EFFECTS OF PRIOR ADMINISTRATION OF Sn(II) COMPLEXES ON IN VIVO DISTRIBUTION OF $^{99m}$Tc-PERTECHNETATE

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This report evaluates the effect of prior administration of several clinically used Sn(II)-containing agents on in vivo distribution of $^{99m}$Tc. Abnormal binding of $^{99m}$Tc to red blood cells can occur after administration of pertechnetate to patients who have previously received tin-containing agents. Increased blood levels of tin from other causes may have similar effects.

The first study of altered tissue distribution of $^{99m}$Tc, attributable to prior Sn(II) administration, was reported by McRae et al. (1). In that study, intravenous administration of as little as 0.02 mg/kg of stannous chloride (in water, gluconate, dextrose, citrate, or saline solutions) altered in vivo distribution of technetium, administered as pertechnetate, one hour to several weeks after the administration of Sn(II). Panneciére and Perez (personal communication, 1974) noted significant accumulation of $^{99m}$Tc activity in the choroid plexus when pertechnetate was given 24 hr after the administration of a typical human dose of stannous pyrophosphate. The present work elaborates on these earlier observations and evaluates the effects of prior administration of several clinically used Sn(II)-containing agents on the in vivo distribution of $^{99m}$Tc-pertechnetate.

MATERIALS AND METHODS

Intravenous Sn(II)-containing complexes. Various Sn(II) reagents used in radiopharmaceutical preparations were injected into the tail veins of female Sprague-Dawley rats (Horton Laboratories, Los Gatos, Calif.) weighing 155–175 gm. The animals had free access to food and water. The preparations studied were 1 mM SnCl$_2$, Sn(II)-HEDP (ethane-1-hydroxy-1,1-diphosphonate), Sn(II)-MIBA (mercaptoisobutyric acid), and Sn(II)-DMSA (2,3-dimercaptosuccinic acid).* Each reagent contained 0.19 mg Sn(II)/ml. In these experiments, the reagent was administered as a single dose such that each animal received 0.036 mg Sn(II)/kg body weight.

Twenty-four hours later, the animals, under light anesthesia with diethyl ether, were given an intravenous injection of 3–5 mCi of $^{99m}$Tc-pertechnetate in 0.1–0.2 ml saline. The in vivo $^{99m}$Tc distribution was then studied 6 and 24 hr after injection. This distribution was compared to that obtained in control animals receiving pertechnetate alone. Tissue activity was expressed as a percentage of the activity remaining in the skinned carcass at the time of assay, so that activity excreted from the body or contained on the skin was excluded. Carcass activity was counted at a fixed geometric distance with a NaI detector. The percent whole-blood activity was based on a total blood volume of 6.7 ml/100 gm body weight (2).

Since our intention was to show altered patterns of $^{99m}$Tc retention in various body tissues, no attempt was made to measure excretion of $^{99m}$Tc activity under the various experimental conditions. Since the actual activity in the animal can be measured during the assay of tissue activity with great reliability and with minimal ambiguity, all tissue data were expressed as a percentage of total activity in the animal at the time of assay. This method of data presentation is also more applicable to scintigraphic studies than the method of expressing data.

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* Instant Livercolloid™ Reagent, MPI Stannous Diphosphonate, MPI Hepato-Biliary Scintigraphin™ Reagent, and MPI Kidney Scintigraphin™ Reagent, respectively, obtained from Medi-Physics, Inc., Emeryville, Calif.
as a percentage of administered activity, since it is the relative localization of activity remaining in the body at the time of the scintigraphic study which will influence the image pattern and not the activity excreted prior to the study.

**Oral administration of Sn(II)-containing materials.**

Three groups of animals were given either water (control), water containing 0.19 mg/ml SnCl₂ (prepared fresh daily), or the beverage Fresca (Coca-Cola Company, Atlanta, Ga.), the label of which states that the product contains 0.025% stannous chloride (~ 0.25 mg/ml). Such oral administration was continued ad libitum for 5 and 12 consecutive days in two groups of animals. The use of Sn(II)-containing compounds before evaluation of subsequent ⁹⁹ᵐTc-pertechnetate distribution is referred to as the pretreatment in the text. Subsequently each animal received pertechnetate intravenously and was examined for in vivo tissue distribution of ⁹⁹ᵐTc 24 hr later.

