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THE TOXICITY OF INHALED Ca-DTPA IN THE BEAGLE DOG

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There are several advantages to the administration of Ca-DTPA by inhalation rather than intravenous drip for the excorporation of certain radionuclides. Among these are the possibility of treating very promptly following an accidental incorporation to achieve maximum treatment effectiveness and convenience for medical management, even to the extent that treatment can be self-administered. The present Investigational New Drug permit allows only treatment by the intravenous route and animal studies are required to justify the new route.

Earlier work in rats and hamsters with Dr. Ballou and Dr. Busch showed five successive daily inhalations of Ca-DTPA aerosols (dose 1-4 times human i.v. dose) produced a transitory emphysema in 17/40 rats serially sacrificed up to 3 weeks following the last exposure and in 10/20 hamsters up to 1 week after exposure. No emphysema was seen in rats sacrified after 3 weeks and in hamsters after 1 week following the exposures. This emphysema is vesicular in its morphology and is not

uncommon in inhalation experiments in rodents and occurred in 6/40 control rats and 2/20 control hamsters in this experiment. Usually it clears up after cessation of treatment as it did in this experiment. To observe effects of such inhalation treatment in a different species, the following experiment was run in beagle dogs.

The dogs were young adult males about 13-months old and weighing about 11-12 kg when entering the experiment. For exposure, the animals were anesthetised with 1 ml/kg of a 2.5% sodium pentothal solution (Abbott) given via the cephalic vein. A Foley-type catheter (8 mm I.D., Fr 34) was put into the trachea and attached very close and directly opposite the Retec nebulizer. The nebulizer was filled with 25% Ca-DTPA or 0.9% NaCl for treatment or control exposures, respectively. The nebulizer operated on the inspiration cycle only from a 50 psi compressed "breathing" air tank and was controlled by a Bird Mark 7 respiratory or a Monaghan 225 ventilator. Aerosol (AMAD or MMAD was 2.4 μm, σ_g = 2.2) was delivered to the dog at 20 psi maximum inspiration pressure; respiratory rate was 25 breaths/min and the minute volume approached 10 l/min. The latter value is about twice the usual minute volume but was chosen, as was delivery by catheter, to more closely simulate the manner in which humans are administered such aerosols. The animals were quite "light" by the end of the 30-minute exposure, recovered quickly, and were usually eating within an hour or two following exposure. There was one exception to this in both control and treated groups wherein these animals went off-feed after four exposures and lost weight with one dog requiring intravenous feeding to avoid excessive dehydration. This seemed more

related to the daily anesthesia than treatment. After five daily treatments, animals were sacrificed at 1, 4, 8, and 18 weeks following the last treatment. The dose of DTPA was estimated from chemical methods and from ^{14}C-label received in urine. It was assumed this represented dose absorbed from the lung since very little was found in feces due to the catheterization, so the gut absorption to urine was minimal. Aerosol retention was estimated at 30% and the dose about 60 mg Ca-DTPA/kg body weight. This is four times the human i.v. dose or as much as 11 times the human dose to the lungs if both species have the same retention of aerosol.

Serum chemistry results obtained from samples taken shortly after or during exposure were not interpretable because of anesthetic affects. In general, changes in measured serum parameters of experimental dogs following exposures were comparable to those observed in control animals.

Mean lymphocyte values of DTPA-exposed dogs were lower than those of control dogs during the 5-day exposure period, whereas mean neutrophil values tended to be higher during the same period. Following exposures, the blood pictures of control and treated animals were essentially similar. The bone marrow was normal with no effects observed after 1 and 4 weeks following treatment, although a mild erythroid hyperplasia was seen in some controls and DTPA-treated dogs sacrificed after 8 and 18 weeks. Urinalyses showed phosphate crystals in both treated and control animals and generally, alkaline urine following treatments, but no effects specifically related to Ca-DTPA were detected. Glucose, casts, blood, WBCs, RBCs and epithelial cells were absent and protein levels were generally normal in the urine. A few animals from the

control and treated groups exhibited, on occasion, high levels of protein (i.e., 300 mg/100 ml). Stools were checked for blood but none was detected.

In three of four dogs sacrificed 1-week postexposure, but not in animals killed later, hyperplasia of lymphoid follicles in the pyloric region of the stomach was observed. In the lung, mild focal inflammation, perivasculitis and focal fibrosis were observed in 13, 12 and 8 of the treated and 6, 7 and 4 of the control dogs, respectively. The origin of the fibrosis is not known but associated with it in six of the dogs were changes in the epithelial cells varying from mild atypia to metaplasia. Such changes were observed in two dogs killed only 1 week after exposure and in one control dog, so it is not clear that they were treatment-related. Gastrointestinal lesions, such as have been reported by Dr. Glenn Taylor, et al., following the injection of split, human doses of Ca-DTPA subcutaneously every 4-5 hours, were not observed, despite the doubling of DTPA residence time following inhalation as compared with the intravenous administration of DTPA.

In summary, hyperplasia of the gastric submucosal lymphoid follicles observed in animals 1 week following the last exposure may be treatment-related, but other observed changes were considered unrelated.

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