Radiochemical Evaluation of Commercial Iminodiacetate Hepatobiliary Radiopharmaceuticals

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The radiochemical purity of commercially available hepatobiliary iminodiacetate radiopharmaceuticals was evaluated up to 24-hr postformulation. We used a rapid miniaturized chromatography system consisting of Gelman ITLC-SA and 20% NaCl to evaluate free pertechnetate and Gelman ITLC-SG and distilled water to evaluate hydrolyzed reduced Tc-99m (Tc-HR). Results indicate that minimal radiopharmaceutical breakdown occurred in all IDA agents tested within 5-hr postformulation. At 8 hr after preparation, some breakdown was observed in specific IDA radiopharmaceuticals as evidenced by increasing pertechnetate levels. Greater radiopharmaceutical instability was observed at 24-hr postformulation. Tc-HR levels remained relatively low (<5%) for all IDA agents throughout the study.

Since their introduction into the nuclear medicine community (*1*), iminodiacetate (IDA) radiopharmaceuticals have gained wide acceptance for hepatobiliary imaging. Several substituted IDA agents are now commercially available in lyophilized kit form; however, the quality of these preparations has not been thoroughly investigated. We evaluated the radiochemical purity of commercially available hepatobiliary imaging agents by determining free pertechnetate and hydrolyzed reduced Tc-99m levels in radiopharmaceuticals up to 24 hr after formulation.

Materials and Methods

Four commercial IDA agents were evaluated including 2, 6-dimethyl IDA (CintiChem, Inc.), p-isopropyl IDA (Medi-Physics, Inc.), p-butyl IDA (Syncor International), and 2,6-diisopropyl IDA (New England Nuclear). Approximately 50, 100, and 150 mCi of [^{99m}Tc] pertechnetate, obtained from a newly received generator that had not been eluted for at least 48 hr to maximize the total quantity of technetium, was added to each of three vials for each specific IDA agent. Levels of free pertechnetate and Tc-HR were determined at 1, 3, 5, 8, and 24 hr after formulation using miniaturized chromatography procedures described previously (*2*).

Free pertechnetate levels were evaluated by using Gelman silicic acid-impregnated glass fibers (ITLC-SA) and 20% NaCl. Free pertechnetate migrated with the solvent front (Rf = 1.0) while Tc-99m IDA remained at the origin (Rf = 0.0). Tc-HR levels were evaluated using Gelman silica gel-impregnated glass fibers (ITLC-SG) with distilled water. With this system, Tc-HR remained at the origin (Rf = 0.0) and both Tc-99m IDA and free pertechnetate migrated with the solvent front (Rf = 1.0). The chromatography procedure is outlined in Table 1. For each specific IDA radiopharmaceutical and time period, four repetitive samples were chromatographically evaluated and the data statistically summarized.

Results

Table 2 shows the results of the radiochemical evaluation for Tc-99m 2,6-dimethyl IDA. Free pertechnetate levels of <4% were observed up to 8 hr after prepa-

TABLE 1. Procedure for Determining Free Pertechnetate and Hydrolyzed Reduced Tc-99m in Commercial Tc-99m Labeled IDA Agents

1. Place approximately 1 ml of 20% NaCl and 1 ml of distilled water in each 10-ml glass vial.
2. Spot radiopharmaceutical 1 cm from bottom of Gelman ITLC-SA and Gelman ITLC-SG chromatography strip (1 × 6 cm strips).
3. Develop SA strip in 20% NaCl and SG strip in distilled water until solvent migrates to top of strip.
4. Cut SA strip 2 cm from origin and SG strip 1 cm from origin.
5. Count all sections for activity (per unit time) using a gamma counter and subtract background. Determine free pertechnetate and hydrolyzed reduced Tc-99m levels.

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TABLE 2. Radiochemical Evaluation of 2, 6-dimethyl IDA (HIDA, CintiChem Inc.)

Free Tc-99m pertechnetate in 2, 6-dimethyl IDA preparations (mean per cent pertechnetate ± standard deviation)			
Time	Amount (mCi) in each preparation		
(hr)	50	100	150
1	0.6 ± 0.05	0.4 ± 0.05	0.6 ± 0.1
3	0.5 ± 0.05	0.8 ± 0.05	0.9 ± 0.2
5	0.9 ± 0.2	1.2 ± 0.1	1.7 ± 0.2
8	1.8 ± 0.5	2.0 ± 0.1	3.6 ± 0.7
24	8.3 ± 0.2	11.1 ± 0.8	13.7 ± 0.6
Hydrolyzed reduced Tc-99m in 2, 6-dimethyl IDA preparations (mean per cent Tc-HR ± standard deviation)			
1	0.2 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
3	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
5	0.3 ± 0.2	0.2 ± 0.05	0.4 ± 0.3
8	0.1 ± 0.05	0.3 ± 0.1	0.4 ± 0.2
24	0.4 ± 0.1	0.8 ± 0.5	0.4 ± 0.2

TABLE 3. Radiochemical Evaluation of p-isopropyl IDA (PIPIDA, Medi-Physics)

Free Tc-99m pertechnetate in p-isopropyl IDA preparations (mean per cent pertechnetate ± standard deviation)			
Time	Amount (mCi) in each preparation		
(hr)	50	100	150
1	3.1 ± 1.2	1.7 ± 1.6	1.2 ± 0.7
3	2.2 ± 1.0	1.6 ± 1.0	2.2 ± 1.1
5	3.5 ± 0.7	5.6 ± 1.7	5.7 ± 0.4
8	9.1 ± 1.0	11.6 ± 0.7	14.0 ± 2.2
24	19.7 ± 3.2	32.4 ± 1.1	37.6 ± 3.7
Hydrolyzed reduced Tc-99m in p-isopropyl IDA preparations (mean per cent Tc-HR ± standard deviation)			
1	0.3 ± 0.05	0.5 ± 0.05	0.5 ± 0.05
3	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
5	0.7 ± 0.05	1.1 ± 0.1	1.0 ± 0.2
8	1.2 ± 0.1	2.3 ± 0.4	1.9 ± 0.2
24	2.5 ± 0.5	1.9 ± 0.2	1.4 ± 0.1

ration. Pertechnetate levels >10% were observed in the preparations containing 100 and 150 mCi at 24-hr postformulation. As a general rule, higher pertechnetate levels were observed with increasing levels of radioactivity. Tc-HR levels in all 2,6-dimethyl preparations remained at <1% throughout the study.

