Teaching Editorial

Safety and Effectiveness Considerations with Particulate Lung Scanning Agents

Several thousand nonradioactive drugs are administered to patients each day in U.S. hospitals. Many of these drugs are potent substances administered multiple times to the same patient during a routine course of therapy. Thus, attendant risks of both acute and chronic toxicity are associated with their use. By contrast, radioactive drugs are typically administered only once or twice and contain subpharmacologic amounts of drug. Therefore, the traditional safety concerns are less significant with radioactive drugs but considerations of radiation dose to the patient replace them. While a relaxed attitude for toxicity concerns may be justified for most radiopharmaceuticals, at least one notable exception exists: radioactive particles for perfusion lung imaging. Typically, the particles used are radiolabeled macroaggregated albumin (MAA) or human albumin microspheres (HAM) and the amount of drug administered requires careful consideration.

From the very beginning when MAA preparations were being developed for lung scanning, much concern was given to the potential deleterious effects of injecting hundreds of thousands of protein particles intravenously. At the same time, concern focused on the potential antigenic effects of denatured protein particles. Following extensive testing, however, Iio and Wagner (*1*) demonstrated that there was no evidence to prove that aggregated human albumin was antigenic to man. This was corroborated in studies by Taplin who reported that "human serum albumin when converted to particulate form by heat treatment and pH adjustment is not made antigenic to man." (*2*).

Another concern was the threat of cerebral microembolization due to particles that enter the systemic circulation either following degradation in the lung or through a right-to-left cardiac shunt. In this regard Taplin (*2*) reported that suspensions of albumin particles, which show initial pulmonary retention, are subsequently cleared from the lungs and transposed to the liver and spleen. Thus, it appeared that if the small particles were able to traverse the pulmonary capillaries, they would also do so through cerebral vessels without significant danger of embolization. In other studies Taplin (*3*) estimated the margin of safety for particles that were not degraded into smaller sizes in the lungs but entered the systemic circulation directly through a right-to-left cardiac shunt. These studies were performed in monkeys receiving direct carotid arterial injections of MAA. From the results, it was estimated that the margin of safety (based on no evidence of behavorial abnormalities or histological changes in brain tissue) was greater than 2,000 if one injected less than 1 mg of aggregates (10–60 μm) for a lung scan. This margin of safety also assumed that there was a 50% shunt to the general circulation, including 10% to the head and 3% to each hemisphere.

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Since lung imaging agents have pulmonary extraction efficiencies greater than 90%, the extent of blood flow occlusion in the lung is a major concern. Early studies demonstrated that the clinical utility and safety of radiolabeled MAA particles in man (*4,5*) was due to the biodegradability of MAA particles and the small percentages of blood vessels actually occluded. Indeed it was shown that the mechanism of MAA clearance was due to particle fragmentation by blood cell bombardment and by continuous forward-and-backward movement within the arterioles until the aggregates were small enough to traverse the pulmonary capillary lumina (6–10 μm) (*3*). Typical preparations of I-131 MAA used for lung scanning cleared the lungs with biological half-times of 4–6 hr (*3*). In a review by Davis (*6*), it was estimated that immediately following administration of a typical lung scanning dose (LSD) of 1×10^6 particles of I-131 MAA, only 0.5–0.7% of the pulmonary arterioles and capillaries were occluded in normal adult human lungs. Taplin's early studies using this agent in dogs demonstrated that the first sign of acute toxicity, observed as a rise in pulmonary arterial pressure (PAP), occurred at a dose of 20 mg/kg body weight, which was greater than 1,000 times the average LSD and about 5,000 times the minimum lethal dose (MLD) (*3*).

A large safety factor appeared to exist for this agent and indeed thousands of clinically useful lung scans were performed with no ill effects.

