPA (9,10).

Experimental procedure. Studies were carried out in female dogs (anesthetized with sodium pentobarbital) for 4–5 hr. An intravenous infusion of isotonic saline was maintained (about 100 ml/hr) and a catheter was inserted for the collection of urine. A tracer dose (0.3–0.5 mCi of ^{99m}Tc -DTPA plus 2–3 mCi of ^{113m}In -DTPA) was injected intravenously

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and a reference standard was also prepared. Blood samples were collected frequently during the first hour and later at hourly intervals, and plasma was separated for counting. Each urinary collection of hourly interval was diluted to 250 ml in water and a sample was taken for counting. Necessary corrections were made to the radioactive counts including decay corrections for ^{113m}In counts; the cross counts of ^{113m}In in ^{99m}Tc channel was less than 8% and that of ^{99m}Tc in ^{113m}In channel was practically 0%.

Plasma clearance (assuming blood volume to be 65 ml/kg and knowing hematocrit) and cumulative urinary excretion curves were drawn for the two agents. Glomerular filtration rates were calculated considering the approximate single exponential clearance of plasma between 1 and 4 hr essentially based on the simplified single injection method (5,6) which is suitable for comparing two agents although it may not provide an absolute value of GFR.

Studies in human subjects (patients with normal and abnormal renal conditions) were carried out to obtain only the comparative GFR values using three plasma samples between 2 and 6 hr following the administration of the double tracer dose (approximately twice the amount used in dogs).

RESULTS

Within a few days of the preparation, most of the kits correlated very well with the second tracer. Plasma clearance, urinary excretion, and the GFR values for the two tracers were almost identical. The ratio of the two tracers in plasma and urine at different times was practically the same as that in the initial tracer dose. Plasma clearance curves showed approximately two components.

Kits deteriorated with storage and showed variable results with a significant divergence from the second tracer. Urinary excretion of ^{99m}Tc was reduced, plasma activity after 2 hr remained elevated, a third component in the plasma clearance curve became evident, and the calculated value of GFR was considerably reduced.

The kits used in the present study showed usually less than 5% of free pertechnetate by paper chromatography with butanol-ethanol-water (2:2:1). However, some old kits which showed over 10% of free pertechnetate were regarded as unacceptable and they showed greatly reduced GFR values (less than half of those obtained with ^{113m}In -DTPA), and such data has not been included in determining the correlation coefficient.

Figure 1 illustrates two typical studies in dogs as examples. The ^{99m}Tc -DTPA prepared with a fresh kit (A) behaved similarly to ^{113m}In -DTPA showing approximately two components in the plasma clear-

ance curve and the same urinary excretion; such kits were classified as good. A 10-day-old kit (B) of the same batch (stored at room temperature) showed considerable divergence from ^{113m}In -DTPA; such kits showing variable amounts of divergence were classified as deteriorated. With ^{113m}In -DTPA, the plasma clearance half-time of the slow component

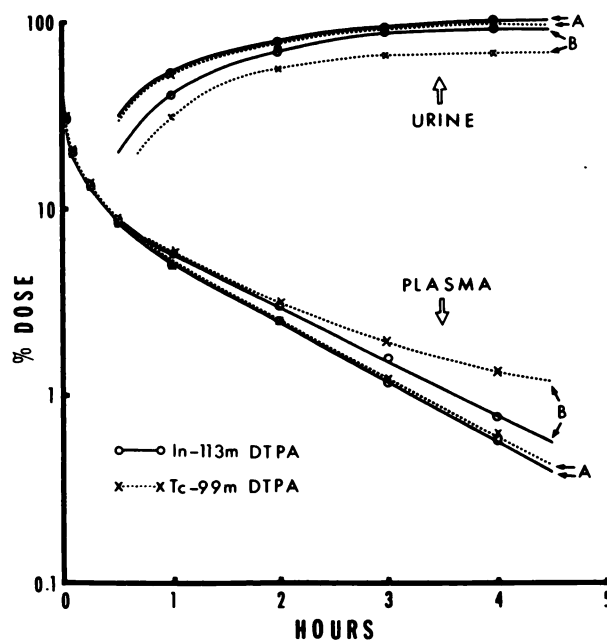


FIG. 1. Illustration of comparative clearances in dogs of good and deteriorated ^{99m}Tc -DTPA preparations against ^{113m}In -DTPA: (A) fresh Sn-DTPA kit, (B) 10-day-old kit (stored at room temperature).

