CARDIAC CHANGES WITH ^{99m}Tc-TIN-PHOSPHATE RADIOPHARMACEUTICALS

With the increasing use of ^{99m}Tc-tin-labeled phosphate complexes for bone scanning, a need has arisen to evaluate these agents with respect to their probable acute toxic effects on patients. Our laboratory has investigated the effectiveness and safety of several bone-scanning agents, ^{99m}Tc-tin-polyphosphate, ^{99m}Tc-tin-diphosphonate, and ^{99m}Tc-tin-pyrophosphate (*1,2*).

The LD_{50} for these radiopharmaceuticals has been reported in the literature to be 100 mg/kg, 100–500 mg/kg, and 72.5 mg/kg, respectively (*3–5*). When these drugs are administered by a rapid bolus intravenous injection into rats, rabbits, and dogs simulating the usual patient dosing method of bolus injection into the antecubital vein, the LD_{50} was found to be below 45 mg/kg for all three agents (*2*). Single rapid injection of the saline vehicle had no apparent effect. When the radiopharmaceuticals are greatly diluted and given by infusion or in divided doses, the results reported by others are achieved.

Using the same rapid injection technique in dogs, miniature swine, rats, and rabbits, acute toxic symptoms of tachycardia, hyperpnea, and tetany were observed to begin at a base level of 30 mg/kg.

During attempts to translate the acute toxicity in laboratory animals to clinical relevance, recordings of the electrocardiographic changes were made during intravenous administration of the drugs to dogs at a dose rate of 2 mg/kg/ml at an infusion rate of 6 ml/min.

Changes in the electrocardiogram were observed in healthy 8.5–10-kg dogs beginning at 20-mg/kg levels. The electrocardiographic changes were consistent with those seen in hypocalcemia (tetany). When calcium chloride was administered by intravenous infusion at or before electrocardiographic abnormalities were detected, the changes could be prevented or reversed. Additional phosphate complex drugs could then be administered to a level of 200 mg/kg without producing severe electrocardiographic changes.

On the basis of the above information, the authors recommend that patients who have severe cardiac abnormalities or extensive skeletal lesions which may drastically influence their calcium physiology should have electrocardiograms performed before obtaining the bone scan and after its completion. The authors do not recommend diluting the radiopharmaceutical or altering administration techniques because this results in unsatisfactory bone scans (*6*).

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THE AUTHORS' REPLY

Several points raised by Stevenson and Dunson in their Letter to the Editor entitled "Cardiac changes with ^{99m}Tc-tin-phosphate radiopharmaceuticals" should be discussed. Our comments will deal mainly with the diphosphonate molecule and not with either pyro- or polyphosphate.

Diphosphonate is not a true "phosphate" as inferred by the title of the Letter to the Editor. It is considered to be a low molecular weight polyphosphonate containing gem-diphosphonate groups, namely $R_2O_3P-\underset{|}{\overset{|}{C}}-PO_3R_2$.

Our lethality data refer to the maximum lethal dose or LD_{100} and not to the minimal lethal dose as incorrectly labeled in our article (*1*). Based on this, our theoretical LD_{50} for diphosphonate lies between 100–200 mg/kg, somewhat greater than the 40 mg/kg reported by the Bethesda group. This difference