Adverse Reactions to Radiopharmaceuticals: Incidence in 1978, and Associated Symptoms. Report of the Adverse Reactions Subcommittee of the Society of Nuclear Medicine

Since 1967 the Society of Nuclear Medicine (SNM) has sought out and recorded cases of known or suspected adverse reactions to radiopharmaceuticals (*1*). From time to time summaries of these tabulations have been reported (*1–4*), but our lack of current information regarding the incidence of these reactions has been a major limitation to our understanding them. Thus, one of the objectives of the Adverse Reactions Subcommittee of SNM has been to measure or to estimate the recent rates of these reactions. We now report data that have allowed the committee to estimate that the overall incidence of adverse reaction to radiopharmaceuticals is between 1 and 6 per 100,000 administrations for the year 1978. Also, our data suggest that reactions to radiopharmaceuticals have been declining. The factors responsible for this decline may include: (a) widespread use of the limulus amoebocyte lysate gelation test for pyrogens (*5*), (b) use of good manufacturing practices (*6*), (c) use of good radiopharmaceutical practices (*7*), and (d) avoidance of the use of materials in radiopharmaceutical formulations that have previously been associated with adverse reactions.

An official definition of adverse reaction is: any experience associated with the use of a drug, whether or not considered drug-related; it includes side effects, injury, sensitivity reactions, or significant failure of expected pharmacological action (*8*). This definition is not directly applicable to radiopharmaceuticals. In practice, adverse reactions have been defined by nuclear medicine personnel who have reported to the registry and have included primarily hives, bronchospasm, anaphylactoid reactions, fever, nausea, vomiting, and flushing. Shani et al. (*3*) have summarized the definition as "An unanticipated physiological response of the patient to the vehicle carrying the radionuclide, not to the radiation itself." However, we have seen reports to oral therapeutic solutions of iodine-131 suggesting gastrointestinal symptoms that may have been caused by radiation. Not included in this definition is unsatisfactory or misleading diagnostic information. This is referred to as a radiopharmaceutical product defect.

Data concerning adverse reactions were obtained from the SNM registry. In 1976, the SNM registry was converted to a combined effort among SNM, the U.S. Pharmacopoeia Convention (USP), and the U.S. Food and Drug Administration (FDA). A single reporting form was developed, the SNM Drug Problem Report, on which both adverse reactions and product defects have been re-

TABLE 1. ADVERSE REACTIONS TO RADIOPHARMACEUTICALS

Radionuclide	1976	1977	1978	1979
Tc-99m HSA	1	1	2	1
Tc-99m MAA	1	1	2	2
Tc-99m HAM	19	14	16	6
Tc-99m sulfur colloid	11 (7)*	19 (10)	13 (12)	11
Tc-99m DTPA (Sn)	1	3		3
Tc-99m DTPA (Fe)	1	3 (1)	1	
Tc-99m HEDP	1		1	
Tc-99m MDP		3	1	6
Tc-99m glucoheptonate	2	2 (1)	2	1
Tc-99m pyrophosphate	10 (9)	2	2	1
$^{99m}TcO_4^-$	1	1		
Tc-99m DMSA	2			
Gallium-67 citrate	1			
NaI (I-131)	2	1	2	1
I-131 cholesterol	2		3	1
Tl-201 chloride		1		
Rose bengal (I-131)	2	1	1	
In-111 DTPA	2		1	1
P-32				1
Orthoiodohippurate (I-131)	1			
	60	52	47	35

* Numbers in ( ) indicate number of reports. Sometimes more than one case is cited per report.

TABLE 2. FREQUENCY OF ADMINISTRATION OF VARIOUS RADIOPHARMACEUTICALS IN 1978

Radiopharmaceutical	% Relative usage MODS	% Relative usage Storey	Total administration f(8,000,000)
Tc-99m sulfur colloid	19.6	19.8	1,584,000
Sodium pertechnetate (Tc-99m)	20.1	17.4	1,392,000
Total bone agents	19.1	16.3	1,304,000
Tc-99m MDP		10.0	800,000
Tc-99m pyrophosphate	11.2	4.8	384,000
Tc-99m HEDP	7.9	1.5	120,000
Total lung agents	13.0	14.0	1,120,000
Tc-99m MAA	11.3	9.4	752,000
Tc-99m HAM	1.7	4.6	368,000
Tc-99m DTPA	8.5	6.1	488,000
Xe-133 gas	6.6	5.1	408,000
NaI (I-131)	6.2	3.5	280,000
Tc-99m glucoheptonate	2.4	3.1	248,000
Ga-67 citrate	2.8	2.1	168,000
Tl-201 chloride	0.1	1.6	128,000
Orthoiodohippurate (I-131)	1.1	1.1	88,000
Tc-99m HSA	0.01	0.28	22,400
Rose bengal (I-131)	0.34	9.23	18,400
In-111 DTPA		0.03	2,400

