LOW PROBABILITY OF ALLERGIC REACTION TO ALBUMIN MICROSPHERES

What is the probability that an intravenous injection of a scanning dose of albumin microspheres will produce a severe allergic reaction in man? Evidence to answer this question comes from several sources; data on reactions of patients to intravenous injections of various types of denatured human serum albumin; data on reactions of animals to injections of various types of denatured serum albumin, and data on reactions of patients receiving serial injections of human serum albumin microspheres.

First: Several forms of denatured human serum albumin: ^{131}I-aggregated human serum albumin, ^{131}I-macroaggregated human serum albumin, and ^{99m}Tc-macroaggregated human serum albumin have been used in patients since 1956 without producing any recorded allergic reactions to the denatured human serum albumin (*1*). The reactions that have been reported with ^{131}I-macroaggregated human serum albumin seem to be due either to overdose in terms of numbers of particles or to hypersensitivity to Lugol's solutions administered to block ^{131}I uptake by the thyroid gland during the metabolism of the radioiodinated radiopharmaceutical (*2*).

Second: Intravenous tracer doses of denatured human serum albumin have been given repeatedly over many months to dogs, rabbits, and monkeys without producing observable reaction. Sensitization has been produced in animals within 1–2 weeks following the administration of large (10–20 mg/kg) doses. This experience was reported by Taplin et al (*1*) using macroaggregated human serum albumin. Our experience with human serum albumin microspheres has been very similar to this. Postinjection reactions have been observed in dogs receiving multiple 10–20 mg/kg doses. However, intradermal injections of microspheres 1–3 weeks following a 1–10-mg/kg dose did not produce reaction at the injection site as expected if the dogs were allergic to the microspheres. Repeat 0.01–0.02 mg/kg doses, i.e., scanning doses, have been given routinely to dogs and calves without ill effects. Also three monkeys were given repeated scanning doses of microspheres for a year without observable reaction (Table 1).

Human serum albumin microspheres have been used to induce sensitivity in guinea pigs. The sensitized guinea pigs died when injected intravenously with 2.5 mg of human serum albumin in solution but did not react to a similar dose of human serum albumin microspheres. Guinea pigs did not become sensitized to guinea pig serum albumin or guinea pig serum albumin microspheres following repeated administration of guinea pig serum albumin microspheres (*3*).

Third: In more than 1,500 injections of human serum albumin microspheres, a reaction which might have been of an allergic type was observed only once (*4*). The patient recovered promptly without medi-

TABLE 1. SERIAL INJECTIONS OF HUMAN SERUM ALBUMIN (HSA) MICROSPHERES IN EXPERIMENTAL ANMIALS

Experimental animal	No	Dose level (mg/kg)	Injection schedule	observations
Guinea pigs (antigenicity study)	6	1–10	Weekly	Animals become allergic to HSA but not to HSA microspheres. Maximum sensitivity at 2 weeks after initial dose.
Monkeys (cirrhosis study)	3	0.01–0.1	0, 1, 12, 13, 24, 25, 50, 51 weeks	No reactions
Dogs (shunt-blood gas study)	3	0.01–0.1	1, 2, 3 weeks	No reactions
Dogs (toxicity study)	3	1–10	1, 2, 3 weeks	No response to final intradermal dose.
Dogs (sympathectomy study)	6	0.01–0.1	1, 7	No reactions
Calves (lung-transplant study)	several	0.01–0.1	Multiple	No reactions

TABLE 2. PATIENTS RECEIVING MULTIPLE DOSES OF DENATURED HUMAN SERUM ALBUMIN FOR LUNG SCANNING DURING PHASE I UROKINASE TRIALS*

Radiopharmaceutical	No patients	No reactions
^{131}I-macroaggregated human serum albumin	140	None
^{99m}Tc-human serum albumin microspheres†	11	One patient experienced acute onset of choking with flushing, which rapidly returned to normal. Patient had no reaction to subsequent microspheres‡

* Dose schedule: 1, 2, 3, 7, 14 days, 3, 6 months, 1 year.
† Three patients received eight doses, two patients received ten doses, five patients received 11 doses and one patient received 12 doses.
‡ Injections in this subject were: 2/10/69; 2/11/69; 2/12/69; 2/13/69; 2/14/69; 2/17/69; 2/18/69; 2/25/69; 5/12/69—reaction; 9/26/70—no reaction; 12/2/70—no reaction.

cal intervention. Subsequently this patient received microspheres on two separate occasions without ill effects.

This patient was one of over 100 patients who were given repeat injections of microspheres in a study of pulmonary embolism. More than 100 other patients were evaluated with repeat injections of ^{131}I-macroaggregated human serum albumin without ill effects. Table 2 summarizes the patients who were treated during Phase I urokinase trials.

In summary this evidence suggests that there is a low probability of a serious allergic reaction of patients to injections of human serum albumin microspheres. Except for urokinase study patients, the probability of an individual patient receiving more than two serial doses of denatured human serum albumin is 0.056. This factor together with the low sensitizing potential of human serum albumin microspheres makes the chances of observing an allergic reaction quite small. From our data between November 18, 1968, and November 17, 1970, the estimated probability of an allergic reaction to an injection of microspheres in patients who have already had two injections is 0.003 and in all patients is 0.0007. If the data from the more than 15 other institutions which have also been using human serum albumin microspheres and have reported no reactions and our own more recent experience were included these probability estimates would be even less.

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IS IT THE BLOOD BACKGROUND?

In a recent article (*J Nucl Med* 11: 173, 1970) entitled "Failure to Detect ^{131}I Positive Thyroid Metastasis with ^{99m}Tc," the authors, Meigan and Dworkin, report a case in which metastatic lesions positive on a regular ^{131}I scan were missed on a $^{99m}TcO_4^-$ scan, supposedly because of a high blood background. We wish to point out that this failure, at least in part, may be attributed to the technical procedure followed in scanning by them.

The authors do not state clearly their reason for repeating a $^{99m}TcO_4^-$ scan after an ^{131}I scan. We presume this was a part of an overall effort to compare the two radiopharmaceuticals for the purpose of detecting metastases due to a thyroid carcinoma. In that case, a better procedure would be to perform a $^{99m}TcO_4^-$ scan first and then follow it with a ^{131}I scan. This would have avoided the problem of interference of one radionuclide to the other. The energy of ^{99m}Tc gamma rays is low (140 keV) compared with those from ^{131}I (364 keV), and therefore there will be no interference in an iodine scan due to the presence of $^{99m}TcO_4^-$. However, this is not true if an iodine scan is performed first and then followed by a $^{99m}TcO_4^-$ scan.

Meigan and Dworkin took the precaution of avoiding this interference by performing a technetium scan 5 days post iodine scan and thereby assumed that no iodine or minimal iodine was left by that time. We calculated that 5 days interval is not sufficient to give an insignificant iodine level and there there may be a substantial amount of iodine present at the time of a technetium scan. The authors do not give the 24-hr