^{99m}Tc-TECHNETIUM DIOXIDE FOR LIVER SCANNING

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In 1937 Perrier and Segré bombarded molybdenum by deuterons and produced for the first time an element not found in nature (*1*). They gave it the fitting name of technetium since "technetos" means artificial in Greek. The chemistry of this remarkable new metal was thoroughly studied by 1939 (*2*) but the radionuclide ^{99m}Tc was introduced only recently into medicine by Harper and others (*3–5*). The desirable chemical and physical properties of this new radioactive element have prompted unusual interest in the chemical oxidation states and compounds of ^{99m}Tc. The preparation and properties of ^{99m}Tc in the +7 oxidation state have been well characterized in the soluble pertechnetate ion used for brain scanning and the insoluble heptasulfide used for liver scanning. Of the six possible remaining oxidation states, the +4 state is the next most stable form of technetium.

We wish to introduce a quantitative method of preparing the +4 state as the ^{99m}Tc-technetium dioxide colloid. In this method the acidified $^{99m}TcO_4^-$ ion is reduced by sodium borohydride to $^{99m}TcO_2$ without the use of carrier metals, stabilizers, heating or cooling. The procedure is simple enough to be used by anyone with a source of ^{99m}Tc.

METHODS AND RESULTS

One milliliter of 0.5 *N* hydrochloric acid and 1 ml of 0.5 *N* sodium borohydride are added to a sterile rubber-stoppered injection vial containing 25 ml sterile $^{99m}TcO_4^-$ in sterile saline solution. The final pH of this solution will be in the range of 4.5–5.5. At this pH the reduced ^{99m}Tc is sufficiently insoluble so that it does not require an additional carrier agent or stabilizer. Sodium borohydride is oxidized in aqueous solution in the presence of heavy metals to sodium borate. The final amount of 4 mg/ml of sodium borate injected in a 1/50 normal concentration is at least 1/1,000 of a toxic dose since the ingestion of 5–10 gm can cause vomiting, diarrhea, shock and death in children (*6*). The preparation time of this clear and colorless colloid takes only a few minutes.

Analysis for soluble $^{99m}TcO_4^-$ by paper chromatography using Whatman 3-mm paper and saline solution as the developing solvent shows that the reduction is almost quantitative with only traces of free $^{99m}TcO_4^-$ ion. The reagents are prepared in bulk ahead of time in autoclavable, multidose, rubber-capped bottles using pyrogen-free water. The hydrochloric acid is sterilized by autoclaving, and the sodium borohydride is sterilized by Millipore filtration. One week's supply is stored under refrigeration. The yield of $^{99m}TcO_2$ colloid depends on the final pH of the reduced $^{99m}TcO_4^-$ solution which ought to be in the range of 4–6.5. The absence of soluble $^{99m}TcO_4^-$ can be shown by paper chromatography. The appearance of only tracer amounts of activity in the urine 5 hr after i.m. injection provides further evidence that no soluble $^{99m}TcO_4^-$ is present. The absence of macroaggregates is demonstrated by negative lung scans. Electron microscopy of the colloidal solution shows a particle size which ranges between 0.5 and 1 micron (Fig. 1). These particles are not found in the physiological saline solution containing the same concentrations of hydrochloric acid and sodium hydroboride. The size and shape of these particles are remarkably uniform and lend themselves well to liver scanning procedures. No attempt was made to analyze this particulate matter chemically. Fifteen minutes after the i.v. administration of $^{99m}TcO_2$ into rats, the liver accounts for 85% of the total activity (Fig. 2). However, while radioactive gold and ^{99m}Tc-sulfur particles are deposited in the liver permanently, $^{99m}TcO_2$ is oxidized in the liver to soluble $^{99m}TcO_4^-$ with a biological half-life of about 32 hr. The soluble $^{99m}TcO_4^-$ is excreted in the urine and feces at about the same rate. Analysis of urine and fecal radioactivity by paper chromatography shows only a single peak for the $^{99m}TcO_4^-$ ion. External monitoring in man shows the rapid deposition of

