

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 LD₅₀ 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 LD₅₀ 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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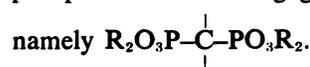
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THE AUTHORS' REPLY

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 poly-

phosphonate containing gem-diphosphonate groups,



Our lethality data refer to the maximum lethal dose or LD₁₀₀ and not to the minimal lethal dose as incorrectly labeled in our article (1). Based on this, our theoretical LD₅₀ for diphosphonate lies between 100–200 mg/kg, somewhat greater than the 40 mg/kg reported by the Bethesda group. This difference

in toxicity values may be due to many factors, one possibility being species variation. We used adult male (20–25 gm) Swiss Webster mice and the Bethesda group used rats, rabbits, and dogs. We administered the diphosphonate at pH 7.0 through the tail vein at a rate of 0.02 ml/sec, not to exceed a volume of 1.0 ml. It is not clear if the Bethesda group used diphosphonate or tin-diphosphonate and the pH, rate of injection, and concentration (mg/ml) of their formulation are not listed. There are additional conditions which influence the toxicity of a given compound resulting in the literature being filled with examples where different lethalties are reported for the same compound (2). Also, which diphosphonate was investigated by the Bethesda group? We manufacture our own diphosphonate (1-hydroxy-ethylidene-1, 1-disodium phosphonate) (3,4). The exact chemical name of their compound as well as information relative to its commercial availability or process of manufacturing are not listed. For expediency we will assume our diphosphonate and the Bethesda group's diphosphonate are similar.

We must turn again to the exact formulation of the compound used in the Bethesda group's toxicity study: tin-diphosphonate or diphosphonate. A tin-diphosphonate molecule which remains intact in vivo would theoretically have less of a hypocalcemic effect than a diphosphonate molecule whose ligands are free to chelate the calcium. If the tin-diphosphonate complex dissociates in vivo, then the toxicity of the tin may have to be considered. One literature value for the lethal dose of stannous chloride in dogs after i.v. administration is 20–50 mg/kg (2).

The toxicity study undertaken by the Bethesda group is of significance in its own right. However, it is important that its clinical relevance be documented. Does this preliminary toxicity data actually warrant contraindications such as those outlined by Stevenson and Dunson? It has been well documented that inorganic polyphosphates and diphosphonates affect the Q-T interval of the ECG (5,6), and we took this information into consideration when establishing our dose. In our clinic the average patient dose is approximately 0.5 mg diphosphonate in 1.3 ml. Assuming a standard person to weigh 70 kg, our diphosphonate dose/kg is 0.007 mg. If

we then define the margin of safety as that range between the dose where acute toxic symptoms of tachycardia, hypernea, and tetany were first observed to begin (Bethesda, 30 mg/kg) and the dose producing the desired diagnostic effect (MGH, 0.007 mg/kg), we would have to administer 4,300 times our clinical dose to approach this nonlethal estimate by Stevenson and Dunson. Also, our clinical concentration of 0.5 mg/1.3 ml/patient can indeed be considered a "super dilution" when compared to the reported LD₅₀ dose of 40 mg/kg. If we were to dilute the 40 mg/kg dose to give a final concentration equal to our clinical concentration for a standard person (0.5 mg/1.3 ml/70 kg), the final volume would be 7280 ml.

The depression of calcium levels following our minute diphosphonate dose, if present, should quickly be normalized as a result of prompt mobilization of the "labile" calcium deposits of bone. During the past year our department has performed approximately 1,000 bone scans with diphosphonate without adverse effects.

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