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Do Colloids Cause You Problems? A Clear Solution Isn't in Sight

Although colloids have been used extensively in nuclear medicine for many years, many facets of the physical nature and biological behavior of these minute particles remain an enigma.

Aside from the colloids produced for use as such, colloids also exist in some preparations as contaminants. The reduction of technetium from pertechnetate by stannous ion (to some mysterious form) is an integral part of forming (a) radiochelates with diethylenetripentaacetic acid, diphosphonate, pyrophosphate, polyphosphate, etc., and (b) the large Tc-99m-labeled particles such as macroaggregated albumin. Unfortunately, colloidal impurities of varying quantities and varying constituencies often are formed in addition to these chelate. These "uninvited" contaminants are variously described as "hydrolyzed reduced" or "colloidal" technetium and are hypothesized to be Tc-99m-labeled stannous oxide or Tc-99m-labeled hydroxide. It appears that these hypotheses may be an oversimplification.

The colloidal contaminants may be phagocytized by the reticuloendothelial system (RES) when skeletal, renal, and other imaging studies are performed and are not handled in a manner similar to the chelate radiopharmaceutical (*1*). Besides contributing to the radiation dose without providing information, colloidal particles can actually reduce the technical quality of the image. A recent study indicated that the colloidal content had to be less than 10% in a diphosphonate (HEDP) preparation to obtain images without detectable liver deposition (*2*). When preparing Tc-99m HEDP or PP_i on a day to day basis, the authors found that the occurrence of colloidal impurities was "unpredictable." While contaminants such as pertechnetate in some commercial bone agents can be minimized by inclusion of an antioxidant such as ascorbic acid, no such remedy is available for preventing colloid formation.

Undesirable colloidal formations appear to be an everpresent consequence when tin is employed as a reducing agent for pertechnetate. Newer hepatobiliary agents have been synthesized employing stannous ion, and the report indicates that colloid formation has not been observed (*3*). In addition, other effective reducing agents for technetium are available (*4*) for which professed minimum colloid formation has been reported, but the long-term safety of these new reducing agents must be demonstrated in humans. Improved formulation of radiopharmaceuticals with regard to components, their quantities, and procedural preparative steps should help to alleviate this problem of unwanted colloid.

The anomalous localization of colloidal particles in the lung may reflect trapping of agglomerated Tc-99m sulfur colloid particles caused by cations such as aluminum in the radiopharmaceutical preparation. In an anecdotal report 5 years ago (*5*) the author stated that increased pulmonary uptake of technetium-labeled sulfur colloid not attributed to particle agglomeration may be the consequence of severe prolonged hepatic disease. Subsequently, investigators have reported increased lung radioactivity in 1.6 to 8% of conventional Tc-99m colloid liver–spleen images (*6*). A myriad of studies have documented increased lung deposition of radioactively labeled colloid in many pathologic states, and multiple assorted mechanisms have been postulated; yet a documented answer is not available. On the other hand, renal uptake of colloid (*7*) has found application in monitoring renal transplant integrity (*8*), and the mechanisms of deposition are just as nebulous. How can these puzzling particles be characterized?

In this issue of the *Journal*, Warbick et al. (*9*) present a detailed study of techniques for colloid particle sizing. This excellent and much-needed study shows that electron microscopy coupled with energy dispersive x-ray fluorescence is the method of choice for assay of particle size, shape, and constituents,

particularly for the smaller colloidal particles where size determination has been especially difficult. Unfortunately in terms of price and availability, the instrumentation required for such analyses is not practical for many clinical centers. Until such time as this method becomes feasible, differential sorting of radioactive colloid solutions through serial layers of different pore size filters (*10*) yields a satisfactory determination of particle size or "activity size." A recent report recommends filtration as a simple procedure for particle sizing (*11*) since particle size distribution by filtration correlates well with results by electron microscopy. While filtration is probably the most readily available procedure for nuclear medicine facilities, the tedious character of the procedure limits its usefulness.

The United States Pharmacopeia has described a standardized method for particle sizing of Tc-99m sulfur colloid (*12*). This procedure, which depends on the relative biologic distribution of colloid in a laboratory mouse, is obviously quite gross. Most hospitals or clinics with a need to document particle size will rarely have such a testing facility and, more significantly, little willingness to institute one. The official method of particle sizing must be more practical, more suitable, and more reliable before it will gain widespread acceptance.

While other procedures in quality control have been simplified with newer techniques (e.g., chromatography), available colloid sizing and counting methods still are either unwieldy, time consuming, exotic, or too expensive. In any case, the usual laboratory situation is one in which no determination in size is performed.

Since the use of colloids in nuclear medicine remains extensive, we must develop methods to prepare and characterize colloids more accurately, eliminate colloids from preparations where they are contaminants, and make a concentrated effort to better understand their biologic fate.

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