

Soft-tissue Concentration of Tc-99m Phosphates Associated with Injections of Iron Dextran Complex

A recent paper by Byun et al. (1) describes accumulation of technetium-99m phosphates in the gluteal area of bone scan patients who had recently received intravenous injections of iron-dextran complex.

This observation was first reported at the San Francisco Meeting of the Northern and Southern California SNM Chapters in October 1974 (2). Also, we have published an abstract describing further work (using thin layer chromatography and in vivo animal experiments) on a possible mechanism for the localization referred to in Ref. 3. Consequently, it would seem only prudent to cite at least the abstract even though such astute scholars as McRae et al. (4) cited the 1974 presentation. We are pleased that Byun and his colleagues agree with our findings, but feel this should be presented as a supporting case report instead of a "new observation."

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A Need for the Standardization of Methods for Reporting Clinical Radiopharmaceutical Data

Current literature does not adequately define the clinical radiopharmacology of bone-scanning agents. Our survey revealed a wide spectrum of methods for acquiring and reporting data for this class of radiodiagnostic agents. The inconsistencies make it difficult to compare the published information from one study to another in a meaningful manner. To illustrate this point, Table 1 lists blood clearance,

urinary excretion, and other data for technetium-99m labeled phosphate and phosphonates from a number of reports in the literature. Further analysis also revealed an inadequate separation of the patient populations. For example, subjects were not divided according to the scan findings (normal compared with abnormal) and those that indicated abnormal subjects did not characterize them according to disease (e.g., bone metastases from breast carcinoma, Paget's disease, etc.).

Addressing this question, we have carried out studies comparing patients with normal volunteers relative to blood clearance, urinary excretion, and tissue distribution (1). Significant differences were noted between patients and volunteers as well as between patients with normal and patients with abnormal studies (Table 1).

To meet FDA Phase I requirements (IND Form 1571, 10.a) an investigator may report clinical radiopharmaceutical data that may vary significantly from those used by other investigators. Consequently there is need for better standardization of procedures for acquiring and reporting the clinical radiopharmacology of agents used in nuclear medicine. These improvements could provide more accurate data for calculating radiation doses to various organs in normal and diseased states. Kaplan and Zimmerman directed their attention to this problem and concluded, "In the generation of future schema for absorbed dose calculations, a greater emphasis could be placed on biologic distributions in the abnormal patient" and "consideration be given to the nonpathologic variables that can produce unusual patterns of radioactive distribution" (2).

Other factors must also be considered (3-15). Simply as an example to illustrate unexpected clinical findings that may be encountered in supposedly healthy volunteers, the following study is brought to your attention. In a published report (16), 29 healthy young male volunteers were screened by history, physical examination, urinalysis, 24 different blood tests, and electrocardiography for admission to an FDA Phase I Drug Investigation. During this screening, 46 abnormal laboratory test values were found from among this group. In fact, only 4 of the 29 subjects had all their test data within the "normal" range. We do not advocate such rigid criteria, but only illustrate the importance of careful volunteer selection.

Besides separating patients into groups having normal studies compared with abnormal studies, a further division into subcategories according to specific clinical information is also indicated. Obviously, clinical factors affecting tissue distribution are numerous, but many can be expressed in general terms. This information might include: disease states that have been confirmed by histologic or laboratory findings; diagnostic information derived from other imaging modalities (e.g., roentgenography and ultrasound); different modes of therapy (e.g., surgical procedures, radiation, pharmaceutical), etc. The pharmaceutical parameters should cover all modes of treatment starting with hormones and chemical agents for the control of tumors, through drugs used for the treatment of supposedly unrelated conditions such as peptic ulcer, to those given simply for the relief of