The results for p-isopropyl IDA are summarized in Table 3. Radiopharmaceutical instability was observed as indicated by higher pertechnetate levels. At 5 hr after formulation, higher activity vials contained in excess of 5% free pertechnetate (5.6% ± 1.7% and 5.7% ± 0.4% for 100-mCi and 150-mCi vials, respectively). Increased pertechnetate levels, up to 14.0% ± 2.2% for the 150-mCi preparation, were observed at 8-hr postformulation and further radiopharmaceutical degradation was observed after 24 hr. Tc-HR levels remained relatively low (<3%) throughout the study.

Table 4 shows the results for the radiochemical evaluation of Tc-99m 2,6-diisopropyl IDA. Less than 2% free pertechnetate was observed in all preparations up to 8 hr after formulation. At 24-hr postformulation, only one preparation contained free pertechnetate levels in excess of 10% (12.6% ± 0.9% for the 150-mCi preparation). Tc-HR levels remained <4% throughout the study.

Table 5 summarizes the results for the Tc-99m p-butyl IDA. The radiopharmaceutical preparations remained stable up to 24 hr after formulation as demonstrated by the low levels of free pertechnetate (<2%). Tc-HR remained at <5% throughout the study.

Discussion

In order to evaluate kit performance under the least favorable conditions, the study was performed with the first pertechnetate eluates obtained from newly received generators. First eluates can affect labeling yields to a greater extent than all subsequent generator eluates. The first eluate contains high quantities of total technetium (Tc-99 and Tc-99m) and upon addition to Sn-radiopharmaceuticals, the usable stannous-tin may become the limiting factor in the labeling reaction resulting in incomplete or depressed labeling (*3*).

The results of our study indicated that free pertechnetate levels remained low for up to 5-hr postformulation. At 8 hr after preparation, some radiopharmaceutical instability was observed especially in the higher activity-containing preparations. Tc-99m p-isopropyl IDA was the least stable preparation at all activity levels. Our results indicate that additional chromatographic quality

TABLE 4. Radiochemical Evaluation of 2, 6-diisopropyl IDA (Hepatolite, NEN)

Free Tc-99m pertechnetate in 2, 6-diisopropyl preparations (mean per cent pertechnetate ± standard deviation)			
Time	Amount (mCi) in each preparation		
(hr)	50	100	150
1	0.3 ± 0.1	0.5 ± 0.3	0.3 ± 0.2
3	0.6 ± 0.2	0.4 ± 0.1	0.4 ± 0.1
5	0.8 ± 0.4	0.5 ± 0.2	0.3 ± 0.1
8	0.8 ± 0.1	0.6 ± 0.1	1.3 ± 0.2
24	4.2 ± 0.5	6.9 ± 0.7	12.6 ± 0.9
Hydrolyzed reduced Tc-99m in 2, 6-diisopropyl preparations (mean per cent Tc-HR ± standard deviation)			
1	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1
3	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1
5	0.5 ± 0.1	0.4 ± 0.1	0.4 ± 0.1
8	0.6 ± 0.1	0.6 ± 0.2	0.5 ± 0.1
24	3.2 ± 1.5	2.3 ± 1.6	3.8 ± 2.3

TABLE 5. Radiochemical Evaluation of p-butyl IDA (Syncor International)

Time (hr)	Amount (mCi) in each preparation 50	100	150
Free Tc-99m pertechnetate in p-butyl IDA preparations (mean per cent pertechnetate ± standard deviation)			
1	0.04 ± 0.01	0.1 ± 0.05	0.8 ± 0.4
3	0.1 ± 0.05	0.5 ± 0.3	1.0 ± 0.4
5	0.2 ± 0.1	0.6 ± 0.4	0.6 ± 0.5
8	0.5 ± 0.4	0.4 ± 0.3	0.6 ± 0.5
24	0.2 ± 0.1	0.8 ± 0.2	1.7 ± 0.5
Hydrolyzed reduced Tc-99m in p-butyl IDA preparations (mean per cent Tc-HR ± standard deviation)			
1	———	3.1 ± 0.9	3.3 ± 0.2
3	———	4.0 ± 0.7	3.6 ± 1.6
5	———	4.2 ± 1.7	4.3 ± 0.5
8	———	4.7 ± 1.7	4.4 ± 0.5
24	———	4.9 ± 1.2	1.9 ± 0.1

control should be performed for this agent if patient doses are withdrawn later than 5 hr after preparation. Tc-HR levels for all IDA radiopharmaceuticals remained low throughout the study for up to 24 hr after formulation, indicating that this radiochemical impurity is minor.

The miniaturized chromatography system for IDA radiopharmaceuticals, as outlined, is rapidly performed and easy to use. Such a system could be incorporated into a radiopharmaceutical quality control program with a minimal amount of inconvenience.

References

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