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BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

REPOSITORY BNL
COLLECTION Human Subjects Research Policies
BOX No 1
FOLDER

DATE: July 11, 1955

TO: Committee on the Use of Radioisotopes in Humans

FROM: J. S. Robertson, M.D.

SUBJECT: General Criteria for the Clinical Use of Intravenously Administered Radioactive Colloids

This memorandum has been prepared in order to provide a background of information pertinent to certain contemplated clinical uses of radioactive colloidal materials. Because the potential clinical applications of the available radioactive colloidal preparations are similar, they will be discussed as a group. Emphasis will be given to the intravenous administration of colloidal preparations of gold (Au^{198}), phosphorus (P^{32}) and yttrium (Y^{90}).

The uses of intracavitary and interstitially administered colloids will not be discussed in any detail; a start toward the extensive literature on this phase of the subject is provided in reference (30).

Physical Characteristics

Gold, Au^{198}

Half-life: 2.7 days
Radiations: 0.97 mev Beta
0.41 mev Gamma
Colloidal form: Au

Phosphorus, P^{32}

Half-life: 14.3 days
Radiations: 1.71 mev Beta
Colloidal form: $CrPO_4$

Yttrium, Y^{90}

Half-life: 61 hours
Radiations: 2.24 mev Beta
Colloidal forms: $Y_2(HPO_4)_3$, YCl_3, YF_3

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Availability

Radioactive colloidal gold, phosphorus and yttrium are available from Abbott Laboratories, Oak Ridge, in sterile, pyrogen-free solutions.

Animal Studies

Perhaps the most important physiological consideration in proposing the use of colloidal preparations is the well-known phenomena that reticulo-endothelial cells take up particulate matter. For example, if India ink is injected intravenously, the Kupffer cells in the hepatic sinusoids become engorged with carbon particles (35).

The early literature on the fate of intravenously injected particulate matter has been reviewed by Dobson and Jones (10). Bacteria (5) and colloidal forms of manganese dioxide (12,34), thorium dioxide (Thoratrast)(41), calcium phosphate (16,17,36) and chromic phosphate (10) show in common high percentage uptakes in the liver and spleen, with the uptake in lung and bone marrow also being prominent, but more strongly dependent upon the particular preparation and species involved.

The University of California group has done much pioneering on the distribution of particulate colloids, initially chromic phosphate (28), and more recently on the distribution of solutions of zirconium, columbium and yttrium (9,18). They have shown that the biological distribution depends upon the nature of the particles. (See also reference (55)). By suitable preparation of the material to be injected (particle size greater than 30μ), it is possible to achieve selective localization in the lungs (37,38,40). A transient concentration in the lungs has also been observed with labeled white cells and platelets (43), which behave like particulate matter after

certain handling procedures. The particles of relatively large size disappear rapidly (half-time, ½ minute) from the blood stream and are deposited primarily in the liver and spleen. Colloids of intermediate particle size disappear more slowly (20 to 80 minutes) and are deposited primarily in the bone marrow and spleen. Once deposited, no significant distribution takes place over a 2- to 4-week period, and body excretion is slow (52).

Hahn et al. (22) established that colloidal ferric hydroxide, given by vein, was distributed in the reticulo-endothelial system roughly in proportion to the phagocytic activity, with maximum concentration in the spleen. Manganese dioxide tended to accumulate in the pancreas (52).

Dobson and Jones (10) have used chromic phosphate to study liver blood flow and to irradiate the liver in mice. With doses of 106 μc of P^{32} per gram of liver, about 95 per cent localized in the liver, and an irradiation dose of 75,000 rep to the liver was achieved. The general picture with this dose was slow loss of weight, followed by death within 4 months. Those animals receiving half this dose were all alive after 4 months, but had lost 10 per cent in weight, and died within 12 months. The dose rate is evidently a factor, because administration of 37,500 rep with colloidal yttrium-90 hydroxy citrate killed mice within 9 days, in contrast with the 4-month survival when this dose was given with chromic phosphate.