TABLE 1. RADIOPHARMACOLOGY

Study No.—Classification										
Agent	Ref.	No. subjects		Nor- mal volun- teers	Patients			Blood clearance Time (%D/Whole Blood)		
		Blood	Urine		Path	Norl	?	T ₁ (%)	T ₂ (%)	T ₃ (%)
HEDP	3	5	5	0	5	0	0	3h (6)		
HEDP	4	5	5	0	0	5	0	5m (26 ± 5.1),	1h (8.7 ± 1.6)	
PPx	5	12	12	0	0	0	12			
PPx	6	10	10	0	0	0	10	4h (10)		
HEDP	6	10	10	0	0	0	10	4h (7)		
MFP	7	10	10	10	0	0	0			
HEDP	7	10	12	12	0	0	0			
PPx	8	17	0	0	0	0	17	3h (10.2)	22h (2)	
PP _i	8	37	0	0	0	0	37	3h (6.8)	21h (2)	
HEDP	8	24	0	0	0	0	24	3h (5.6)	8h (2)	
PP _i	9	5	5	0	0	0	5			
PP _i	10	10	10	0	0	0	10			
PPx	10	10	10	0	0	0	10			
PP _i	11	15	15	0	15	0	0			
MDP	12	6	6	6	0	0	0	5m (39.2)	1h (9.74)	3h (3.22)
HEDP	12	6	6	6	0	0	0	5m (45.4)	1h (12.2)	3h (4.68)
PP _i	12	6	6	6	0	0	0	5m (37.9)	1h (13.0)	3h (7.95)
PPx	12	10	10	10	0	0	0	55m (46.1)	1h (16.6)	3h (10.6)
HEDP	13	10	10	10	0	0	0			
HEDP	14	35	6	10	25	0	0			
PP _i	14	35	6	10	25	0	0			
PPx	14	28	5	5	23	0	0			
PPx''	14	27	—	5	22	0	0			
PPx'	15	9	7	0	0	0	9			
PPx'''	15	5	1-5	0	0	0	5			
PP _i '	15	5	5	0	0	0	5			
PP _i ''	15	15	6-14	0	0	0	15			
HEDP	15	5	1-5	0	0	0	5			
HEDP	1	5	5	5	—	—	—	5m (25.9 ± 73)	1h (8.43 ± 2.57)	4h (2.44 ± 1.14)
	1	8-23	4-10	—	—	4-23	—	5m (21.23 ± 6.84)	1h (2.44 ± 1.14)	4h (2.14 ± 1.39)
	1	13-14	6-7	—	6-14	—	—	5m (16.86 ± 6.39)	(5.99 ± 3.22)	

P = Patients; NV = Normal Volunteers.

HEDP = ethyldiene diphosphonate; PPx = polyphosphate; MFP = monofluorophosphate; PP_i = pyrophosphate; MDP = methylene diphosphate; PP_x', PP_x'' =

TABLE 2. NORMAL BLOOD VALUES*

	Men	Women
Blood volume (ml/kg BW)	61.54 ± 8.59	58.95 ± 4.94
RBC volume (ml/kg BW)	28.28 ± 4.11	24.24 ± 2.59
Plasma volume (ml/kg BW)	33.45 ± 5.18	34.77 ± 3.24

* Ref. 20, p. 27.

symptoms. One or more of these drugs could affect tissue distribution. Investigators are also becoming more aware of changes in drug pharmacokinetics by disease states (17).

The ingredients of the radiopharmaceutical, a record of the time between kit formulation and patient administration, and quality-control results should also be indicated.

There are numerous publications outlining the methods for gathering pharmacokinetic blood and urine data. We have found References 18-19 quite helpful in this regard. One noticeable discrepancy in the reporting of blood-clearance data focuses on the percentage of the administered dose remaining in the vascular compartment with time (Table 1). The manner of this reporting has included "percent dose/liter of plasma," "percent dose/liter of whole blood," and "percent dose/whole blood volume." We suggest reporting the radiotracer content in the blood as "percent dose/whole blood volume," using the mean "standard" values for calculating the vascular compartmental volume

from Table 2 (20). These values are listed for "normal" individuals and use of Table 2 for calculating similar values in pathologic states may increase the uncertainty of such numbers. In such cases use of this table is suggested with an additional value reported relating radiotracer concentration. Also, the comprehensive ICRP report on Reference Man may be of assistance (21).

The need for standardization of methods of reporting data on radiopharmaceutical distribution in humans is outlined. Suggestions have been made to help achieve this goal. We expect this letter to generate additional recommendations as well as stimulate constructive discussion of our proposals.