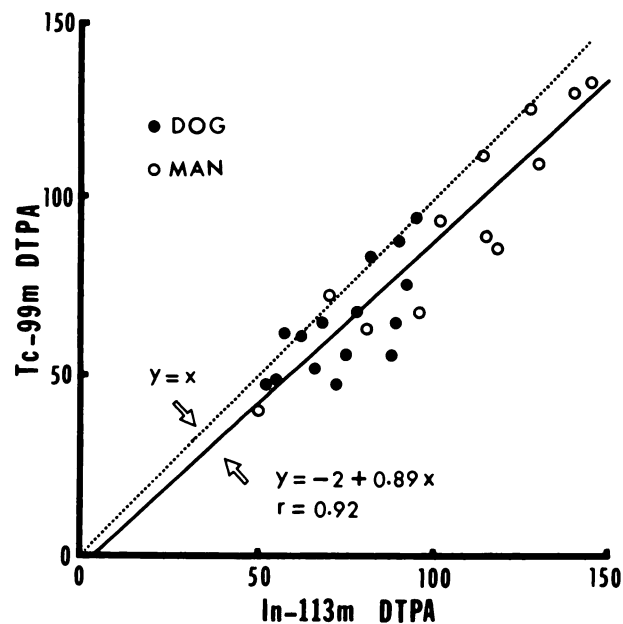


FIG. 2. Correlation of ^{99m}Tc -DTPA with ^{113m}In -DTPA clearances (glomerular filtration rates as ml/min obtained by single injection method) in 12 patients and 15 dogs.

ranged between 50 and 65 min, and the urinary excretion in 4 hr ranged between 80 and 95% of the injected dose.

Figure 2 represents the correlation of the calculated values of GFR obtained with the two tracers in 12 patients and 15 dogs using randomly chosen 27 Sn-DTPA kits during 2 years of study. Technetium-99m-DTPA appeared to correlate well with ^{113m}In -DTPA ($r = 0.92$). However, when the correlation coefficients were recalculated separately for good (9 kits) and deteriorated (18 kits) products, the results for r were found to be 0.99 and 0.85, respectively. Indeed, the results of good kits were almost on the line of 1:1 correlation.

DISCUSSION

Technetium-99m-DTPA prepared with Sn-DTPA kits of different sources behaved essentially in a similar manner. However, the results could be divided into two categories corresponding to good and deteriorated preparations. Deteriorated preparation could mean the presence of radiochemical impurities which caused the variation in the biological behavior. Chromatographic results on the free pertechnetate did not correlate well with the divergence in the clearance between ^{99m}Tc -DTPA and ^{113m}In -DTPA. Some good products (no significant divergence) showed 3–4% of free-pertechnetate and some deteriorated products showed less than 2% of free pertechnetate. This could be explained by accepting the presence of some impurities other than free pertechnetate which did not resolve in chromatography, and sometimes some free pertechnetate was generated in the process of chromatography.

There are reports on significant differences in kinetic and metabolic fates of the various preparations of radiochelates (11–13). Konikowski, et al (13) have obtained a faster clearance of ^{99m}Tc -(Sn)-DTPA in mice compared with ^{14}C -inulin which was not the case in the present study in dogs and human subjects knowing ^{14}C -inulin clearance to be similar to that of ^{113m}In -DTPA (5). It is understandable that ^{99m}Tc -DTPA could contain considerable amounts of radiochemical impurities which would behave in a manner significantly different from a radiochelate excreted by glomerular filtration. Certain discrepancies in the results of Eckelman and coworkers (7,11) as pointed out by Saha and Farrer (14) could be explained in the light of the present study. The results on the correlation of GFR in the present study appeared similar to those obtained by Klopper, et al (7). However, acceptance of such a correlation without any reservation is not appropriate since it is influenced by a deterioration which systematically reduced the GFR values obtained with ^{99m}Tc -DTPA.

A Sn-DTPA kit without prior evaluation cannot be regarded as reliable for the measurement of GFR. Moreover, the third component in the plasma clearance curves became significant probably due to radiochemical impurities. Evidence of the third component could be obtained in any prolonged study with ^{99m}Tc -DTPA (11) but its magnitude would depend on the amount of radiochemical impurities. In addition, the exact chemical status of ^{99m}Tc -DTPA is not well defined (15) and it could be anticipated that the stability of ^{99m}Tc -DTPA may not be as high as the metal chelates of higher stability.

A fresh batch of Sn-DTPA kits could be evaluated with the present technique for its acceptance and its efficacy with aging or other factors could be monitored. Indeed, it has been found that storage of kits in a refrigerator prolongs the shelf-life to about a month instead of about a week at room temperature. Similarly, freshly prepared kits could be stored for several months under frozen or lyophilized condition. Commercial kits (liquid) are susceptible to variable degrees of deterioration in shipment. Minor deterioration that may not affect scans would reduce renal clearance which could only be assessed by the double tracer technique. Indium-111-DTPA (16) could also be used conveniently instead of ^{113m}In -DTPA as the second tracer. The whole method could also be simplified to a great extent by taking only one plasma sample at about 3 hr. Normalizing the ratio of ^{99m}Tc to the second radionuclide in the tracer dose as one, the ratio in the plasma would be significantly greater than one with a deteriorated product. In the present study such values for good and deteriorated kits were 0.98–1.09 and 1.22–2.86, respectively.

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