In 1966 Dworkin (*7*) reported the first fatality linked to the administration of I-131 MAA particles for a lung scan. The patient was a 38-year-old woman with a $2\frac{1}{2}$-year history of adenocarcinoma of the breast. Within 1–2 min after injection of I-131 MAA (11 mg of albumin or 0.219 mg/kg body weight) she complained of faintness, and became cyanotic, diaphoretic, and agitated, with distended neck veins. The pulse rate rose rapidly and blood pressure fell. The patient responded to oxygen therapy and returned to pre-scan status within several hours. The next day, however, she experienced a rise in temperature and increased dyspnea and died 26 hr after the lung scan. Microscopic examination of the lungs showed extensive occlusion of arteries and lymphatics with adenocarcinoma. The factors that linked the MAA dose to the cause of death were: (1) the degree of tumor embolization probably compromised the lungs' ability to tolerate the dose of MAA; (2) the amount of albumin administered was among the largest doses used, due to low specific activity of the preparation; and (3) the particle size injected was larger than usual, with 74% being greater than 20 μm compared to the usual 34%.

In the final analysis, it was stated that in cases as just described, the usual compensatory mechanisms (dilatation of vessels producing A-V shunts), which respond to embolic vascular occlusion, were probably already fully operational and therefore could not respond further to the additional occlusion caused by the MAA particles. Thus, it was concluded that the wide margin of safety reported for normal subjects was of questionable value in patients with significant pulmonary vascular complications. These suggestions followed: (1) limit the size of the dose to no more than 0.020 mg/kg; (2) use a high specific activity product, with particle size 10–50 μm; and (3) inject the dose slowly, e.g., over 2 min in patients with similar pathology while observing for increasing dyspnea, tachypnea, and cyanosis. In addition, it was suggested that the minimum amount of albumin compatible with an adequate lung scan should be determined.

After this report others also appeared in the literature (*8–10*) linking suspected severe pulmonary pathology and the close association of MAA dose administration, patient symp-

toms, and death. In all of these reports the patients suffered from severe pulmonary hypertension; their underlying diseases had caused narrowing and occlusion of the pulmonary vessels. In each case, immediately following injection of the MAA dose, clinical deterioration occurred manifested by respiratory distress, cyanosis, hypertension, and eventual death. Each of these reports discussed the need in such cases to decrease the number of particles injected and to restrict their size below 50 μm, preferably in the 10–30 μm range.

In response to these reported problems, several investigators embarked on the task of determining the ideal number of particles that would produce a satisfactory lung scan. In 1974 Heck and Duley (*11*) reported the results of their investigation to determine the number of particles of Tc-99m albumin microspheres (15–30 μm) required to provide satisfactory lung images. Their analysis demonstrated that increasing the number of counts, by increasing the collection time, did not improve image uniformity unless an adequate number of particles were present in the lungs. Spurious scan abnormalities (patchy scans) resulted when less than 15,000 particles were administered. When a dose containing 30,000 particles was injected, scan patchiness near the periphery of the lung was observed. This abnormal pattern was noted first in the periphery because this area of the lung has minimal tissue thickness. Further, since the total number of particles viewed by the detector was lowest in this region, the percent variability of particle distribution was greatest near the lung edge. Because of these results and the observation that a syringe may retain particles, particularly with small volume doses, a minimum of 60,000 microspheres was recommended for an adequate lung image. At the same time greater than 150,000 microspheres was determined to be unnecessary.

In 1977 Dworkin (*12*) reported the results of a similar study that determined the effect of particle number on lung images with 10–50-μm sized particles of Tc-99m stannous MAA in dogs. The results confirmed the work of Heck and Duley and concluded that the minimum number of particles required for a satisfactory lung scan was 60 particles/g of lung or 60,000 particles/study if one assumes that the weight of the lungs in standard man is 1,000 g. The upper limit of 250,000 particles for a lung scan was suggested since little is to be gained above this number where the chances of toxicity are increased.