TABLE 3. ESTIMATED RANGE FOR INCIDENCE OF ADVERSE REACTIONS TO RADIOPHARMACEUTICALS IN THE U.S. IN 1978

Radiopharmaceutical	Relative percent of all reports* minor or intermediate	Relative percent of all reports* severe	Estimated range for incidence† in 1978 only
Tc-99m HSA	100	0	18–89
Tc-99m HAM	94	6	13–65
Tc-99m sulfur colloid	100	0	2–8
Tc-99m glucoheptonate	100	0	2–8
NaI (I-131)	100	0	1–7
Tc-99m pyrophosphate	93	6	1–5
Tc-99m MAA	100	0	1–3
$Na^{99m}TcO_4$	100	0	0.01–0.4
Tc-99m DTPA	92	8	N.E.‡
Orthoiodohippurate (I-131)	100	0	N.E.
Iodocholesterol (I-131)	100	0	N.E.
Rose bengal (I-131)	100	0	N.E.
In-111 DTPA	100	0	N.E.
Tc-99m HEDP	100	0	N.E.
Tl-201 chloride	100	0	N.E.
Tc-99m DMSA	100	0	N.E.
Ga-67 citrate	100	0	N.E.
All radiopharmaceuticals	97	3	1–6

* Data include all reports from 1976 through 1979.
† Adverse reactions per 100,000 administrations.
‡ Not estimated.

ported. These forms are mailed approximately three times a year to the SNM membership under a cover letter from the President of SNM. The USP is responsible for mailing the forms. The FDA reviews the returns, evaluates the reports, and follows up when indicated. Individual members fill in and file the reports with the USP following suspected adverse reactions or other problems. The USP obtains additional verification data by telephone, if needed, from the reporter and supplies copies of the original report, plus any other data, to both the SNM Subcommittee and the FDA. The FDA evaluates the reports and follows up when indicated. The FDA also places the information into a computerized data file and retrieves, on request, summary reports that are used by the subcommittee together with the copies of the original reports.

The present report includes all registry data from 1976 through 1979. These reports have been used to establish: (a) estimates of the total incidence; (b) severity of the reactions; (c) the treatment, if required; and (d) the outcome.

The data to determine the total and relative numbers of radiopharmaceutical administration were obtained from the MODS (Medically Oriented Data System) of the FDA (*9*) and from R. Storey (personal communication). In both of the studies, data on the number and type of nuclear medicine procedures from a representative sample of services were tabulated. A total of 133,000 procedures were surveyed. The relative frequency of radiopharmaceutical administrations as determined by these two independent sources for the same period of time was similar (Table 1). The Storey data were used for our calculations since his categories were more convenient to our application.

The total number of administrations was estimated to be 8,000,000 for 1978. This number is the final estimate derived from the MODS data (*10*).

The ratio between total adverse reactions and reported adverse reactions is estimated by the committee members based on their personal experience. Our estimate is that between $\frac{1}{2}$ and $\frac{1}{10}$ of the observed reactions are actually reported, so that the estimate is obtained from the equation:

$$\text{Estimated range of adverse reactions} = \frac{2\,N}{f(8{,}000{,}000)} - \frac{10\,N}{f(8{,}000{,}000)}$$

where N is the number of reported reactions and f is the relative frequency of use of an individual radiopharmaceutical.

During the period from 1976 to 1979, 372 reports were made to the registry. Among these there were 194 cases of adverse reactions. Forty-seven cases occurred in 1978. The majority of the adverse reactions to radiopharmaceuticals were allergic in nature, although a few "pyrogen-like" reactions were also documented. *No* deaths were directly attributed to administration of a radiopharmaceutical during this four-year period.

Allergic reactions have been characterized by their severity as: *minor*—resolved with no therapy; *intermediate*—requiring some form of therapy for relief, but not life-threatening; and *severe*—dangerous signs and reactions requiring prompt and aggressive therapy of a condition that may result in death. The majority (97%) of adverse drug reactions that occurred were minor to intermediate, with symptoms that resolved quickly—i.e., within minutes to a few hours. Exceptions were two cases of rash that persisted for over 24 hours. Severe reactions, involving anaphylactic shock or cardiac arrest, were reported for five cases.

Table 1 lists the number of reactions (N) by year for each radiopharmaceutical listed among the reports. Table 2 lists the frequency (as percent of total number of doses) and the total number of administrations (f·8,000,000). Table 3 gives the number of reports rated by degree of severity for all four years, then gives the estimated range of rates for 1978. Table 4 lists the reported symptoms for reactions in 1978.

