METASTATIC CALCIFICATION AND BONE SCANNING

The case report by McLaughlin (*1*) brings to a total of five the number of patients in whom metastatic calcification has been detected through scanning after the intravenous injection of a technetium–phosphate complex. From these studies a few general conclusions may now be drawn. Although the patients had various underlying diseases, such as carcinoma (*1–3*), vitamin D intoxication (*4*), or multiple myeloma (*3*), the common denominator among them appears to have been renal failure accompanied by hypercalcemia and hyperphosphatemia. (McLaughlin does not give the serum phosphorus value for his patient but there can be little doubt that it was elevated.) In the presence of renal failure the kidneys' ability to excrete phosphorus is reduced. If hypercalcemia occurs, the solubility product for calcium and phosphorus may be exceeded and precipitation of these substances occurs in soft tissues. When a technetium–phosphate complex is injected intravenously it appears to enter into the metabolically active depositions in the soft tissues so that a diffuse uptake in these tissues is noted when scanning is attempted. Through this mechanism metastatic calcification of the lungs and stomach has now been strikingly demonstrated. Several of the patients described have also had metastatic calcification of the kidneys; this, of course, cannot be detected through scanning because even normal kidneys show up clearly during bone scanning as a result of their role in excreting phosphorus.

Some points of practical importance emerge from these observations. In a patient with renal failure, hypercalcemia, and hyperphosphatemia, increased uptake of a technetium–phosphate complex in the lungs or stomach may be accepted as a sign of metastatic calcification. Biopsy is probably no longer necessary to make the diagnosis, as it has been in the past. Since the scanning procedure may be repeated without hazard to the patient it may prove to be a useful guide to the progress of treatment. The heart is another organ that may be involved in metastatic calcification. This has not yet been demonstrated through scanning with a technetium–phosphate complex but, with special techniques to obviate the obscuring effect of the overlying ribs and sternum, it no doubt will be in time.

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BEHAVIOR OF ^{99m}Tc-LABELED DIPHOSPHONATE ON SEPHADEX AND BIO-GEL

Gel chromatography using Sephadex has proven to be a suitable analytical tool for the quality control of ^{99m}Tc-labeled radiopharmaceuticals because of its ability to separate ^{99m}Tc-labeled compounds, ^{99m}Tc-pertechnetate, and reduced uncomplexed ^{99m}Tc (hydrolyzed reduced technetium) (*1*).

As pointed out by Valk, et al (*2*) the results obtained from Sephadex G-25 gel chromatography are sometimes inconsistent with the in vivo biologic behavior of the radiopharmaceutical preparation being tested. The authors assumed an interaction between weak ^{99m}Tc complexes and Sephadex (a cross-linked polysaccharide), which may act as a chelating agent because of the high density of hydroxyl groups. It was hypothesized that weak complexes of technetium in competition with Sephadex lost the radionuclide to the column.

This point of view was supported by the results obtained by Richards and Steigman (*3,4*) from studies on column stripping of reduced ^{99m}Tc by elution

TABLE 1. GEL CHROMATOGRAPHY COLUMN SCANNING DATA*

Gel	Time: Interval between preparation and first elution	Time: Interval between first and second elution	Hydrolyzed reduced ^{99m}Tc (bound to top of column)	^{99m}Tc-diphosphonate: Total	^{99m}Tc-diphosphonate: Fraction remaining on gel after second elution
G-25	10 min	20 min	0	100	33
P2	10 min	20 min	0	100	11
G-25	10 min	4 hr	0	100	38
P2	10 min	4 hr	0	100	12
G-25	10 min	6 hr	0	100	63
P2	10 min	6 hr	0	100	12
G-25	1.5 hr		0	100	
G-25	5 hr		0	100	
P2	7 hr		0	100	

* Gel chromatography was performed on Sephadex G-25 medium and Bio-Gel P2 (column dimensions: 1 × 26 cm). First elution was with 6 ml 0.9% NaCl; second elution with 30 ml 0.9% NaCl. GCS profiles were registered by scanning the column with a Berthold thin-layer scanner II.

with solutions of complexing materials. Recently, Billinghurst and Palser (*5*) compared Sephadex G-25 and Bio-Gel P10 as gel medium for the chromatography of ^{99m}Tc radiopharmaceuticals in order to clarify whether the interaction assumed is limited to the polysaccharide Sephadex or not. Contrary to Sephadex, Bio-Gel (polyacrylamide gel) did not retain any of the ^{99m}Tc that was originally associated with the radiopharmaceuticals even in the case of weak chelates.

To check quality and in vitro stability of ^{99m}Tc-labeled diphosphonate (ROTOP-diphosphonate kit; GDR) both thin-layer chromatography and gel chromatography column scanning (GCS) (*6*) on Sephadex G-25 M and Bio-Gel P2 were performed.