**RESULTS AND DISCUSSION**

Table 1 shows the effect of intravenous pretreatment with SnCl₂ on the in vivo distribution of ⁹⁹ᵐTc, administered as pertechnetate, compared to controls receiving pertechnetate alone. The animals were killed 6 and 24 hr after administration of the ⁹⁹ᵐTc. In the SnCl₂-pretreated animals the average ⁹⁹ᵐTc remaining in whole blood at 6 and 24 hr was 62.1% and 71.7%, respectively, compared to 4.2% and 1.4% for the controls. The activity distributions in the liver and spleen were similar for both the experimental and control animals, suggesting that any stannous chloride remaining in hepatic and splenic reticuloendothelial tissue did not cause ⁹⁹ᵐTc fixation in these tissues. As anticipated, control animals showed relatively higher levels of ⁹⁹ᵐTc in the gastrointestinal tract compared to that seen in the SnCl₂-pretreated group; this result is probably directly related to the fixation of ⁹⁹ᵐTc in the blood.

Increased blood-pool activity in the pretreated animals was found in the washed red blood cells, and not in the plasma. These observations are consistent with those reported by McRae et al (1). It has been suggested that Sn(II) can become fixed to certain cellular elements, such as hemoglobin, while retaining its ability to reduce pertechnetate.

A comparison of the ⁹⁹ᵐTc distributions in controls and in animals pretreated with Sn(II)-HEDP (diphosphonate) is also shown in Table 1. As with the stannous chloride animals, pretreatment with Sn(II)-HEDP also resulted in a marked increase in whole-blood activity to 55.1% (control, 4.2%) at 6 hr and 57.1% (control, 1.4%) at 24 hr. There was a similar decrease in gastrointestinal activity.

Stannous mercaptoisobutyric acid, an agent proposed for studying hepatic and biliary structure and function (3), had a somewhat less marked effect on ⁹⁹ᵐTc distribution (Table 1). Pretreated animals showed 10.4% (control, 4.2%) of the ⁹⁹ᵐTc remaining in the blood at 6 hr after administration of pertechnetate. At 24 hr after administration the blood activity was 37.3% (control, 1.4%). The decrease in gastrointestinal activity is less pronounced than that seen in the two previous experiments.

The least effect on ⁹⁹ᵐTc distribution (Table 1) was seen in the animals pretreated with Sn(II)-2,3-dimercaptosuccinic acid (4), an agent used for imaging the renal cortex. Here the blood activity was only 8.0% (control, 4.2%) at 6 hr and 10.1% (control, 1.4%) at 24 hr. This group also showed the least change in gastrointestinal activity compared to control values. Note that the activities remaining in the kidneys of the experimental and control animals are essentially identical. Either Sn(II) does not concentrate in the renal tubular cells, or the tin, if concentrated in the kidney, is unable to fix ⁹⁹ᵐTc. In these four experiments, the activity retained in all other tissues examined did not significantly differ from control values.
Judging from these and previously reported animal data, any unusual or altered distribution of $^{99m}$Tc-
pertechnetate encountered in clinical studies should be interpreted with care, especially in patients requiring serial imaging studies, since prior administration of Sn(II)-containing drugs may result in increased blood-pool activity. Moreover, in selecting Sn(II)-
containing radiopharmaceuticals, one should prefer those containing the least amount of Sn(II). Table 2 lists the Sn(II) dose in a variety of imaging agents routinely used in nuclear medicine. The total-dose figures were calculated on the assumption that the entire amount of Sn(II)-containing radiopharmaceutical in a given vial is administered to a 50-kg patient.

Note those agents (marked with dagger) that may result in a patient dose of Sn(II) at or above the threshold of 0.02 mg/kg. This is approximately the lower level of Sn(II) ion that altered $^{99m}$Tc distribution in the studies performed by McRae et al (1). Of the commercially available liver-imaging agents, hydrated stannous chloride is well below the threshold of 0.02 mg Sn(II)/kg, while two phytate preparations are at or above this level. This is more striking when one compares the two diphosphonate bone agents with two polyphosphate and pyrophosphate preparations. Tetracycline was the only kidney agent containing a significant amount of Sn(II). Chandler and Shuck recently reported retention of $^{99m}$Tc activity in the blood pool during routine pertechnetate brain studies following bone imaging with stannous pyrophosphate (5). They also noted increased tin and technetium uptakes in the red blood cells of these patients. Walker reported similar findings in brain studies following both polyphosphate and pyrophosphate bone studies (6). However, none of the patients having diphosphonate bone studies prior to brain studies showed this effect.

The effect of oral ingestion of SnCl$_2$ in water and of Fresca on the in vivo distribution of $^{99m}$Tc-
pertechnetate, compared to control rats receiving only water, is shown in Table 3. Oral SnCl$_2$ in water ad libitum for 5 and 12 days resulted in an increase in whole-blood activity to 14.7% and 12.5%, respectively, compared to the 1.0% seen in the control group. Fresca ingestion over the same period resulted in a $^{99m}$Tc distribution similar to the control values.