Hahn and Sheppard (21) surveyed the reactor-produced isotopes and selected Au^{198} as the one most likely to succeed in producing worth-while therapeutic results. The P^{32} and Y^{90} preparations, however, are pure beta emitters, and their use may achieve a more desirable localization of the irradiation than is possible with a gamma emitter (30).

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In rats injected intravenously, colloidal Au^{198} and P^{32} compounds followed the expected pattern, with 80 to 100 per cent of the material being found in the liver, spleen and lungs, and with most of the isotope localizing in the liver. "The distribution of $Y_2^{90}(HPO_4)_3$ and $Y^{90}F_3$, however, was different. The spleen in each case contained much more Y^{90} than the liver, on an isotope per gram basis 8 to 15 times as much. The skeletal deposition was calculated to be about 20 per cent, and a very significant amount was found in the lungs. Apparently, the compounds were quite selectively localized in the blood forming organs, the spleen especially receiving large amounts of the beta radiation," (30).

Clinical Applications

The chief clinical applications of colloidal preparations have been in intracavitary and interstitial administration in the treatment of cancer, and in which the depression of hematopoiesis is undesirable. Therefore, in such treatments, the particle size, chemical form, half-life, etc. have been selected to avoid, insofar as possible, escape from the site of administration with subsequent uptake by the liver, spleen, and other parts of the reticulo-endothelial system. Data on the degree of translocation from various sites of injection and a number of key references on this subject are given in reference (30), but will not be discussed here.

Clinical experience in the use of intravenously administered colloids seems to be vanishingly small. As in the case of almost all kinds of ionizing radiations, major complications, and limiting factors, are leukopenia, thrombocytopenia and anemia (11). Damage to the liver is also a limiting factor (1,41). If a dose of 3,000 rep to the liver is regarded as permissible,

a 1,400 gram liver could be allowed to retain 4.5 mc of P^{32} on the basis that 1 μc delivers 885 gram rep (37). Extensive liver damage has been reported from doses of 12,000 rep and up in rats (29) and dogs (23). Exploratory work on the therapy of the splenomegaly and hepatomegaly of chronic leukemia with doses of up to 4 mc of P^{32} chromic phosphate gave no effects on the size of the liver or spleen or on the peripheral blood levels (11,33). Chromic phosphate was used by Lawrence and Low-Beer in one case of melanosarcoma with a definite, but very temporary, benefit (33). Hahn (21,24,25) has had some success in treating leukemia with radiocolloids, but the use of soluble P^{32} is more common (8). Andrews and Tyor (1) gave 23 to 45 mc of colloidal gold intravenously to 6 patients with chronic granulocytic leukemia, and obtained distinct falls in the white cell counts. The greater amount of activity was in the liver.

Aggeler and Low-Beer treated a case of thrombocytopenic purpura with P^{32} chromic phosphate. With what appears from a graph to have been 6,000 rep, there was a marked decrease in the circulating formed elements and death of the patient 3 months later (33).

No evidence was found in the present search of the literature to indicate that any of the reticulo-cell type sarcomas or other tumors have the phagocytic properties of the normal reticulo-endothelial system. On the contrary, neoplasms in the liver displace the reticulo-endothelial cells and have been shown not to concentrate colloidal gold (44). Antihistamines may be used to depress the phagocytic activity of the liver, but the effect is a general depression of the reticulo-endothelial system's activity and is not specific for the liver (14).

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Conclusion

Attainment of the goal of achieving selective localization of radioactivity in tumors by intravenous administration of colloidal preparations does not appear imminent from the present literature survey. Depending upon the particle size, such preparations normally tend to concentrate in the liver, spleen, bone marrow and/or lungs, and no evidence has been found to encourage the concept that any tumor can successfully compete with these normal processes. In any event, irradiation of the liver and bone marrow constitute limiting factors in the dose of activity which can be administered.

To a large degree, the negative tone of this conclusion stems from an absence of reports, rather than on actual negative findings, and, therefore, if for this reason alone, it does still appear to be worth while cautiously to investigate the uptake of colloidal particles by selected types of tumors. The above considerations emphasize that in such investigations, attention must be given to the effects of localization as a function of particle size of the preparation, in addition to the more usual considerations of the type of radiation, half-life and limiting complications.