The estimated range for the incidence of adverse reactions for radiopharmaceuticals is lowest for sodium pertechnetate (Tc-99m). Since no reactions were reported for this radiopharmaceutical in 1978, a value of 0.5 (the four-year average) was used in the calculation. Tc-99m DTPA was not estimated because it was available in two forms—one using iron and ascorbic acid as the reducing agent and one using tin—and we do not assume that they are the same since reactions are attributed to the formulating constituents rather than the tracer substance itself. The numbers for most of the other radiopharmaceuticals were so low that no estimates were attempted, but the data suggest that none are higher than the overall rate. Thallium chloride and gallium citrate may be lower; they probably have about the same incidence as that for sodium pertechnetate.

The total incidence of reported adverse reactions was 47 per 8,000,000 administrations (0.59 per 100,000) to give an estimated overall total range between 1 and 6 per 100,000. The average reported reactions for 1967–1970 were 1 per 9979 (*3*), giving an estimated overall total average of between 20 and 100 per 100,000 if we assume the same ratio of reports to actual reactions. This estimate is less than that made by Williams in 1974 for Great Britain (*11*). His preliminary survey indicated a range of one reaction per 36 administrations for MAA (the highest), to 1 per 3000 for DTPA. This is approximately of the same order of magnitude as that for adverse drug reactions in hospitalized patients given therapeutic drugs, namely, 10–20% (*12*).

TABLE 4.

Radiopharmaceutical	Reported symptoms in order of decreasing frequency of observation, with time of onset (summary of 1978 data only)
Tc-99m HSA	Up to 1 hr: flushing, respiratory difficulty, rapid pulse; rash; high temperature
Tc-99m HAM	1 hr: flushing, respiratory distress, cyanosis; itching, rash; pyrogen; bronchospasm; anaphylactic shock
Tc-99m sulfur colloid	1 hr: hives, rash, itching, redness/swelling; nausea, vomiting, dizziness, loss of consciousness; respiratory difficulty, flushing, cyanosis; pain at injection site; bronchospasm; pyrogen reaction after 1 hr: rash; pyrogen reaction
Tc-99m glucoheptonate	rash, hives; nausea, dizziness, chills
Tc-99m DTPA (Fe)	seizure; dizziness, hypotension; swelling, redness, itching
Tc-99m DTPA (Sn)	hives, itching; flushing, hypertension
Tc-99m MAA	Up to 1 hr: hives, itching, redness; respiratory difficulty; cardiac arrest; metallic taste
NaI (I-131)	Several hours: nausea, vomiting, chest pain, tachycardia; itching skin, rash, hives
Orthoiodohippurate (I-131)	Immediate: anaphylactic shock
In-111 DTPA	1 hr: pyrogen reaction. several hours: meningitis

The incidence of adverse reactions to radiopharmaceuticals also appears to be lower than that found for contrast media. Coleman et al. (*13*) reported the incidence of allergic reactions in 10,000 consecutive intravenous urographies. They found an incidence of untoward reactions of 8.53%; these included 1.68% allergic reactions. Witten et al. (*14*) studied 32,964 consecutive patients referred for IVP at Mayo Clinic. They found 5.1% minor side effects and 1.72% total acute reactions. Ansell (*15*) observed an incidence of intermediate reactions to urography of 0.044%; severe reactions, 0.0075%; and deaths, 0.0025%.

We conclude that the current probability of an adverse reaction to a radiopharmaceutical is about one hundredth of that for therapeutic drugs or contrast media (*3*). It is further concluded that the incidence of adverse reactions to radiopharmaceuticals has been significantly reduced (by a factor of roughly 20) during the last 10 years. Many of the earlier adverse reactions have been attributed to iron-containing preparations, gelatin-stabilized preparations, and materials, such as albumin, contaminated with pyrogens (*3,11*). Many of the materials implicated in earlier reactions are no longer used in radiopharmaceutical formulations.

Another factor that has probably contributed to this reduction in the incidence of adverse reactions is the great improvement in radiopharmaceutical manufacturing and quality control that has occurred during the past decade. Perhaps the best example of this is the introduction and widespread use of limulus amoebocyte lysate gelation test for pyrogens. The use of this test has helped to eliminate the once widespread problem of aseptic meningitis from cisternographic agents, due to pyrogen contamination, that the USP rabbit test (*16*) failed to detect.

In summary, if we take 1978 as a sample year, the incidence of adverse reactions to radiopharmaceuticals probably ranges from nearly 90 per 100,000 for some products containing human serum albumin, down to less than one for simple carrier-free salt solutions, such as sodium pertechnetate, thallium chloride, and gallium citrate. Only 3% of these were classified as severe. Thus the estimated range for the incidence of severe reactions over all four years was only 0.02–0.09 per 100,000. No deaths were attributed to radiopharmaceuticals.