The presence of unreacted pertechnetate in the radiopharmaceutical could be excluded by means of thin-layer chromatography using methyl ethyl ketone as eluant. It was found in GCS studies on both types of gel that there was no radioactivity at the top of the column, i.e., no reduced hydrolyzed technetium could be detected, if the analysis was made with freshly prepared ^{99m}Tc-diphosphonate.

There was only one peak corresponding to ^{99m}Tc-diphosphonate. According to the features of the GCS method all radioactivity remains in the column. After column scanning, the radioactivity, except for the reduced hydrolyzed ^{99m}Tc, can be eluted by additional saline solution.

In the case of the ^{99m}Tc-diphosphonate investigated it became evident that after GSC the elution of the complex from the columns was dependent on both the type of gel and the time interval during which diphosphonate is in contact with the gel.

The results obtained are shown in Table 1. Both gel types have provided identical data with respect to the quality of ^{99m}Tc-diphosphonate when the radiopharmaceutical preparations were investigated by the GCS method. Thus it can be concluded that gel chromatography of ^{99m}Tc-diphosphonate on Sephadex does not exhibit any artifact as in the case of weak complexes. The behavior is related to that of ^{99m}Tc-DTPA (*5*). On the other hand, there is an interaction between ^{99m}Tc-diphosphonate and Sephadex as can be seen from the data of the column scanning after second elution. The kind of interaction is unknown.

It is supposed that ^{99m}Tc radiopharmaceuticals show decomposition on Sephadex either due to an enhanced hydrolysis in the presence of Sephadex or in order to form a ^{99m}Tc Sephadex complex. Depending on the rate of decomposition this effect may cause artifacts in routine quality control as in the case of weak ^{99m}Tc complexes whereas in the case of stronger complexes the quality control is less affected or not at all, but an interaction can be demonstrated by the technique described.

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A REPLY

Dr. Johannsen has clearly demonstrated one of the advantages of gel chromatogram scanning as opposed to elution of the gel column, since it avoids the question of whether the activity retained on the column is hydrolyzed, reduced technetium or whether it is due to a reaction between the Sephadex column and the technetium chelate. If Sephadex is chosen for gel chromatography, then the column scanning technique is faster, since less elution time is required, and the results are unambiguous.

His conclusion, however, that the results he provides indicate that technetium diphosphonate does not exhibit any artifact as in the case of weak complexes is incorrect. The fact that for a total time interval of 30 min 33% of the ^{99m}Tc remained on the Sephadex column as opposed to 11% on the Bio-Gel column clearly shows that it is a weak complex compared to the ^{99m}Tc-DTPA (*1*), which showed no association with the Sephadex column other than that of the hydrolyzed, reduced technetium. It would appear, however, that the strength of the ^{99m}Tc-diphosphonate was more like that of ^{99m}Tc-glucoheptonate than either the ^{99m}Tc-pyrophosphate or the ^{99m}Tc-gluconate (*1*). On the other hand, as has been pointed out by Valk and McRae (*2*), the binding on the Sephadex column depends on a number of undefined parameters, and comparisons of nonidentical systems are not very reliable.

With all chelates there is a definable dissociation constant and related rate constant; it is these constants together with the rate of elution that determine the amount of ^{99m}Tc left on the column. Steigman and Williams (*3*) correctly point out that if the eluant is a solution of the complexing agent, i.e., diphosphonate in this case, then all the ^{99m}Tc is recovered from the column. In such a case the technetium that becomes associated with the column material is also subject to dissociation from the column material and if the eluant is a complexing agent it will probably then associate with the eluant rather than reassociate with the column. However, if the eluant is saline then the reduced technetium has only the column material to complex with once the bolus of labeled complexing agent has passed.

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RADIATION DOSE TO THE LIVER FROM ^{201}Tl

To show the effectiveness of ^{201}Tl for myocardial scanning, Bradley-Moore, et al (*1*) have presented data on its retention and distribution in goats and estimated the radiation doses in humans. Because we had also recently calculated the radiation dose from ^{201}Tl we compared their results with ours. With the exception of the dose to the liver, our results compare well with their published dose estimates. Using the biologic data from their paper, we calculate the liver dose to be 0.43 rads/mCi of ^{201}Tl administered; their estimate is 0.17 rads/mCi. When we assume that the liver has little or no activity and is only irradiated by activity in surrounding organs and the remainder of the body, we obtain an estimate that agrees with their estimate of 0.17 rads/mCi. However, Table 1 of their paper shows that 15.4% of the ^{201}Tl is in the liver 25 min after administration. The 0.17 rads/mCi value is apparently the dose to the liver when the activity in the liver is not included in the calculation of the dose.

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