The acute cardiopulmonary toxicity associated with injecting particles for lung scans has been studied in animals. Allen (*13*) investigated several physiologic variables in dogs following the injection of various sized doses of Tc-99m stannous MAA (30–50 μm). The most sensitive indication of a "toxic" effect was elevation in PAP. In all instances, a single dose of 1×10^6 particles (typical LSD) produced no detectable PAP change in the normal dog. No increases in PAP were observed until more than 60 LSDs had been injected; whereas 100–150 times the LSD routinely produced a 10–20% elevation and 1428 times the LSD produced death. If dogs with sustained elevated PAP caused by previous microembolization were given a single LSD, no further changes in PAP were noted except when the PAP was greater than 300% of normal. Apparently, this experiment was done to simulate conditions of giving an LSD to patients with pre-existing pulmonary hypertension. It was concluded that the usual human LSD produced no measurable effect in normal or abnormal dog. When extrapolated to man the minimum dose expected to increase the PAP was 125 times the LSD, which is substantially smaller than the safety factor of 1,000 times the LSD previously reported for I-131 MAA (*3*). The substantial reduction in safety factor for Tc-99m MAA

may be due to its stannous ion content and the difference in chemical and physical properties compared to I-131 MAA.

In a subsequent study Allen (*14*) evaluated the acute cardiopulmonary toxicity of microspheres using a similar experimental dog model. From this study it was shown that the toxicity of lung scanning radiopharmaceuticals was essentially the result of the numbers and sizes of particles injected. Thus, microspheres with mean diameter of 15.8 μm required 2,250 times the LSD to double the PAP; whereas microspheres of 115 μm diameter required only 15 times the LSD for the same response. This inverse relationship between particle size and acute toxic response is derived from the fact that larger particles block larger sized pulmonary arterioles, which are fewer in number in the lungs. Additional studies on particle size as it relates to safety in lung scanning were reported by Davis (*15*) who worked with mircospheres in mice and rats. He demonstrated that the acute toxic response was not associated with nonbiodegradability of particles but was due solely to the occlusion of vessels by particles. Similar to the results of Allen, the safety factor was found to be inversely related to particle size. Davis determined the relationship between particle size and MLD in mice and rats. The MLD was the smallest dose that caused death. Based upon this MLD and an injected dose of 1 million microspheres/70-kg man, particles with mean diameters of 13.5, 28, 45.4 and 90.7 μm could have safety factors of 6,283, 1,663, 401, and 36, respectively. In other words, it would require about 401 lung scanning doses of 1 million microspheres 45.4 μm in diameter to cause death. Allen (*14*) found that the safety factor for similar sized microspheres was only about 150. His criterion was doubling the PAP, which is a more conservative measure of safety than the MLD and, therefore, 150 is a more realistic safety factor. If only 100,000 particles are injected these safety factors would be 10 times larger; this emphasizes why it is desirable to limit the number of particles administered to only that number that will give satisfactory lung scans, i.e., 100,000 to 150,000. While safety factors for 100,000 particles appear large, it must be emphasized that they are for normal lungs and must be considered with caution in patients with severe pulmonary disease. Thus, in patients with pulmonary hypertension only the minimum number of particles (60,000) is recommended if a lung scan is performed.

In addition to patients with pulmonary hypertension, the pediatric patient requires special consideration. Heyman (*16*) makes note that a significant increase in the number of alveoli and pulmonary arteries occurs during the first few years of life, reaching adult levels at about 8 years of age. Further, the increase in alveolar development is 10–33% of adult values during the first year of life and up to 50% the adult number by 3 yr. He suggests limiting the number of particles to 50,000 in the newborn infant and 165,000 in children up to 1 yr. Under such circumstances Davis (*17*) describes a technique for preparing pediatric doses whereby excess particles from MAA kits are discarded while a number that can be radiolabeled with pertechnetate to achieve the desired concentration for pediatric doses is retained.

In conclusion, several factors must be considered before a lung scanning dose of radiolabeled particles is administered to a patient. Most important are particle size and number and the patient's condition. It appears that the minimum number of particles required for a satisfactory lung scan is 60,000 with a recommended maximum of about 250,000. Commercially available MAA kits contain the majority of particles in the 10–90 μm range but

each kit varies considerably in its total number of particles. Thus, a protocol should be established in each department for the preparation of lung scanning doses based on the type of kit used, and the age and condition of the patient. It is strongly recommended that separate protocols be established for the preparation of lung scanning doses for normal adults, patients suspected of pulmonary hypertension, who should receive only the minimum number of particles, and pediatric patients, who should receive the appropriate fraction of the adult dose.

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