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OF Tc-99m BONE AGENTS

Blood clearance T _{1/2b} (% component)			Blood clearance Time (%D/Liter Blood ^a or Plasma ^b)			Cumulative Urinary Excretion		
I (%)	II (%)	III (%)	T ₁ (%)	T ₂ (%)	T ₃ (%)	T ₁ (%)	T ₂ (%)	T ₃ (%)
6m (>50)	19m (—)	158m (—)				24h (56)		
						4.5h (30)		
30m (—)	264m (—)		4h (2.2) ^a			4h (28.2)		
30m (—)	294m (—)		18m (7.3) ^a	1h (3.7) ^a	3h (2.7) ^a	4h (33.3)		
30m (—)	168m (—)		10m (8.2) ^a	1h (3.4) ^a	3h (1.8) ^a	4h (33.8)		
			6h (1.21 ± 0.16) ^a			6h (51.21 ± 2.21)		
						6h (79.88 ± 2.81)		
486m (13.3)								
630m (8.0)								
192m (10.8)			1h (4) ^b	5h (1.3) ^b	24h (0.99) ^b	24h (38.16 ± 13.0)		
13.6m	380m		4h (9.5) ^a			1h (16.4)	4h (31.7)	
13.6m	512m		4h (12) ^a			1h (15.8)	4h (29.5)	
Authors report blood and urine values are similar to Ref. 9								
0.04h (77.6)	0.85 (21.1)	1.5h (14.5)				1h (40.7)	3h (58.9)	6h (68.2)
0.05h (74.2)	1.04 (21.5)	7.62h (2.5)				1h (30.9)	3h (55.5)	6h (67.7)
0.03h (74)	0.64 (18.3)	53.7h (7.4)				1h (29.0)	3h (42.7)	6h (49.8)
0.04h (71.3)	0.82 (19.3)	23.5h (9.4)				1h (25.8)	3h (40.0)	6h (46.0)
21.8m (—)	155m (—)		5m (7.22) ^a	1h (3.66) ^a	3h (0.73) ^a	1h (34.5)	3h (55.8)	6h (70.6)
			6h (0.59)-P ^a	6h (0.77)-NV ^a		1h (41.11 ± 1.15)	3h (65.52 ± 2.52)	6h (79.88 ± 2.00)
			6h (1.24)-P ^a	6h (1.21)-NV ^a		1h (32.09 ± 1.42)	3h (47.99 ± 1.59)	6h (54.43 ± 1.00)
			6h (2.21)-P ^a	6h (2.41)-NV ^a		1h (33.65 ± 3.39)	3h (49.16 ± 4.73)	6h (58.63 ± 5.00)
			6h (1.97)-P ^a	6h (1.59)-NV ^a				
			30m (7 ± 1.8) ^b	1h (5.1 ± 1.3) ^b	3h (2.6 ± 0.6) ^b	3h (16 ± 14)		
			30m (6.5 ± 1.5) ^b	1h (4.7 ± 1.3) ^b	3h (2.9 ± 1.0) ^b	3h (24 ± 17)	6h (43 ± 8)	24 (58)
			30m (5.7 ± 1.0) ^b	1h (4.0 ± 0.9) ^b	3h (2.3 ± 0.8) ^b	3h (13 ± 14)	6h (20 ± 20)	24 (38 ± 13)
			30m (7.3 ± 1.4) ^b	1h (5.0 ± 0.9) ^b	3h (3.0 ± 1.0) ^b	3h (28 ± 13)	6h (37 ± 14)	24 (56 ± 8)
			30m (5.7 ± 0.8) ^b	1h (4.5 ± 1.1) ^b	4h (1.4 ± 0.6) ^b	3h (39 ± 23)	6h (52 ± 22)	24 (57)
3.5m (78.7)	27m (14.1)	144m (7.2)				1h (32.16)	4h (42.14)	7h (51.79)
3.5m (78.7)	27m (14.1)	144m (7.2)				1h (13.18)	4h (24.79)	7h (30.42)
3.5m (78.7)	27m (14.1)	144m (7.2)				1h (13.74)	4h (33.89)	

similar agent—different mfg; PP₁, PP₂ = similar agent—different mfg; T_{1/2b} = biological half-life.

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