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Hepatic Clearance Mechanism of Tc-99m-N-(Acetanilido)-Iminodiacetic Acid Derivatives

Harvey et al. recently demonstrated in the *Journal* (*1*) the competitive inhibition of N(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid (Tc-99m HIDA) biliary elimination by bromosulfophthalein (BSP). From the data obtained, the authors inferred that elevated serum bilirubin interferes with Tc-HIDA elimination, suggested that radiopharmaceuticals designed to measure hepatobiliary function should possess in vivo clearance patterns independent of serum bilirubin levels, and that these processes could be achieved either through the use of radiolabeled cations or bile salts.

In view of the available data, I believe that in nonobstructive jaundice biochemical alterations induced by cholestasis and that lead to hepatocyte damage, rather than high serum bilirubin *per se*, are the primary limiting factors of biliary elimination of Tc-HIDA and other synthesized Tc-iminodiacetic acid (IDA) derivatives (*2*). In liver cell damage, the degree of impaired elimination varies among the Tc-IDA derivatives. Although labeled bile salts could offer excellent indications of the liver cell functional status, it is unlikely that they will represent ideal indicators of the hepatobiliary function. After crossing the plasma membrane, bilirubin and other anions are bound by Ligandin (Y) as well as by other soluble (Z, X) proteins of the hepatocytes (*3, 4*). Published data might suggest that the binding sites for bilirubin and BSP are not completely identical and that quantitative variations might exist between the binding ability and/or the degree of competitive inhibition occurring between anions (*5, 6*). Through bilirubin infusion in rabbits it was shown that high bilirubinemia (up to 15 mg/dl unconjugated bilirubin) neither significantly decreases the liver uptake of both Tc-dimethyl and Tc-diethyl-IDA nor hinders the visualization of the biliary tract and duodenum (*7*).

Important changes were noted instead by Bahre et al. (*8*) in both T-max and excretory half-life on liver time-activity curves of Tc-diethyl-IDA in dogs with galactosamine-induced hepatitis, even in the presence of only slightly increased bilirubin levels. Similarly, a comparative study of the biliary elimination of several Tc-IDA derivatives in rabbits with carbon tetrachloride-induced liver insufficiency (*9*) showed significantly decreased eliminations of all derivatives tested in the presence of high values of serum aldolase and both GO and GP transaminases, but with only minimal increase of bilirubin levels. In those experimental conditions leading to functional and morphological liver cell damage with a slight increase of serum bilirubin, the fact that the uptake and elimination of Tc-IDA derivatives were significantly decreased could indicate the importance of the role of metabolic processes, perhaps primarily those associated with membrane structures. For instance, that at high serum bilirubin levels reached in the study by Jansholt et al. (*7*), an increased urinary excretion was found for Tc-HIDA. This finding confirms the data obtained by Harvey et al. in dogs (*1*), as well as for pyridoxylidene glutamate, but not for Tc-diethyl-IDA and rose bengal (RB).

Fritzberg et al. (*10*) assessed the influence in rats of BSP infusion at a rate of approximately twice the T-max of BSP on both Tc-diethyl-IDA and RB biliary elimination. In these conditions their results showed a reduction of the biliary elimination to around 20.75 and 52.50% from the values eliminated before BSP infusion for RB and Tc-diethyl-IDA, respectively, whereas infusions of BSP at levels over twice the T-max in dogs (*1*) produced a similar lowering of RB elimination (30%) but decreased Tc-dimethyl-IDA to 2.75% from the values eliminated before BSP infusion. Although species differences might account for the variations noticed in the impairment of Tc-IDA derivatives after BSP infusion, the resemblance of RB-impaired elimination in both experiments points to a different competitive ability of these two IDA derivatives with BSP, so much so that the patterns of biliary elimination seem to be similar in dogs and rats (*11*).

Labeled bile acids, one of the possible radiopharmaceuticals to measure hepatobiliary function suggested by Harvey et al. (*1*), are indeed independent from both serum bilirubin levels and anionic pathway elimination. They are certainly sensitive indicators of the liver cell function, since one of the earliest manifestations of the hepatocellular dysfunction is a reduction in the capacity to transport bile acids (*12*). This disturbed capacity leads to increased serum bile acid concentrations far before the appearance of hyperbilirubinemia and might even be the only modified parameter of the liver excretory function with the exception of the increased serum enzyme levels, e.g., in anicteric hepatitis (*12*). In view of the data established by the biliary imaging agents, Tc-IDA derivatives included, it is, however, unlikely that labeled bile acids could provide a better tool for the assessment of the hepatobiliary function because, aside from the fact that their excretion is dependent upon the functional status of the liver cells, their reabsorption from the jejunum and ileum (*13*) will hinder the differential diagnosis between the obstructive and medical jaundice.

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