The possible effects of other exogenous sources

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**TABLE 2. MAXIMUM Sn(II) DOSE AFTER ADMINISTRATION OF COMMON Sn(II)-CONTAINING RADIOPHARMACEUTICALS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg/kg)</th>
<th>Agent</th>
<th>Dose (mg/kg)</th>
<th>Agent</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SnCl$_2$</td>
<td>0.0076</td>
<td>Diphosphonate</td>
<td>0.0076</td>
<td>DMSA</td>
<td>0.0076</td>
</tr>
<tr>
<td>Phytate†</td>
<td>0.02</td>
<td>Diphosphonate</td>
<td>0.0032</td>
<td>DTPA</td>
<td>0.0042</td>
</tr>
<tr>
<td>Phytate†</td>
<td>0.04</td>
<td>Polyphosphate†</td>
<td>0.02</td>
<td>Glucophosphate</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyrophosphate†</td>
<td>0.04</td>
<td>Tetracycline†</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Assumes that the entire dose of Sn(II)-containing radiopharmaceutical in a given commercial vial is administered to a 50-kg patient.
† Agent results in Sn(II) dose of 0.02 mg/kg or more, the reported threshold for interference with pertechnetate distribution.

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**TABLE 3. EFFECT OF ORAL INGESTION OF SnCl$_2$ AND FRESCA ON IN VIVO DISTRIBUTION OF $^{99m}$TcO$_4^-$**

<table>
<thead>
<tr>
<th>Tissue*</th>
<th>Control</th>
<th>SnCl$_2$</th>
<th>Fresca</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 days†</td>
<td>5 days‡</td>
<td>12 days†</td>
</tr>
<tr>
<td>Whole blood</td>
<td>0.96 ± 0.89</td>
<td>14.65 ± 7.99</td>
<td>12.10 ± 4.88</td>
</tr>
<tr>
<td>Liver and spleen</td>
<td>6.60 ± 2.10</td>
<td>3.02 ± 1.61</td>
<td>7.70 ± 3.60</td>
</tr>
<tr>
<td>Kidneys</td>
<td>15.87 ± 3.74</td>
<td>12.44 ± 8.13</td>
<td>9.82 ± 1.75</td>
</tr>
</tbody>
</table>

* No significant change found in: lungs, heart (washed), thymus, salivary glands, muscle, trachea, adrenals, stomach, guts, gonads, brain, pancreas, cervical nodes, mesenteric nodes, and carcass. All values expressed as percent of activity in given tissue or organ per activity in excoriated carcass 24 hr after intravenous administration of $^{99m}$TcO$_4^-$ (mean ± 1 standard deviation, obtained in five rats).
† Days of oral administration of water ad libitum containing 0.19 mg/ml SnCl$_2$ prior to administration of $^{99m}$TcO$_4^-$.  
‡ Repeat study.
of stannous ion, such as that found in toothpastes, are still to be investigated. Various pharmacologically active agents (possibly tin-free) or certain pathologic conditions may also result in abnormal 99mTc distribution. Whether the altered distribution of 99mTc under such circumstances is a result of increased Sn(II) levels in tissues remains to be evaluated. Figure 1 shows an unusual distribution found in a series of pertechnetate brain-imaging studies (D. Judah and G. Chaney, personal communication, 1975). The patient had no other nuclear medicine procedures before or during her admission. The second brain study (middle row) shows abnormal retention of activity in the blood pool; it is best seen in the posterior and lateral views and in the anterior image of the neck and chest. This observation was not seen in the normal-appearing brain studies performed before and after this episode. Blood activity was predominantly in the red blood cells.

A similar case was recently brought to our attention by G. Greenspan and E. Goldstein in 1975, in which 97% of the blood activity was found to be associated with red blood cells. In this instance, a blood sample was obtained for determination of tin content. The red blood cells were found to contain 3.6 parts Sn per million by weight, compared to a control value of 0.5 parts per million. The serum contained 1 part per million (control serum 0.5). Analyses for iron, copper, zinc, manganese, and magnesium showed no significant differences from normal values.

Clinicians should be alert to possible abnormal binding of 99mTc to red blood cells in patients who have received tin-containing agents in the past. Similar binding to red blood cells may occur in patients having increased blood levels of tin from other causes. Indeed, these findings may not be specific for abnormal tin levels in blood and may occur in the course of therapy with various agents or as a part of some pathologic process.

In summary, it would appear prudent at this stage of our knowledge to utilize radiopharmaceutical agents containing a minimal amount of tin.

ACKNOWLEDGMENT

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REFERENCES


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