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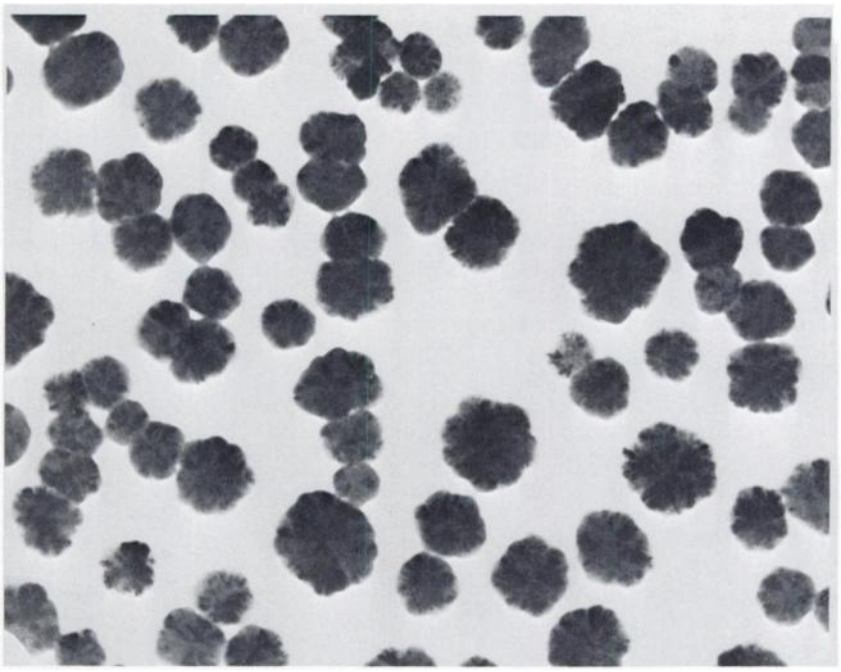

FIG. 1. Electronmicrograph of $^{99m}TcO_2$ particles 0.5–1 micron dia.

$^{99m}TcO_2$ in the liver and the rapid clearance from the blood with a half-time of about 5 min. Fifteen minutes after the i.v. administration of 800 μCi of $^{99m}TcO_2$ a liver scan in the same normal subject took 7 min.

CONCLUSION

The $^{99m}TcO_2$ can be produced by chemical reduction of sodium pertechnetate to an insoluble precipitate of $^{99m}TcO_2$. This precipitate consists of uniform particles about 0.5 micron in diameter. After intravenous injection, 85% of the radioactive particles are deposited in the liver, and rapid scans with good resolution are obtainable. The $^{99m}TcO_2$ particles are oxidized in the liver to soluble $^{99m}TcO_4^-$ and excreted. The uniform particle size of $^{99m}TcO_2$ and the absence of soluble $^{99m}TcO_4^-$ may lead to more reliable blood-flow studies than have been possible with currently available colloidal radionuclides.

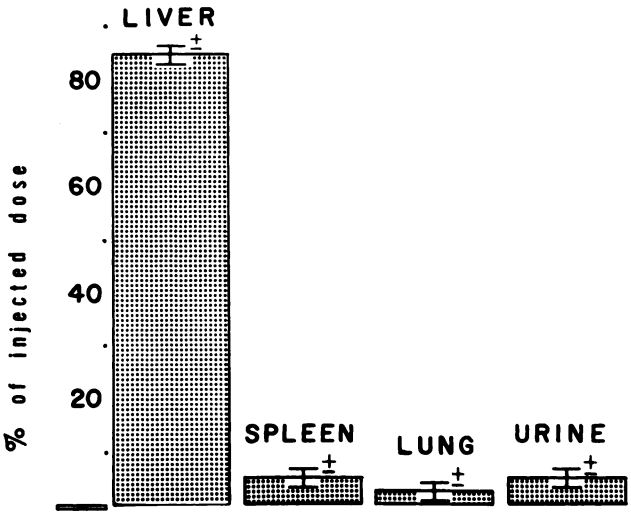

FIG. 2. Organ distribution of $^{99m}TcO_2$ activity (percent of injected dose and standard deviations) in five rats 15 min after i.v. injection of $^{99m}TcO_2$.

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